Reducing the chronic disease burden in China: tailoring a self-management intervention among Chinese people with chronic lung disease

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General introduction

Introduction

The burden of hypertension and chronic lung disease

In China, chronic diseases such as hypertension and chronic lung disease (CLD) threaten health and well-being, representing a high public health burden. Hypertension affects more than 32.5% of Chinese people and accounts for nearly 2.1 million cardiovascular deaths annually in China [1,2]. Among the patients with hypertension in China, around 67.8% are accompanied by frailty [3]. Frailty is a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which can be caused by various variables and increases the risk of adverse outcomes [4]. The coexistence of hypertension and frailty leads to a higher risk of disability and mortality and increases healthcare utilization compared to patients with hypertension without frailty [3,5].

Similarly, CLD – with chronic obstructive pulmonary disease (COPD) and asthma being the most prevalent – pose a high disease burden in China [6]. More than 144 million Chinese people have CLD [7,8]. In China, disability-adjusted life years caused by COPD was 1,445.53/100,000 in 2017, higher than those worldwide in the same year, i.e., 1,038.02/100,000 [9]. Notably, COPD ranks as the fourth leading cause of death in Chinese urban areas and third-leading in Chinese rural areas [10,11]. In addition, CLD leads to considerable healthcare costs [12,13]; the annual cost for CLD is more than $156.3 billion in China [12,13]. The exacerbations cause most of the medical expenses [12,13]. Exacerbation is the sustained worsening of a patient's condition beyond normal day-to-day variations that are acute in onset, which may also require a change in medication and/or hospitalization [14]. Identifying cost-effective approaches to help patients manage their disease is essential to reducing the Chinese chronic disease burden [15,16].

Self-management interventions can help to reduce the chronic disease burden

A promising approach to improving health outcomes and reducing healthcare costs associated with chronic conditions is self-management (SM) [17]. There are many definitions of SM [18-20]. Richard et al. have defined SM as "an individual's ability to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent to the life with a chronic condition" [18]. Audulv et al. defined SM as "strategies an individual undertakes to manage an illness and life with that illness." [19]. Furthermore, SM has been described by Miller and his colleagues as an ongoing process of fulfilling the individual's needs to care for a chronic illness [20]. They argued that "SM is a fluid, iterative process during which patients incorporate multidimensional strategies that meet their self-identified needs to cope with chronic illness within the context of their daily living." [20]. In this thesis, the SM definition by Richard et al. is used because it specifies patients' primary tasks, e.g., treatment,

emotion, and role management [18]. SM puts the patient in a central position in the healthcare process. During the SM process, patients are informed and supported by healthcare professionals (HCPs) to increase patients' responsibility in decisions affecting their healthcare [21].

Self-management intervention (SMI) refers to interventions that aim to increase patients' involvement and control in their treatment with or without support from HCPs [22]. Studies have shown that SMI can help to reduce the chronic disease burden [19,23]. To explain, SMI can be delivered face-to-face, digitally (through eHealth), or blended care. eHealth refers to health services and information delivered or enhanced through the internet and related technologies [24]. It can include, for example, video calls, web platforms, and applications [24]. Blended care is a treatment program that uses face-to-face and eHealth intervention elements, including integrating and sequential treatment formats [25].

SMI can help people with chronic diseases improve their SM capacity to tackle chronic disease, consequently contributing to improved healthcare outcomes and reduced disease burden [26,27]. Evidence focusing on people with CLD reported that (blended) SMI could help to prevent patients' adverse outcomes (e.g., mortality), reduce hospital readmission, and improve physical and psychosocial functioning [28-30]. Besides, previous systematic reviews have demonstrated that SMI can help patients with hypertension improve their SM and reduce their blood pressure [31,32].

Collectively, SMIs are beneficial for people with chronic diseases, especially those with poor SM. Chinese people with CLD have shown poor SM [31-33 34,35]. For example, a study showed that this group did not use regular daily controller medications before admission [34,35], which indicates poor SM. The irregular medication use led to an increased exacerbation time that needed treatment and resulted in higher medical costs [34,35]. Effective SMIs are needed to help such patients improve their SM, which can optimize their health outcomes and decrease medical expenditure.

Currently, most research on SMI tackling chronic diseases has been developed and tested in high-income countries, whereas the chronic disease burden is highest in low-and middle-income countries [36,37]. To illustrate, around one-fourth of the global burden of CLD is in China, and in this country, there is inefficient care and poor SM [38-40]. SMIs developed and tested in high-income countries may not be (fully) appropriate for patients in China and may result in decreased effectiveness. The inappropriateness of the intervention is due to the different health, economic, and cultural backgrounds between high-income countries and China [36,37]. Therefore, it is necessary to identify what can be done to align such SMIs with Chinese healthcare settings.

Tailor a SMI tackling CLD in the Chinese context

Evidence has shown that SMI implementation may fail due to a mismatch between the selected SMI and the local context. The implementation – an act of carrying an intervention into effect – is a challenging process [41]. When implementing a SMI from a high-income country, e.g., the Netherlands, to a low-and middle-income country, e.g., China, the implementers should consider the local context. Context is a set of unique characteristics and circumstances surrounding the implementation effort [42]. Local context refers to the set of characteristics and circumstances surrounding the implementation effort, such as the local beliefs, health- and political- infrastructure, socioeconomic aspects, and the network of the relevant stakeholders [42]. It is necessary to identify feasible implementation strategies to improve the alignment between the SMI and the local context. Implementation strategies are any action aimed at integrating innovation into practice [43]. One implementation strategy is tailoring effective interventions to another context [44,45]. Evidence has demonstrated that tailoring a SMI to the local context is vital because the tailored SMI can help improve patient outcomes and optimize local resource use [46-48]. Thus, it is necessary to tailor the proven-effective SMI in a different context [49,50]. However, there is a lack of evidence on tailoring SMI to another context, especially in low-and middle-income countries. To meet this need, this thesis aims to tailor a proven-effective SMI tackling CLD, developed and tested in a high-income country, to the Chinese context. CLD is a focus of this thesis because it is a severe chronic disease, leading to a high disability and mortality rate and economic burden [9,38]. Second, exacerbations cause a significant disease burden [12,13]. Recent studies on the effectiveness of SMIs in people with CLD have reported that SMIs focusing on exacerbation management optimize patients' quality of life and lead to reduced healthcare visits and hospital admission [51-53]. Furthermore, compared with other diseases, such as hypertension, the research to advance the effective treatment of CLD has been woefully inadequate [54].

Aligned with previous research [55,56], tailoring a SMI for Chinese people with CLD will be done in this thesis as follows (**Figure 1**): (a) identify the Chinese context, (b) select SMI and mode of delivery, (c) identify factors that influence the SMI implementation, and (d) integrate SMI into the Chinese context.

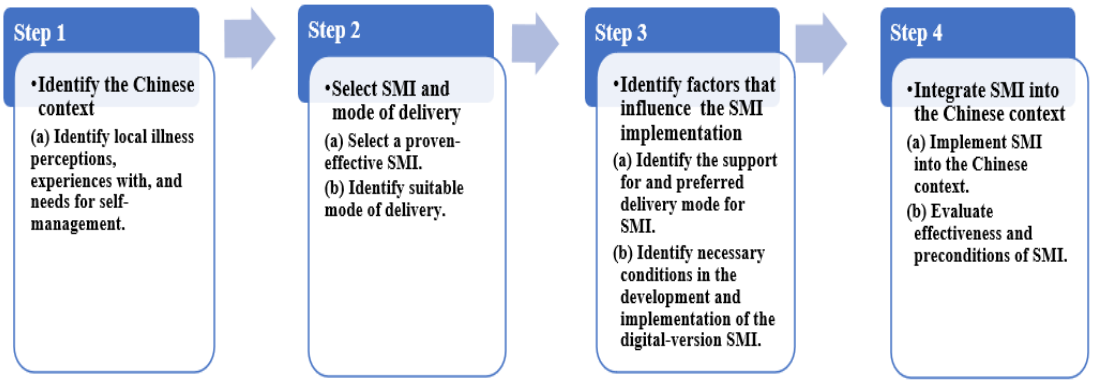

Figure 1. Process of tailoring self-management intervention (SMI) into the local context

In summary, this thesis will tailor a SMI for people with CLD, which has been proven effective in a high-income country, to the Chinese context. Researchers and other professionals who wish to implement a SMI for chronic diseases in a different setting can use the methods and lessons learned from the tailoring process.

Identify the Chinese context

Local context (e.g., illness perceptions, experience with and needs for SM) matters when transferring an intervention from one setting to another and translating the research into everyday practice [57,58]. The contextual information in China can also help tailor SMI to the Chinese context, improving the possibility of implementing SMI successfully and optimizing local resource use [59].

To date, no research has examined the local context of CLD in China. Yet, Kurmi et al. reviewed the patterns of COPD burden and management of COPD in China [60]. The review showed that despite the substantial burden of COPD, research on illness understanding and disease management is limited in China [60]. Thus, this thesis will help to identify the local context to understand (a) how patients and HCPs perceive the disease, (b) how patients self-manage their disease and (c) the unmet needs in the existing SMIs.

Identifying illness perceptions helps to inform SM strategies within a context [61-64]. Over the last two decades, health and illness behaviors have changed significantly after the advocation of Engels [65]. Specifically, a disease-oriented medical model has transitioned to the theoretical conceptualizations emphasizing environmental factors and individual perceptions of health and illness [65]. Leventhal et al. developed a self-regulatory model of illness (SRMI), which integrated the above factors within a patient's common-sense representations of health and illness [61,66]. The SRMI has been used widely to help understand chronic illness and treatment perceptions [62,63,67,68]. Recent illness perception reviews – focusing on COPD patients in high-income countries – have demonstrated that

assessing the illness perceptions about COPD offers opportunities to identify goals for SM [63]. To identify how Chinese people with CLD cope with the disease, SRMI is applied to identify the illness perceptions of Chinese people with CLD and HCPs in this thesis. Next, identifying experiences with and needs for SM from the patients and HCPs will help tailor the SMI to the local context [69-71]. For example, recent reviews have demonstrated that understanding patients' experiences with SM can support HCPs in identifying effective SMIs [69,70]. Besides, there is evidence that identifying the experience with and unmet needs for SMI from the perspective of HCPs can assist in reforming transitional care practices for chronic disease [70,71]. Altogether, identifying the local context through illness perceptions, experiences with, and needs for SM, in patients and HCPs, can help to increase the uptake and implementation success of SMIs.

Select the SMI and mode of the delivery

In the pilot study by Hallensleben et al., they developed and tested a SMI –REducing Delay through edUcation on eXacerbations or REDUX – for patients with COPD in the Netherlands [51]. The REDUX intervention was designed to educate patients on symptom management by helping them recognize their early-onset symptoms and teach them how to react when this happens. The essential part of the program is a personalized paper-based action plan completed by patients and HCPs [51]. The action plan includes four boxes. The first box helps patients determine how they can recognize the worsening of symptoms; patients can fill in their personal, specific early signs of an exacerbation. In the second box, personalized advice is given on medications to use in case of worsening symptoms. The third box details how long patients need to use increased medication dosage when the medication gives relief. The last box provides advice about what the patient should do when the symptoms worsen, explicitly indicating how long the patient should wait until contacting the general practitioner [51]. The pilot study showed that REDUX increased patients' SM; that is, there was a decrease in the number of days between exacerbation recognition and time to seek medical help, and REDUX helped reduce the disease burden [51]. One training session about coaching patients using the action plan is delivered to HCPs, including general practitioners and nurses in primary care settings.

Given the previous positive effect on people with COPD in the Netherlands, REDUX shows the potential to help people with CLD self-manage the disease effectively in China. Notably, the action plan is helpful for patients to engage in their disease management actively in two aspects. First, patients gain disease knowledge and SM skills on self-managing the exacerbations by filling in the action plan together with HCPs. This knowledge and these skills can help patients self-manage their exacerbations at home [49]. Second, the implementation of REDUX matches the local long-term policy priority, which reflects the needs of Chinese people with CLD. It is pointed out in the Action for

Healthy China 2030 that public education will support progress toward improved medication use [72]. Therefore, this thesis selects REDUX as the effective SMI.

SMIs with different delivery modes – face-to-face intervention, digital treatment, and blended care – can help improve patient healthcare outcomes and reduce the disease burden [27-29,73,74]. To illustrate, (fully) online SMI using a health application or web page has helped patients self-manage their disease [27,73]. Blended care, including face-to-face and digital care, is an alternative to fully online treatment. Blended SMI could retain the positive aspects of face-to-face intervention and online treatment by mitigating their negative aspects [28,29]. For example, blended SMI could help patients reduce face-to-face consultation time by offering online support or materials (e.g., psychoeducation). The preferred or suitable delivery mode also depends on the target population and context. For example, patients in remote districts can benefit from online education since it is difficult to assess the healthcare settings physically [27-29,73,74]. Conversely, older patients may prefer face-to-face education because they can gain SM skills during the interaction with HCPs [74]. Not all patients benefit from a 'one size fits all' intervention [49], so it is vital to identify what delivery mode is suitable within the local context.

However, it is unclear which mode of delivery is preferred in China regarding SMI. This thesis will identify the preferred SMI delivery mode in China by assessing the locally preferred mode to deliver a SMI, such as REDUX. Currently, REDUX consists of a paper-based action plan that patients and HCPs complete during a face-to-face consultation [51]. It is possible to transfer such an action plan into a digital one. With this adaption, patients could access the action plan and professional help without time or place restrictions [27,73]. Altogether, the thesis will select REDUX as the proven-effective SMI. The suitable mode of delivery will be determined after identifying the local preferred ones.

Identify factors that influence the SMI implementation

Implementing the REDUX intervention depends on whether it is feasible and compatible within the specific context [16,75]. And thus, it is necessary to identify the factors influencing the REDUX implementation.

Local stakeholders play an essential role in the SMI implementation [75]. Stakeholders are groups or individuals affected by or are in some way accountable for the outcome of a specific undertaking [76]. It has been demonstrated that one fundamental way to improve the implementation success of a SMI in a different context is to engage the local stakeholders [75-80]. To illustrate, local stakeholders such as patients, HCPs, and policymakers can make efforts to promote the adoption and sustainability of SMI within the local context. Yet, frequently, stakeholder analysis studies on

innovations in healthcare only focus on policymakers [81-85]. However, it is also necessary to hear the voices of other stakeholders, such as patients, HCPs, and those involved in developing and implementing healthcare innovations [75-80]. That is because these stakeholders play an essential role in the SMI implementation (**Figure 2**) [75-85]. A comprehensive overview of the factors influencing the SMI implementation from different stakeholders will optimize implementation successes [77].

Accordingly, this thesis will include patients, HCPs, policymakers, app developers, and cyber-security officers to identify the factors influencing the REDUX implementation. Specifically, the support for REDUX from patients, HCPs, and policymakers can help determine whether REDUX will be adopted in China. Furthermore, their preferred mode to deliver REDUX can help shape the feasible method to implement the intervention, which can assist the program implementation successfully [51,86-88].

Given that Chinese stakeholders can prefer the digital version of REDUX, it is crucial to identify the conditions that should be addressed when developing and implementing the digital version of REDUX. To our knowledge, there needs to be more evidence on the conditions to develop and implement a digital version of a SMI in China. Such missing information may result in these interventions failing in a different context [89]. Therefore, this thesis will identify the necessary conditions to develop and implement the digital version of REDUX by collecting data from Chinese app developers and cyber-security officers.

To sum up, the factors that influence SMI implementation will be identified in different stakeholders. Specifically, the support for and preferred version of REDUX will be identified in patients, HCPs, and policymakers. The necessary conditions in the digital-version REDUX development and implementation will be observed in app developers and cyber-security officers.

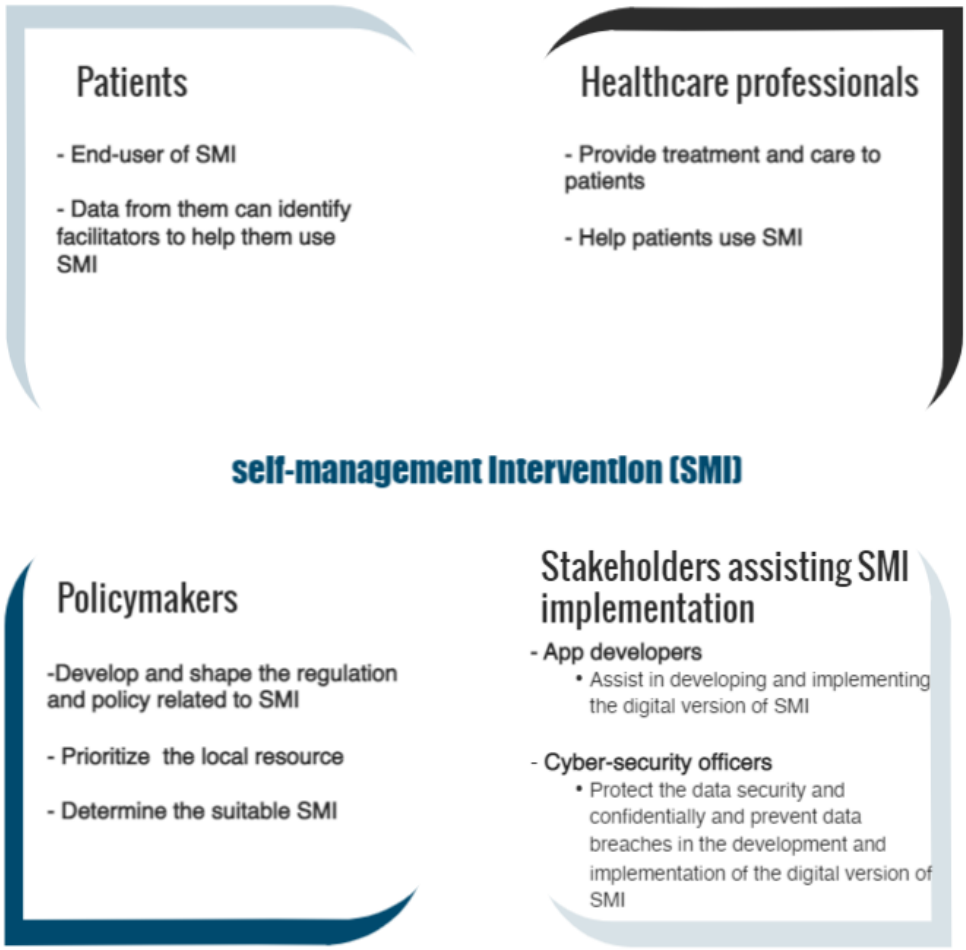

Figure 2. The roles of different stakeholders in the self-management intervention implementation

Integrate SMI into the Chinese context

Lastly, it is necessary to integrate REDUX into the Chinese context and evaluate the effectiveness of REDUX in people with CLD. Identifying such information can help identify the potential of REDUX in exacerbation management. Also, it is recommended that the preconditions, e.g., acceptability, appropriateness, and feasibility, should be measured in the pre-implementation phase to determine the intervention uptake [90]. Most studies targeting SMI implementation have examined the effectiveness of the SMI [91-95], but few address the (partly) preconditional measurement indicators [95,96]. For example, a study protocol focusing on COPD only evaluated the feasibility and acceptability of SMI for patients [96]. Yet, it is still being determined whether the intervention is effective or appropriate for patients. A comprehensive evaluation of the effectiveness and preconditions is essential to determine the desired service delivery and clinical outcomes [90].

This thesis aims to conduct a study to examine these measurements and evaluate their effectiveness and preconditions. Such evaluation can provide preliminary insights into the uptake of such interventions, which will help optimize sustainable use in the future.

The planned study is designed on a small scale, i.e., pilot study design. Pilot studies refer to so-called feasibility studies, which are "small scale version(s), or trial run(s), done in preparation for the major study" [97]. This thesis describes the study with a pilot design that can help optimize resource use and provide insights for a full-scale study [98]. Subsequently, full-scale REDUX implementation in China can inform future research on tailoring SMIs in different contexts.

Therefore, this thesis will set up a study to evaluate the effectiveness and preconditions of REDUX in China with a pilot study design.

Aim and research objective

This thesis aims to (a) provide fundamental insight into the disease burden for Chinese people with chronic diseases and (b) reduce the disease burden with SMI through a tailored, context-sensitive SMI. Specifically, the disease burden in Chinese people with chronic disease is assessed by identifying the prevalence of frailty and risk factors in Chinese people with hypertension (**Chapter 2**). Then, a systematic review and meta-analysis is conducted to get an up-to-date and comprehensive overview of the effect of SMI on people with CLD (**Chapter 3**). A four-step process is employed to tailor SMI addressing CLD, which can help reduce the disease burden in China. First, a mixed-method study identifies the local context in Chinese HCPs and people with CLD in Chinese primary and secondary care (**Chapter 4**). Next, we identify factors influencing the REDUX implementation in China with a stakeholder analysis (**Chapter 5**). This chapter evaluates the level of support for and the preferred version of REDUX with the qualitative approach in patients, HCPs, and policymakers. The factors influencing the digital version of REDUX development are assessed with the quantitative approach of app developers and cyber-security officers. The knowledge gained about tailoring SMI will allow us to tailor REDUX to the Chinese context. The study design on the effectiveness and preconditions of culturally tailored REDUX for people with CLD in China is described in **Chapter 6**.

In the end, in **Chapter 7**, the main findings from other chapters are summarized and discussed. Furthermore, the thesis' limitations and implications are presented.

Chapter 2

Associations between obesity and multidimensional frailty in older Chinese people with hypertension

Song XY, Zhang WH, Hallensleben C, Versluis A, van der Kleij R, Jiang ZL, Chavannes NH, and Gobbens R JJ, "Associations between obesity and multidimensional frailty in older Chinese people with hypertension," Clinical Intervention in Aging, vol. 15, pp. 811-820, 2020.
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Abstract:

Background

There is a high prevalence of hypertension. Frailty and obesity were the risk factors for hypertension.

Objectives

To investigate the prevalence of multidimensional frailty in older people with hypertension and to examine a possible relationship of general obesity and abdominal obesity to frailty in older people with hypertension.

Methods

A sample of 995 community-dwelling older people with hypertension, aged 65 years and older and living in Zhengzhou (China), completed the Tilburg Frailty Indicator (TFI), a validated self-report questionnaire for assessing multidimensional frailty. In addition, socio-demographic and lifestyle characteristics were assessed by self-report, and obesity was determined by measuring waist circumference and calculating the body mass index.

Results

The prevalence of multidimensional frailty in this older population with hypertension was 46.5%. Using multiple linear regression analysis, body mass index was significantly associated with physical frailty ($p = .001$), and waist circumference was significantly positively associated with multidimensional frailty and all three frailty domains. Older age was positively associated with multidimensional frailty, physical frailty, and psychological frailty, while gender (woman) was positively associated with multidimensional, psychological, and social frailty. Furthermore, comorbid diseases and being without a partner were positively associated with multidimensional, physical, psychological, and social frailty. Of the lifestyle characteristics, drinking alcohol was positively associated with frailty domains.

Conclusions

Multidimensional frailty was highly prevalent among Chinese community-dwelling older people with hypertension. Abdominal obesity could be a concern in physical frailty, psychological frailty, and social frailty, while general obesity was concerning about physical frailty.

Introduction

Evidence suggests that frailty becomes more prevalent with increasing age and decreasing well-being in the older population [99,100]. Frail older people show declines in physiological reserves and function across multiorgan systems, leading to increased morbidity and mortality [101]. Currently, there is no unified definition of frailty [102-104], as some researchers define frailty based on biomedical indicators [102,103], while others define frailty more broadly [104,105]. In the broader definition of frailty, besides physical frailty, aspects of both the psychological and social domains are included in frailty and collectively this model is referred to as 'multidimensional frailty'[106].

In this study, we adopted the definition of multidimensional frailty outlined by Gobbens et al: "Frailty is a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes" [104]. Chronic disease is an important determinant of multidimensional frailty, and hypertension is one of the most common chronic diseases among those aged 65 years and older. Hypertension is not only the main risk factor for cardiovascular diseases, but is also associated with multidimensional frailty [107-109]. Multidimensional frailty is closely associated with a risk of falling and a lower quality of life [110,111]. Greater awareness of the relationship between hypertension and frailty may help reduce adverse outcomes and decrease the prevalence of frailty [102,103].

There has been a steady increase in the prevalence of obesity in older populations, and its negative impact on everyday life increases significantly with age [112,113]. The prevalence of obesity in older populations is a growing concern, because as fat mass increases and muscle mass decreases, in addition to age-related declines in basal metabolic rate, muscle strength and physical activity [114]. Obesity is also associated with other diseases, including diabetes mellitus, hypertension, coronary artery disease, and chronic heart failure [115]. Commonly used measures of obesity include body mass index (BMI) and waist circumference (WC). The former is more closely related to general obesity and body weight, while the latter may more accurately reflect abdominal obesity and is more closely associated with metabolic disorders. There is evidence that obesity, especially in older people, increases the risk of physical inactivity and poor functional performance [116,117]. Several earlier studies examined a possible association between obesity and physical frailty [118-120]. Crow et al. reported that in older adults, frailty was associated with a greater likelihood of high WC (both in dichotomized and continuous measurements) [118]. In addition, obesity is associated with the risk of frailty and frailty syndrome in older women [119,120]. In other studies, obesity was found to be a predictive factor for physical frailty [121,122].

However, studies on a possible link between obesity, fat distribution, and multidimensional

frailty are scarce, and few studies have focused on the relationship between obesity and multidimensional frailty in older people with hypertension.

Obesity has also been associated with psychological problems, e.g., depression and anxiety, although the direction of the association has not yet been established [123,124]. Moreover, obesity, and especially abdominal obesity, has a measurable impact on physical and mental health, health-related quality of life, and generates considerable direct and indirect costs [125]. Therefore, it is reasonable to hypothesize that obesity and multidimensional frailty may be linked.

In this study, our aims were (1) to investigate the prevalence of multidimensional frailty in community-dwelling older people with hypertension, and (2) to explore the relationship of general and abdominal obesity to multidimensional frailty in this specific population.

Methods

Subjects

Between May 2016 and May 2017, a cross-sectional survey was performed in the community of Zhengzhou (China), which included community-dwelling older people ≥65 years old diagnosed with hypertension by a physician (physician diagnosis reported by the participants). Hypertension is defined by a systolic pressure of ≥ 140 or diastolic pressure of ≥ 90. Individuals were excluded if they had an active malignancy, dementia or psychiatric disorders. A random multi-stage cluster sampling method was used to select participants aged 65 and older from the Hangdong, Nanguan, and Qinling communities. In the first stage, the three communities (Hangdong, Nanguan and Qinling) in Zhengzhou were selected, including one in the east, one in the south, and one in the center of the city. The second stage involved the systematic random sampling of community centers from the three chosen communities, 20 in total. During the third stage, a list of residents by age and number of hypertension cases was compiled for each selected site (provided by the local residential committee), and a total of 1200 older people with hypertension were selected, of whom 995 completed the questionnaire. The response rate was 83%.

Ethics

This study was approved by the Institutional Review Board of Zhengzhou University. All information was collected after written consent was obtained from all participants.

Frailty

Frailty was assessed by the Tilburg Frailty Indicator (TFI), a self-report questionnaire [104]. The TFI is divided into three domains: a physical domain, a psychological domain, and a social domain. Physical frailty includes eight components: physical health, unexplained weight loss, difficulty in walking, lack of strength in hands, physical tiredness, difficulty in maintaining balance, poor hearing and poor vision. Psychological frailty consists of four components: cognition, depressive symptoms, anxiety, and

coping. Social frailty includes three components: living alone, lack of social relations, and lack of social support. Eleven items in the TFI have two response categories ("yes" or "no"), while the remaining items (cognition, depressive symptoms, anxiety, lack of social relations) have three response categories ("yes", "no", or "sometimes"); these items were dichotomized. For a detailed description on scoring the TFI, including the dichotomization, we refer to a previous study [106]. Each item was scored with 0 or 1, with a maximum score for overall frailty of 15. For the physical, psychological, and social frailty domains, the maximum scores were 8, 4, and 3, respectively. Total scores greater than or equal to 5 indicate frailty. The physical frailty cutoff is 3, which means people who score 3 in that domain are physically frail [106]. We used the Chinese version of the TFI, which was recently validated in community-dwelling older people [126]. In the present study, the internal consistency and reliability of the Chinese version was acceptable (Cronbach's α=0.747).

Lifestyle characteristics, Body Mass Index and Waist Circumference

The included lifestyle characteristics were smoking (Do you smoke? ("yes" or "no")), drinking alcohol (Do you drink? ("yes" or "no")), physical activity (How often do you take exercise? (always = more than 4 times a week; sometimes = 2- 4 times a week; hardly ever = 0 -1 times a week)), and breakfast (Do you have breakfast every day? ("yes" or "no")). In addition, body mass index (BMI) and waist circumference (WC) were assessed. Weight, height, and WC were measured in each subject. These measurements were carried out by trained nursing postgraduates using electronic scales (model SH-10XD) and flexible, inelastic belt-type tapes, respectively. Measurements were taken twice. Mean values of the two measurements were used for the analyses. BMI was calculated as the weight in kg divided by the square of the height in meters. Subjects were initially categorized into four BMI groups according to the World Health Organization guideline for Asians: underweight (<18.5 kg/m^2), normal weight (from 18.5 to 22.9 kg/m^2), overweight (from 23 to 24.9 kg/m^2), and general obesity (over 25 kg/m^2) [127]. Abdominal obesity was defined as a WC ≥ 90 cm in men and ≥ 80 cm in women [128,129].

Socio-demographic characteristics and disease

The socio-demographic characteristics measured were: age, gender, marital status (two categories: married/with partner or other (unmarried, divorced, or widowed)), educational level (five categories: no schooling, primary school, middle school, high school, or university), and monthly income (yuan) (four categories: <1000; 1000~1999; 2000~2999; 3000~). Five categories of disease, including four chronic diseases common in the Chinese population, were assessed using self-report: cardiovascular disease, cancer, chronic respiratory diseases, diabetes, or other diseases.[130] The total number of chronic diseases was used in our analyses.

Data analysis

Descriptive statistics were used to determine the characteristics of participants (N = 995). The data are presented as the mean ± SD and frequencies (percentages). Because the underweight group was small

(n = 5), this group is only included in the descriptive statistics and a single analysis (see below). Bivariate analyses were conducted to determine the associations between demographic characteristics, lifestyle characteristics, comorbid diseases, BMI, WC, multidimensional frailty, and three frailty domains (physical, psychological, social). The Chi-square test was used to compare the prevalence of frailty for categorical variables. One-way ANOVA analyses were selected to compare the detailed frailty scores (physical frailty, psychological frailty and social frailty) in categorical groups. We then carried out multiple linear regression analyses with the goal of determining the individual effects of BMI and WC on multidimensional frailty and its three domains, adjusted for other variables in the model (socio-demographic characteristics, lifestyle characteristics). All statistical analyses were performed with SPSS 20.0 (SPSS Inc., Chicago, IL, U.S.A.). The statistical significance level was set at $p < .05$.

Results

Participant characteristics

The characteristics of participants by BMI and WC category are shown in **Table 1**. A total of 995 subjects were recruited, 47.7% men and 52.3% were women. Mean age was 75.1 (± 7.38) and 82.0% were married or with partners. General obesity was found in 99 participants (9.9%) and 492 participants (49.4%) had abdominal obesity. The prevalence of multidimensional frailty and physical frailty was 46.5% and 45.1%, respectively. **Table 1** also presents the demographic and lifestyle characteristics based on the BMI and WC of the participants.

Table 1 Characteristics of participants by categories of BMI and WC (N=995)

Variables	BMI *n* (%)				WC (cm) *n* (%)	
	Under-weight 5 (0.5)	Normal 524 (52.7)	Overweight 367 (36.9)	Obese 99 (9.9)	<90 (M) <80 (W) 492(49.4)	≥90 (M) ≥80 (W) 503 (50.6)
Socio-demographic characteristics						
Age						
65-74	1 (20)	304 (58)	159 (43)	47 (48)	246 (50)	265 (54)
75-84	2 (40)	178 (34)	142 (39)	34 (34)	172 (34)	184 (37)
≥85	2 (40)	42 (8)	66 (18)	18 (18)	85 (16)	43 (9)
Gender						
Men	4 (80)	299 (57)	130 (35)	39 (40)	232 (46)	240 (49)
Women	1 (20)	225 (43)	237 (65)	60 (61)	271 (54)	252 (51)
Marital status						

Married/with partner	4 (80)	465 (88)	279 (76)	72 (73)	394 (78)	422 (86)
Others	1 (20)	65 (12)	88 (24)	27 (27)	109 (22)	70 (14)
Monthly income (yuan)						
<1000	1 (20)	90 (17)	61 (17)	17 (17)	113 (23)	55 (11)
1000-1999	1 (20)	219 (41)	130 (35)	49 (50)	195 (39)	133 (27)
2000- 2999	3 (60)	106 (20)	125(34)	29 (29)	137 (27)	160 (32)
≥3000	0 (0)	114 (22)	51 (14)	4 (4)	58 (11)	144 (29)
Educational						
No schooling	0 (0)	15 (3)	61 (17)	32 (32)	77 (15)	31 (6)
Primary school	2 (40)	34 (7)	138 (38)	45 (46)	133 (27)	86 (18)
Middle school	1 (20)	225 (42)	155 (42)	20 (20)	203 (40)	198 (40)
High school	2 (40)	166 (32)	9 (2)	0 (0)	66 (13)	111 (23)
University	0 (0)	84 (16)	4 (1)	2 (2)	24 (5)	66 (13)
Comorbid						
0	2 (40)	117 (22)	78 (21)	31 (31)	141(28)	87 (18)
1	2 (40)	141 (27)	110 (30)	18 (18)	146 (29)	125 (25)
≥2	1 (20)	266 (51)	179 (49)	50 (51)	216 (43)	280 (57)
Lifestyle characteristics						
Smoking						
Yes	4 (80)	178(34)	120 (33)	27 (27)	183 (36)	143 (29)
No	1 (20)	346 (66)	247 (67)	72 (73)	320 (64)	349 (71)
Drinking alcohol						
Yes	1 (20)	142(27)	126 (34)	49 (49)	185 (37)	133 (27)
No	4 (80)	382 (73)	241 (66)	50 (51)	318 (63)	359 (73)
Physical activity						
Always	4 (80)	251 (48)	182 (50)	47 (48)	211 (42)	273 (55)
Sometimes	1 (20)	148 (28)	111 (30)	35 (35)	198 (39)	97 (20)
Hardly ever	0 (0)	125 (24)	74 (20)	17 (17)	94 (19)	122 (25)
Breakfast						
Yes	5 (100)	508 (97)	359 (98)	96 (97)	478 (95)	490 (99.6)
No	0 (0)	16 (3)	8 (2)	3 (3)	25 (5)	2 (0.4)
Multidimensional frailty						
Yes	1 (20)	189 (36)	211 (58)	59 (60)	302 (60)	161 (33)
No	4 (80)	335 (64)	156 (42)	40 (40)	201 (40)	331 (67)
Physical frailty						
Yes	3 (60)	106 (20)	120 (33)	38 (38)	173 (34)	94 (19)
No	2 (40)	418 (80)	247 (67)	61 (62)	330 (66)	398 (81)

BMI = Body Mass Index; WC = Waist Circumference.

Associations between BMI, WC, and frailty

Table 2 presents the associations between socio-demographic characteristics, disease, lifestyle characteristics, BMI, WC and frailty. In terms of BMI category, subjects in the general obesity group had higher multidimensional frailty scores than subjects in the overweight group and the

underweight/normal group (5.82 ± 3.55 vs. 5.38 ± 3.31 vs. 4.05 ± 3.17, p < .001). Regarding categories of WC, obese subjects (men with WC > 94 cm, and women with WC > 80 cm) had higher frailty scores than other subjects (5.67 ± 3.49 vs. 3.74 ± 2.86, p < .001).

Table 2. Associations between socio-demographic characteristics, diseases, lifestyle characteristics, BMI, WC and frailty (N=990)

Variable	Physical frailty		Psychological frailty		Social frailty	
	(*m*,*SD*)	*p*	(*m*,*SD*)	*p*	(*m*,*SD*)	*p*
Socio-demographic Characteristics						
Age		<0.001		0.001		<0.001
65~74	1.74±1.82		1.07±1.18		0.93±0.86	
75~84	2.63±2.07		1.54±1.24		0.97±0.80	
≥85	3.81±1.88		2.06±1.10		1.50±0.90	
Gender		0.025		0.002		<0.001
Men	2.12±2.02		1.19±1.18		0.84±0.81	
Women	2.50±2.05		1.52±1.28		1.18±0.88	
Marital status		<0.001		<0.001		<0.001
Married/with	2.11±1.97		1.21±1.22		0.79±0.68	
Others	3.28±2.10		2.04±1.12		2.06±0.84	
Monthly income in yuan		<0.001		<0.001		<0.001
<1000	2.92±2.12		1.59±1.28		1.40±0.88	
1000~1999	2.65±2.12		1.49±1.29		1.11±0.90	
2000~2999	1.90±1.84		1.24±1.19		0.88±0.73	
≥3000	1.89±1.91		1.14±1.16		0.75±0.86	
Educational level		<0.001		<0.001		<0.001
No schooling	3.40±2.06		2.09±1.20		1.69±1.01	
Primary school	2.64±2.02		1.39±1.20		1.02±0.87	
Middle school	2.06±1.96		1.26±1.21		0.98±0.79	
High school	2.06±2.09		1.27±1.27		0.88±0.84	
University	1.90±1.84		1.04±1.18		0.90±0.84	
Comorbid diseases		<0.001		<0.001		<0.001
0	1.71±1.81		1.02±1.11		0.80±0.75	
1	2.43±2.01		1.56±1.31		1.08±0.89	
≥2	3.54±2.02		1.89±1.22		1.43±0.90	
Lifestyle characteristics						
Smoking		0.538		0.013		0.376
Yes	2.32±2.03		1.43±1.28		1.05±0.88	
No	2.30±2.09		1.22±1.16		0.95±0.83	
Drinking alcohol		0.414		0.678		0.086

Yes	2.21±2.02		1.34±1.25		0.98±0.84	
No	2.55±2.08		1.41±1.23		1.09±0.91	
Physical activity		0.001		<0.001		<0.001
Always	2.13±1.92		1.24±1.21		0.96±0.83	
Sometimes	2.81±2.20		1.73±1.24		1.21±0.90	
Hardly ever	2.08±1.99		1.14±1.22		0.89±0.85	
Breakfast		0.002		0.151		<0.001
Yes	2.29±2.02		1.34±1.24		1.00±0.86	
No	3.30±2.61		1.96±1.34		1.70±0.91	
BMI (kg/m^2)		<0.001		0.002		<0.001
Normal	1.93±1.90		1.23±1.20		0.85±0.80	
Overweight	2.70±2.08		1.51±1.25		1.18±0.89	
Obese	2.97±2.24		1.53±1.37		1.32±0.92	
WC (cm)		<0.001		<0.001		<0.001
>90 men >80 women	2.75±2.11		1.64±1.29		1.25±0.92	
≤90 men ≤80 women	1.87±1.88		1.07±1.12		0.78±0.73	

BMI = Body Mass Index; WC = Waist Circumference

Table 2. Associations between socio-demographic characteristics, diseases, lifestyle characteristics, BMI, WC and frailty (N=990) (continued)

Variable	Multidimensional frailty	
(*m*,*SD*)		*p*
Socio-demographic Characteristics		
Age		<0.001
65~74	3.73±3.05	
75~84	5.14±3.26	
≥85	7.37±2.91	
Gender		<0.001
Men	4.14±3.22	
Women	5.20±3.36	
Marital status		<0.001
Married/with partner	4.11±3.08	
Others	7.38±3.12	
Monthly income in yuan		<0.001
<1000	5.90±3.33	
1000~1999	5.26±3.42	
2000~2999	4.03±2.98	
≥3000	3.78±3.22	
Educational level		<0.001

No schooling	6.99±3.34	
Primary school	5.06±3.13	
Middle school	4.30±3.11	
High school	4.20±3.54	
University	3.84±3.12	
Comorbid diseases		<0.001
0	3.53±2.82	
1	5.07±3.32	
≥2	6.86±3.24	
Lifestyle characteristics		
Smoking		0.147
Yes	4.81±3.35	
No	4.48±3.30	
Drinking alcohol		0.008
Yes	4.53±3.26	
No	5.05±3.46	
Physical activity		<0.001
Always	4.32±3.00	
Sometimes	5.74±3.59	
Hardly ever	4.11±3.36	
Breakfast		0.011
Yes	4.63±3.30	
No	6.96±4.02	
BMI (kg/m^2)		<0.001
Normal	4.01±3.15	
Overweight	5.38±3.31	
Obese	5.82±3.56	
WC (cm)		<0.001
>90 men >80 women	5.65±3.49	
≤90 men ≤80 women	3.73±2.86	

BMI = Body Mass Index; WC = Waist Circumference

Regression analyses

Multiple linear regression analyses revealed that general obesity was only significantly positively associated with physical frailty (p = .018), adjusted for all socio-demographic and lifestyle characteristics in the model. Abdominal obesity was significantly positively associated with all four frailty variables (for multidimensional frailty, p < .001, for physical frailty, p = .001, for psychological frailty, p < .001, social frailty, p < .001), adjusted for all variables in the model (see **Table 3**).

The regression analyses also showed that older age was significantly positively associated with multidimensional frailty, physical frailty, and psychological frailty, while gender (women) was positively associated with multidimensional, psychological and social frailty. High monthly income

was negatively associated with social frailty. Comorbid diseases and an unmarried or without partner status were significantly positively associated with all frailty domains.

It is worth noting that among the lifestyle characteristics, drinking alcohol and eating breakfast were the only domains that significantly associated with three or two frailty variables, respectively. The R^2 values demonstrated that the variables in the model together explained a significant portion of the variance of multidimensional frailty (physical frailty, psychological frailty, and social frailty) (see **Table 3**).

Table 3. Effects of the socio-demographic and lifestyle characteristics on frailty: multiple linear regression analyses (N=990)

	Physical frailty			Psychological frailty			Social frailty		
	B	*SE*	*p*	*B*	*SE*	*P*	*B*	*SE*	*p*
Socio- demographic characteristics									
Age	0.090	0.008	<.001	0.039	0.005	<.001	0.004	0.003	.213
Gender	0.332	0.159	0.037	0.221	0.101	.029	0.269	0.062	<.001
Marital status	0.395	0.151	.009	0.468	0.096	<.001	1.034	0.059	<.001
Monthly income	-0.118	0.109	.275	0.016	0.069	.818	-0.138	0.042	.001
Education level	0.103	0.082	.206	-0.044	0.052	.397	0.061	0.032	.056
Co-morbid diseases	0.808	0.070	<.001	0.358	0.045	<.001	0.211	0.027	<.001
Lifestyle characteristics									
Smoking	0.197	0.159	.215	-0.089	0.101	.380	0.043	0.062	.488
Drinking alcohol	0.396	0.148	.008	0.234	0.094	.013	0.125	0.057	.030
Physical activity	0.064	0.070	.360	0.006	0.044	.898	0.004	0.027	.870
Breakfast	0.595	0.346	.086	0.349	0.220	.113	0.448	0.134	.001
Obesity									
General obesity	0.298	0.126	.018	0.053	0.082	.521	-0.018	0.050	.719
Abdominal obesity	0.398	0.118	.001	0.356	0.075	<.001	0.244	0.046	<.001
Constant	-7.622	0.888	<.001	-3.863	0.565	<.001	-1.796	0.336	<.001
R^2	0.297		<.001	0.228		<.001	0.437		<.001
Adjusted R^2	0.289		<.001	0.218		<.001	0.430		<.001

Table 3. Effects of the socio-demographic and lifestyle characteristics on frailty: multiple linear regression analyses (N=990) (continued)

	Multidimensional frailty		
	B	*SE*	*p*
Socio-demographic characteristics			
Age	0.132	0.012	<.001
Gender	0.486	0.179	.007
Marital status	5.837	1.502	<.001
Monthly income	-0.334	0.162	.040
Education level	0.174	0.122	.154
Co-morbid diseases	1.400	0.105	<.001
Lifestyle characteristics			
Smoking	-0.251	0.206	.223
Drinking alcohol	0.502	0.207	.016
Physical activity	0.105	0.104	.313
Breakfast	1.230	0.517	.018
Obesity			
General obesity	0.201	0.192	.296
Abdominal obesity	1.051	0.177	<.001
Constant	-15.010	1.957	<.001
R^2	0.409		<.001
Adjusted R^2	0.401		<.001

Discussion

Of the participants in our study, almost half (46.5%) showed multidimensional frailty. This outcome is higher than that reported by Dong et al.[131] (13.1%), a similar study but conducted in Jinan, a socioeconomically developed city in Eastern China, whereas our study in Zhengzhou, a still-developing city in central China, included older people with a lower educational level and lower monthly income compared to Jinan. Previous studies have shown that both of these important socioeconomic factors are associated with higher multidimensional frailty scores [132,133]. In our study, 45.1% of the participants experienced physical frailty, a prevalence figure much higher than that found in earlier studies conducted in China (12.4%) [131,132]. One possible explanation for the difference in findings was that our participants were older people (≥65 years old) with hypertension, while the participants in the other studies were below 65 years of age and with or without chronic diseases. Furthermore, the prevalence figures for physical frailty (45.1%) and multidimensional frailty (46.5%) were very similar and in line with our previous study in the Netherlands.[106]

Our results indicate that both general obesity and abdominal obesity are positively associated with physical frailty, a finding consistent with a previous report by Garcia-Esquinas et al.[134] The concordance with this earlier study may be due to the use of the phenotype of frailty, which measures physical frailty [135]. This phenotype consists of five domains, including weakness, slow walking speed, unintentional weight loss, exhaustion, and low physical activity; four of these criteria are also included in the TFI. However, a recent study suggested that the phenotype of frailty should be re-calibrated for people who are overweight and obese [136]. According to Boutin and colleagues, overweight and obesity reduce the risk of adverse outcomes in community-dwelling older women (death, fall risk, hip fracture). By contrast, a systematic review reported a positive relationship between BMI and physical frailty [137]. Thus, further studies of the association between general obesity or abdominal obesity and physical frailty are clearly needed.

We found that obesity was positively associated with physical frailty in older people with hypertension, a finding supported by a previous study [138]. Physical frailty is closely and negatively associated with medication adherence and treatment adherence in older people with hypertension [109,139,140]. Poor medication adherence and treatment adherence cause adverse outcomes such as hospitalization and disability. In turn, these adverse outcomes increase the prevalence of physical frailty. Second, in this study multidimensional frailty coexisted with hypertension in 46.5% of patients. Older people with hypertension who are either generally obese or abdominally obese have less muscle mass due to fat infiltration of the muscle and obesity-associated inactivity [141]. Older people with hypertension who are abdominally obese also have a high level of insulin resistance, which may in turn increase the risk of frailty [142]. Additionally, the ratio of fat mass to muscle mass or the amount of

visceral versus peripheral fat may be strongly associated with frailty. Our study also demonstrated that abdominal obesity was associated with psychological frailty and social frailty. To the best of our knowledge, this is the first study to investigate the association between obesity and multidimensional frailty, so the results could not be compared with previous studies regarding psychological and social frailty. However, associations between individual components of psychological or social frailty and obesity were investigated in earlier studies. One five-year observational study showed that general obesity at baseline was associated with an increased risk of depression five years later [143]. Another study showed that people who were obese had a higher risk of depression and anxiety. Depression and anxiety are closely associated with psychological frailty and social frailty [142]. Besides the emerging evidence on obesity and frailty, the distinction between the association between abdominal obesity and frailty and the association between general obesity and frailty has been largely unexplored.

In addition to the findings discussed above, a higher multidimensional frailty risk was found in the alcohol abstention group compared to the alcohol consuming group. Similarly, a recent longitudinal study in older people reported a lower incidence of functional limitations associated with alcohol intake versus abstention [144]. In addition, light-to-moderate alcohol consumption is reportedly protective against all-cause mortality and cardiovascular diseases [145]. The present study also showed that older people who do not eat breakfast tend to be multidimensional frail. One explanation could be that people without an appetite for breakfast have less motivation in terms of functional exercise and social interaction [146]. More detailed explanations should be explored in future studies. Our analyses also showed that the socio-demographic characteristics older age, gender (women), unmarried or without a partner, and high monthly income were associated with at least two of the four frailty variables. That unmarried or without a partner is associated with both multidimensional and social frailty is not surprising, because the TFI used for measuring multidimensional frailty includes living alone as a component of social frailty.

Some limitations of our study should be noted. First, most data were obtained by self-report, and recall errors may have resulted in some incorrect answers. Second, our data included possible confounders (e.g., regions, occupations), and we weren't able to rule out all possible confounding factors. This means that there may be some unavoidable selection bias in our study. Future large-scale studies should expand classifications to reduce this limitation. Third, we only included individuals with hypertension, which limits the generalizability of our findings. Finally, the cross-sectional design of this study does not allow strict cause-effect interpretations of the associations between obesity and multidimensional frailty.

Conclusion

Age-related multidimensional frailty is a daily reality for community-dwelling older people with hypertension. This study showed that abdominal obesity (thus a larger WC) is closely associated with increased risk for multidimensional frailty, while general obesity (a higher BMI) is associated with physical frailty in older people with hypertension. A better understanding of the associations between obesity and multidimensional frailty may help improve the health and quality of life of older people living with hypertension.

Chapter 3

The effect of blended self-management interventions on disease burden in chronic obstructive pulmonary disease and asthma patients: A systematic review and meta-analysis

Song XY, Hallensleben C, Zhang WH, Jiang ZL, Shen HX, Gobbens JJ R, Van der Kleij R, Chavannes NH, and Versluis A, "Blended self-management interventions to reduce disease burden in patients with chronic obstructive pulmonary disease and asthma: systematic review and meta-analysis," Journal of Medical Internet Research, vol. 23, no. 3, Mar, 2021. doi: 10.2196/24602.

Abstract

Background

There is a high prevalence of and high disease burden in Chronic Obstructive Pulmonary Disease (COPD) and asthma. Blended self-management interventions, which combine eHealth with face-to-face interventions, could help to reduce the disease burden.

Objectives

This systematic review and meta-analysis was performed to examine the effectiveness of blended self-management interventions on health-related effectiveness and process outcomes for people with COPD or asthma.

Methods

PubMed, Web of Science, COCHRANE Library, Emcare and Embase were searched in December 2018 and updated in November 2020. Study quality was assessed using the Cochrane risk of bias (ROB)2 and the Grading of Recommendations Assessment, Development, and Evaluation.

Results

Fifteen COPD and seven asthma randomized controlled trials were included. The meta-analysis of COPD studies found that the blended intervention showed a small improvement on exercise capacity (standardized mean difference [SMD] = 0.48, 95% CI: 0.10-0.85), and a significant improvement on the quality of life (QoL) (SMD = 0.81, 95% CI: 0.11-1.51). Blended intervention also reduced the admission rate (Relative Ratio (*RR*) = 0.61, 95% CI: 0.38-0.97). In the COPD systematic review, on the exacerbation frequency, both studies found the intervention reduced exacerbation frequency (*RR* = 0.38, 95% CI: 0.26-0.56). A large effect was found on body mass index (d = 0.81, 95% CI: 0.25-1.34); however, the effect was inconclusive because only one study was included. On medication adherence, two of three studies found a moderate effect (d = 0.73, 95% CI: 0.50-0.96), and one study reported a mixed-effect. On self-management ability, one study reported a large effect (d = 1.15, 95% CI: 0.66-1.62), and no effect was reported in the one study. No effect was found on the other process outcomes. The meta-analysis of asthma studies found that blended intervention had a small improvement on lung function (SMD = 0.40, 95% CI: 0.18-0.62) and QoL (SMD = 0.36, 95% CI: 0.21-0.50), and a moderate improvement on asthma control (SMD = 0.67, 95% CI: 0.40 to 0.93). A large effect was found on body mass index (d = 1.42, 95% CI: 0.28-2.42) and exercise capacity (d = 1.50, 95% CI: 0.35-2.50), yet one study was included per outcome. There was no effect on other outcomes. Furthermore, the majority of twenty-two studies showed some concerns about the risk of bias, and the quality of evidence varied.

Conclusions

In COPD patients, the blended self-management interventions had mixed effects on health-related outcomes, with the strongest evidence found for exercise capacity, QoL and admission rate. Furthermore, the review suggested that the intervention resulted in small effects for lung function and QoL and a moderate effect on asthma control in asthma patients. To conclude, there is some evidence for the effectiveness of blended self-management interventions for COPD and asthma patients; yet more research is needed.

Introduction

Chronic lung diseases are the leading cause of disability and death worldwide [147]. Of all chronic lung diseases, chronic obstructive pulmonary disease (COPD) and asthma are the most prevalent ones [148]. There were approximately 251 million cases of COPD globally in 2015, and COPD is predicted to become the third leading cause of death by 2030 [149]. Around 300 million people have asthma worldwide, with a projected increase of an additional 100 million people by 2025 [149]. The impact of a health problem, measured by financial cost, morbidity and other indicators, is called disease burden. It is often quantified in terms of disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs) [147]. In 2017, the loss of DALYs was the first for COPD and the second for asthma [147]. Additionally, a loss in health-related quality of life (QoL) is seen in many patients (e.g., a decline in health, increased hospital admissions, and high medication costs). The World Health Organization estimates the cost of a QALY for COPD ranges from $6700 to $13400 due to exacerbations and medication. In asthma patients, the annual costs vary from less than $150 to $3000 [150-152]. There is increased awareness that self-management represents a promising strategy to decrease disease burden [150-152]. Self-management could improve patient outcomes and decrease disease burden by supporting the patients to positively adapt their health behaviors and develop skills to manage their diseases [153].

Self-management refers to an individual's ability to manage their symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent to life with a chronic condition [154]. In traditional face-to-face self-management interventions, COPD and asthma patients are equipped with the knowledge and skills to manage their health condition successfully [155]. Previous studies have found these self-management interventions to be effective on disease knowledge and self-efficacy [156,157]. These face-to-face self-management interventions are, however, limited by their accessibility (e.g., lower accessibility for patients who are more distant to the healthcare provider or when the healthcare provider lacks time) [158].

eHealth is an alternative to traditional face-to-face interventions. The most cited definition of eHealth is: "health services and information delivered or enhanced through the Internet and related technologies" [24]. Compared with traditional face-to-face interventions, eHealth interventions can be cost and time saving and offer better accessibility and flexibility [159,160]. Moreover, eHealth interventions can help to optimize the therapeutic process, increase treatment efficiency, and decrease costs by enhancing (online) communication possibilities between healthcare providers and patients [159,160].There have been promising results with eHealth self-management interventions [161]. A meta-analysis has shown that, for COPD patients, eHealth self-management programs (e.g., web-based phone calls, online interventions) led to a significant improvement on the symptoms [161]. However, eHealth interventions typically allow for limited tailoring to patients' needs and lower patient

engagement [162]. There have also been concerns about reliability, security, confidentiality, and lack of education and training [163]. These factors can negatively impact the implementation and effectiveness of these interventions.

The most recent development is the blended intervention. There are different definitions of blended interventions [25,164]. We use the definition by Erbe *et al.* : "Treatment programs that use elements of both face-to-face and internet-based interventions, including both the integrated and the sequential use of both treatment formats." [25]. Blended interventions could retain the positive aspects of face-to-face interventions and eHealth by mitigating their negative aspects. Furthermore, blended intervention could diminish the number of face-to-face contacts needed and provide the support that is available at all times [165]. With eHealth, patients can also monitor their health condition throughout the day and convey their health information to healthcare providers without the time and distance limitation. Patients can also get quick assistance during critical periods of care facilitated by real-time alerts and reminders, which could help patients adhere to their action plan. For COPD and asthma patients, blended interventions can include varied elements [28,29] (e.g., training, education and action plans) with different blended intervention components (e.g., internet-based phone calls and individual face-to-face intervention, web platform combined with individual face-to-face intervention) [22,23]. Some studies have shown that blended self-management interventions are effective in improving QoL for COPD and asthma patients [166,167].

Current reviews suggest that blended interventions could be effective [25,164], but these reviews are limited for several reasons. First, the reviews focus on mental health, not chronic lung diseases [25]. Second, the reviews focus on health-related effectiveness outcomes and not on process outcomes [25,164]. Third, the reviews do not specifically focus on self-management interventions [25,164]. To conclude, a comprehensive overview or meta-analysis of the effect of blended self-management interventions on the disease burden of COPD and asthma patients, including process outcomes and health-related effectiveness outcomes, is missing. Therefore, a systematic review will be performed to assess the effectiveness of blended self-management interventions in COPD and asthma patients. When appropriate, a meta-analysis will be conducted. Internet-based, telephone, and SMS delivered interventions are included because all of these are parts of eHealth [24]. Thus, this study aims to investigate the effectiveness of blended self-management interventions in COPD and asthma patients.

Methods

This review follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [168]. The review was registered in PROSPERO (number 2019: CRD42019119894).

Search strategy

A search strategy was set up in collaboration with a certified librarian to identify relevant studies of blended self-management interventions in COPD and asthma patients. Five electronic databases (i.e., PubMed, Web of Science, COCHRANE Library, Emcare and Embase) were searched on December 28th, 2018 and updated on November 30th, 2020. There were search terms related to four areas: (1) COPD or asthma, (2) eHealth, (3) face-to-face intervention, and (4) blended intervention (see **Multimedia Appendix 1**). The search terms related to COPD or asthma and blended intervention were first combined and resulted in 84 studies. Due to the limited number of studies, the search terms associated with COPD or asthma were combined with terms about eHealth and face-to-face interventions. In every database, the search was limited to peer-reviewed publications. The search strategy was not restricted based on publication year, as we aimed to provide a comprehensive overview of how blended intervention can be used in COPD and asthma patients. Additionally, reference lists of the included studies and previous reviews were searched to identify additional studies that might be eligible for inclusion.

Eligibility criteria

The PICOS (patient, intervention, comparison, outcome, study design) tool was used to develop an effective search strategy and determine the inclusion and exclusion criteria [169]. The following inclusion criteria were used to identify the studies: (1) Participants: adults (≥ 18 years old) with COPD or asthma, (2) Intervention: blended self-management intervention (consisting of an eHealth component combined with a face-to-face component), (3) Comparison: eHealth intervention with or without usual care (UC), face-to-face intervention with or without UC or only UC, (4) Outcome measures: health-related effectiveness or process outcomes, and (5) Individual randomized controlled trials (RCTs). Studies were excluded if: (1) The participants were Children or adolescent, (2) The eHealth applications were only used to collect data, (3) Outcomes were not about the health-related outcomes, and (4) studies were cluster RCTs.

Study selection

After the removal of duplicates, the identified titles and abstracts were screened for eligibility. If insufficient information was described, the full-text paper was screened. When a full-text paper was not available, a request was sent to the authors. Studies that did not meet the inclusion criteria were excluded. Screening the titles, abstracts, and full-texts was performed by two reviewers independently (Song and Jiang). Any disagreements between the two authors were resolved by a third reviewer (Hallensleben).

Data collection & coding

Data collection was performed with a standardized data extraction form. It included: (1) study characteristic (e.g., first author, publication year, country, number and age of patients, percentage of female patients, disease severity/diagnosis, setting (i.e., home, primary or secondary care), intervention and follow-up duration), (2) intervention characteristic (i.e., category and functionality of the eHealth and face-to-face component), (3) behaviour change techniques (BCTs) used in the blended self-management intervention, and (4) the health-related effectiveness and process outcomes. Information was extracted from each publication by Song and Jiang. Inter-rater reliability, as assessed with Cohen's kappa, indicated that there was strong agreement (kappa value of .90) [170].

Classification of COPD severity was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [171]. Patients were considered to have COPD when the ratio between forced expiratory volume in 1s (FEV1) and full forced vital capacity (FVC) is smaller than < 0.70. The degree of obstruction was defined as follows: (1) GOLD I: FEV1 ≥ 80% predicted (mild); (2) GOLD II: 50% ≤ FEV1 < 80% predicted (moderate); (3) GOLD III: 30% ≤ FEV1 < 50% predicted (severe), and (4) GOLD IV: FEV1 < 30% predicted (very severe). There was not a standard classification of severity for asthma patients.

As mentioned above, different intervention characteristics were extracted from the publications. First, the eHealth component of the intervention was categorized as a mobile application (e.g., phone call or SMS), an internet-assisted intervention (e.g., web page, chat room), or multiple component interventions with multiple eHealth technologies. Second, the function of the eHealth application was categorized into informing, instructing, displaying, guiding, reminding/alerts, and communicating (i.e., between provider and patients) [172]. Third, face-to-face interventions were classified as an individual (e.g., home visits, primary/secondary care visits) or as a group-based intervention (e.g., group pulmonary rehabilitation). Fourth, the function of the face-to-face intervention was classified as (1) education: introduction of disease-related information and how to use eHealth; (2) training: provide information about self-management; (3) consultation: discuss individual action plan; (4) assessment: test and assess the patient's performance, or (5) monitoring: provide reminders to improve intervention adherence [173,174].

Outcome indicators were classified into health-related effectiveness outcome or process outcome indicators. Health-related effectiveness outcome indicators included outcomes related to disease status and health condition (i.e., exercise capacity, dyspnea, lung function, QoL, admission, mortality, exacerbation frequency and BMI). Process outcome indicators included intermediate outcomes during the implementation process (e.g., visits, satisfaction, costs, smoking, self-management ability, physical activity, medication and therapy adherence, psychosocial, symptom

management, nutrition and alcohol). A positive effect was ascribed when there was a significant positive effect of the intervention on the outcome measure compared to the control group (CG). When the outcome measure did not significantly differ between the intervention group (IG) and CG, it was rated as 'no effect'. A mixed effect was ascribed when multiple measures were used to measure a similar outcome, and the effect on the measures was in different directions (e.g., in the study by Garcia [29], there was a significant positive effect on inhaler treatment adherence. At the same time, there was no effect on oral treatment adherence).

Quality assessment

Study quality was assessed using the Cochrane risk of bias (RoB)2 [175]. The tool assessed five domains of potential bias including (1) randomization, (2) deviations from the intended interventions (effect of assignment to intervention), (3) missing outcome data, (4) the measurement of the outcome, and (5) the selection of the reported result. Each domain had a few signalling questions. Based on the authors (Song and Jiang)' responses to the signalling questions, a judgment on the risk of bias ('low', 'some concerns' or 'high') for each domain could be made to assess the bias that might confound the study findings [175]. The quality of the clinical evidence was critically appraised using the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE) [176], which evaluated the risk for bias, inconsistency, indirectness, and imprecision for each outcome. Four categories were used to define the quality of evidence: high quality of evidence (the true effect lies close to that of the effect estimate), moderate quality of evidence (the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different), low quality of evidence (the true effect may be substantially different from the effect estimate), very low quality of evidence (the true effect is likely to be substantially different from the effect estimate) [177]. The quality assessment was done by author Song and Jiang, and any disagreements were resolved through discussion. Inter-rater reliability, as assessed with Cohen's kappa [170], indicated that there was strong agreement between raters (kappa value of .80).

Data analysis

When an outcome was assessed using different measurements in one study, data from the most specific disease-related questionnaire was used. For example, in the study by Garcia [29], QoL was measured with both the Saint-George's Respiratory Questionnaire (SGRQ), a specific QoL questionnaire, and Euroqol, a generic health-related QoL questionnaire. SGRQ was selected and analyzed in the meta-analysis because it was the most specific disease-related questionnaire.

First, a systematic review was conducted to present the result. For continuous data, Cohen's d was recommended to calculate the effect size [170,178] (i.e., Cohen's d > .2 = small effect, Cohen's d > .5 = moderate effect, Cohen's d > .8 = large effect). For dichotomous data, Relative Ratio (RR) was

calculated to assess the effect size. An RR greater than 1 indicates a increased likelihood that the stated outcome is achieved in the IG. If the RR is less than 1, there is a decreased likelihood the outcome is achieved in the IG. A ratio of 1 indicated no difference (i.e., the outcome was just as likely to occur in the IG as it is in the CG) [179].

When three or more studies reported on the same outcome measure, this outcome was included in the meta-analysis [180]. For continuous data, the standardized mean difference (SMD) accounted for the same outcomes measured with different assessment tools (e.g., QoL was assessed using SGRQ, COPD assessment test (CAT), and chronic respiratory questionnaire (CRQ)). SMDs were used to standardize the results of the studies to a uniform scale before they could be combined in the quantitative synthesis. SMDs and associated 95% CIs were used to calculate the mean difference and standardized deviation difference between the change in the intervention group and the change in the control group for each study. When the mean or SD was not mentioned, the author was contacted for the missing information. Cohen *d* was used to interpret the data [170,178]. For dichotomous data, RR was calculated to assess the effect size [181]. Publication bias was tested if more than ten studies report on the same outcome measure [181]. $P < .05$ was considered significant for the effect estimate.

A random-effect model was used because the variance of study populations and intervention designs was anticipated as heterogeneity across included studies [182]. The heterogeneity was assessed using chi-square tests and I^2 statistics [183]. A P value of < .1 indicates statistically significant heterogeneity. The I^2 statistic was used to quantify the size of the heterogeneity between studies: 25%, 50%, and 75% can be considered small, medium, and substantial heterogeneity [184]. Outliers were identified using the value of the standardized residual [185]. The study whose standardized residual was equal to or larger than 1.96 were identified as an outlier and were excluded from the meta-analysis. No subgroup analysis was planned due to the limited studies. All analyses were performed using the software packages Review Manager (RevMan version 5.4; The Cochrane Collaboration) and Stata version 14.0 (StataCorp, College Station, USA) [186].

Results

Search Results

The literature search identified a total of 4495 potentially eligible records, and 2657 records remained after duplicates were excluded. After screening the titles and abstracts, an additional 2531 records were excluded for other reasons (see **Figure 1**). The full texts of the remaining 126 studies were assessed, and twenty-two RCTs [28,29,166,167,187-204] were included in this review. Two of twenty-two RCTs were pilot RCT study [187,193], and one was feasibility RCT [190]. These studies were included because they followed the Consolidated Standards of Reporting Trials checklist [187,193], and they were

small sample size RCTs [190,193]. Fifteen RCTs focused on COPD patients [29,166,187-199] and of these studies, eleven were included in the meta-analysis [29,166,187,189,190,192,193,196-199]. The remaining four studies [188,191,194,195] were excluded because no available means and SDs were reported or obtained after contacting the authors. Seven studies focused on asthma patients [28,167,200-204]. Five of seven asthma studies with available data were pooled into meta-analysis [167,200,202-204]. The other two studies were not included in the meta-analysis because of the lack of means and SDs after contacting the authors.

Study Characteristics

The fifteen COPD studies [29,166,187-199] were published between 2006 and 2020, and were conducted were conducted in China (n = 5) [190,196-199], United States (n = 2) [166,193], Denmark (n = 2) [191,194], Canada (n = 1) [195], England (n = 1) [187], Spain (n = 1) [29], Germany (n = 1) [192], Australia (n = 1) [188], and one in both Spain and Belgium [189]. The sample size ranged from 39 to 242 (with a total sample size of 1477). The average age of COPD patients ranged from 64.10 to 73.50 years. Eight of the fifteen COPD studies had UC as a CG [29,166,188,189,191,196,198,199], five had a 'visit' as CG (meaning that the healthcare provider visited the patients' home or patients visited the primary or secondary care) [187,190,193,194,196], and two studies had both UC and/or visits in the CG [192,195]. The setting was home and secondary care (n = 9) [29,166,188,189,195-199], home (n = 2) [187,190] and home and primary care (n = 4) [191-194]. The duration of the blended self-management interventions ranged from 4 to 48 weeks, with a mean of 22.13 weeks (SD = 16.20). Follow-up duration ranged from 17 to 48 weeks.

The seven asthma studies [28,167,200-205] were published from 2003 to 2020, and were conducted in the Netherlands (n = 3) [167,203,204], Germany (n = 1) [201], England (n = 1) [28], United States (n = 1) [202] and China (n = 1) [200]. Study sample size ranged from 16 to 200 (with a total N = 527). The mean age of asthma patients ranged from 24.80 to 52.00 years old. CG included UC (n = 4) [28,167,202,204], visits (n = 3) [200,201,203]. The duration of the blended self-management interventions ranged from 3 to 48 weeks, with a mean of 15.88 weeks (SD = 13.48). Follow-up duration ranged from 36 to 120 weeks. An overview of the study characteristics is shown in **Table 1**.

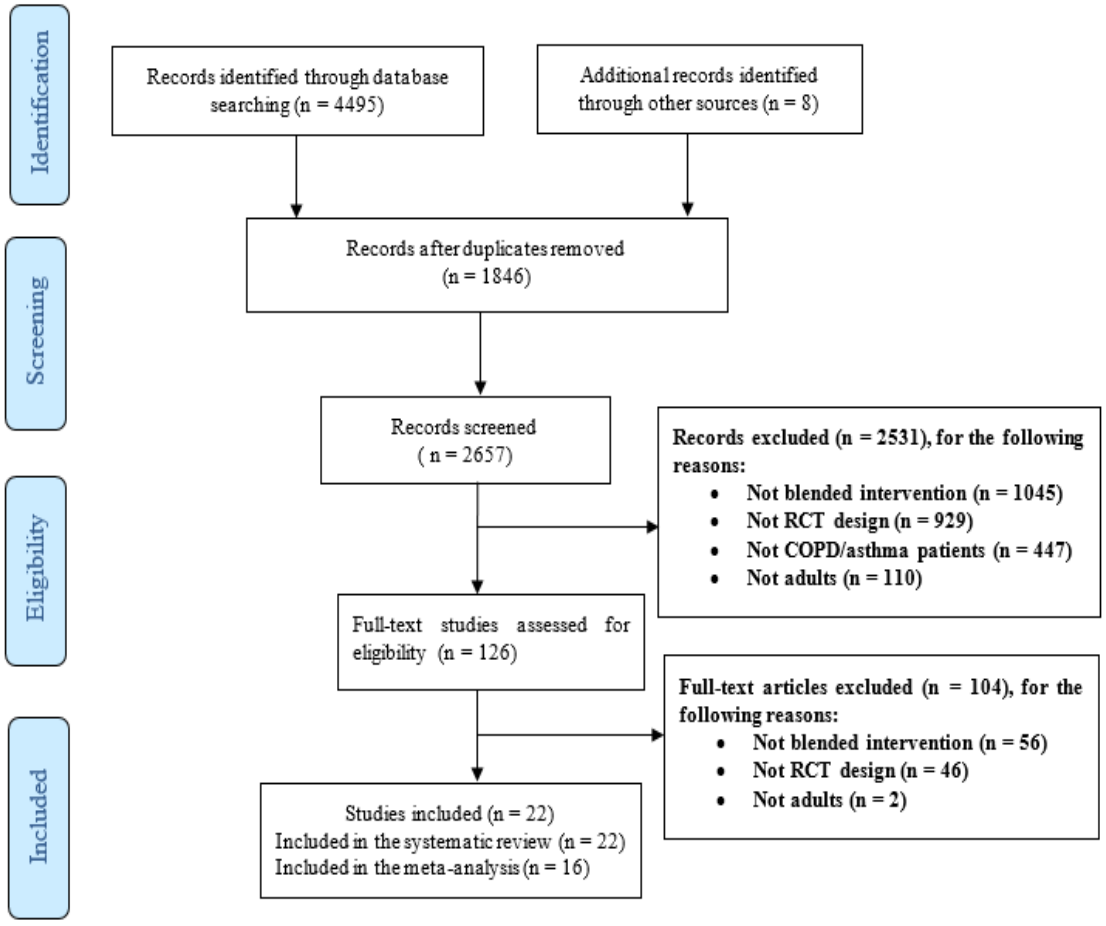


Figure 1. PRISMA flowchart of the systematic review and meta-analysis.

Quality assessment

Methodological quality

The risk of bias was summarised in Table 2. Among the fifteen COPD studies, the risk of bias rated as "some concerns" in ten studies [29,188,189,191,194-199], and as "high" in five studies [166,187,190,192,193]. Besides, two studies had some concerns in randomisation process [190,192], and thirteen studies showed a low risk of bias in the randomisation process [29,166,187-189,191,193-199]. The majority of the studies showed some concerns [29,187-189,191,193-199] while three studies showed high risk from intended intervention [166,190,192]. Low risk of bias due to missing outcome data was found in fourteen studies [29,166,187,188,190-199], while one showed some concerns [189]. The risk of bias in the measurement of the outcome was some concerns in thirteen studies [29,166,187,188,190-193,195-199] and low risk of bias in two studies [189,194]. Low risk of bias in the

selection of the reported result was found in the majority studies [29,166,188-192,194-199], and two had some concerns [187,193].

In asthma studies, the overall risk of bias was some concerns in four studies [28,167,203,204] and high risk in three studies [200-202]. Four studies showed a low risk of bias in the randomization process [28,167,203,204], and three showed some concerns [200-202]. All studies indicated some concerns due to deviations from intended intervention [28,167,200-204]. Six studies showed a low risk of bias outcome data [28,167,201-204], and one had some concerns due to missing outcome data [200]. All studies showed some concerns in the measurement of the outcomes and low risk of bias in the selection of the reported result [28,167,200-204].

Quality of evidence

In COPD studies, there were nineteen different outcome measures included (i.e., exercise capacity, dyspnea, lung function, QoL, admission rate, exacerbation frequency, mortality, BMI, visits, satisfaction, costs, smoking, medication adherence, self-management ability, physical activity, psychosocial, symptom management, nutrition and alcohol). Two outcome measures were rated as high quality of evidence (i.e., exercise capacity and mortality), one measure had a moderate quality of evidence (i.e., admission rate), six had a low quality of evidence (i.e., dyspnea, lung function, QoL, visits, satisfaction and physical activity), and the other ten showed the very low quality of evidence (exacerbation frequency, BMI, adherence, self-management ability, smoking, costs, psychosocial, symptom management, nutrition and alcohol). In asthma studies, there were ten different outcome measures included (i.e., admission rate, BMI, exercise capacity, asthma control, lung function, QoL, asthma knowledge, adherence, visits and exacerbation frequency). Seven of the ten outcomes were rated as very low quality of evidence (i.e., admission rate, BMI, exercise capacity, asthma knowledge, adherence, visits and exacerbation frequency). Asthma control, lung function and QoL were rated as the moderate quality of evidence (see **Multimedia Appendix 2**).

Table 1. Study characteristics of COPD and asthma studies.

Study[a]	Country	N (IG/CG)[b]	Setting[c]	Age mean (SD)[d] (IG/CG)	Gender (% female)[e]	Severity[f]	CG[g]	Intervention/ Follow-up(weeks)
COPD (Included in the meta-analysis)								
Bentley et al. (2014)	England	25/23	Home	67.20 (11.60) 65.90 (9.40)	____	____	Home visits	8/32
Chau et al. (2012)	China	22/18	Home	73.50 (6.10) /72.20 (6.10)	3	II-IV	Home visits	8/____

Casas et al. (2006)	Spain & Belgium	65/90	Home & SC	70.00 (90.00) /72.00 (90.00)	23	I-IV	UC	4/48
Garcia et al. (2007)	Spain	21/41	Home & SC	73.00 (6.00) /74.00 (8.00)	13	____	UC	48/____
Jehn et al. (2013)	Germany	32/30	Home & PC	64.10 (10.90) /69.10 (9.20)	23	II-IV	UC + PC visits	36/____
Koff et al. (2009)	USA	20/20	Home & SC	66.60 (9.10) /65.00 (8.20)	53	III-IV	UC	12/____
Nguyen et al. (2008)	USA	19/20	Home & PC	68.00 (8.30) /70.90 (8.60)	44	____	Home visits	24/____
Wang et al. (2017)	China	55/65	Home & SC	69.30 (7.80) /71.90 (8.10)	53	II-IV	UC	24/48
Wang et al. (2020)	China	39/39	Home & SC	63.20 (7.50)/ 64.40 (7.00)	30	II-IV	SC visits	48/___
Wei etal. (2014)	China	42/45	Home & SC	65.20 (8.10)/ 63.90 (6.20)	33	I-IV	UC	24/48
Xin et al. (2016)	China	114/ 113	Home & SC	64.20(14.20) /64.60 (14.50)	62	____	UC	48/____
COPD (Not included in the meta-analysis)								
Cameron et al. (2016)	Australia	35/30	Home & SC	68.00 (9.90) /70.00 (6.80)	60	I-IV	UC	8/17
Haesum et al. (2017)	Denmark	47/43	Home & PC	70.20 (9.00) 69.50 (10.10)	52	I-IV	UC	4/40
Sorknaes et al. (2013)	Denmark	121/ 121	Home & PC	71.00 (10.00) 72.00 (9.00)	____	I-IV	PC visits	12/26
Stamenova et al. (2020a)	Canada	41/41	Home & SC	71.98 (9.52)/ 71.76 (7.28)	41	II-IV	SC visits	24/____
Stamenova et al. (2020b)	Canada	41/40	Home & SC	71.98 (9.52)/ 72.78 (9.16)	46	II-IV	UC	24/____

Asthma (Included in the meta-analysis)								
Cao et al. (2018)	China	37/30	Home & SC	39.10 (14.30)/ 41.40 (12.00)	78	____	SC visits	12/____
Ostojic et al. (2005)	USA	8/8	Home & PC	24.80 (6.30) 24.50 (7.00)	44	M	UC	16/____
Türk et al. (2020a)	The Netherlands	7/10	SC	41.57(12.54)/ 41.90(8.58)	77	____	SC visits	12/48
Türk et al. (2020b)	The Netherlands	14/10	SC	41.57(9.73)/ 41.90(8.58)	79	____	SC visits	12/48
Van Meer et al. (2009)	The Netherlands	101/ 99	Home & SC	36.00 (19.00; 50.00)/ 37.00 (18.00; 50.00)	70	____	UC	12/36
Van Gaalen et al. (2013)	The Netherlands	47/60	Home & SC	36.00 (8.70)/ 37.00 (8.00)	71	____	UC	48/120
Asthma(Not included in the meta-analysis)								
Barbanel et al. (2003)	England	12/12	Home & SC	45.00 (17.00)/ 47.00 (17.00)	54	____	UC	12/____
Kohler et al. (2020)	Germany	41/41	Home & PC	49.00 (12.00)/ 52.00 (8.00)	37	____	PC visits	3/____

[a] Study by Bentley et al. (2014) and Nguyen et al. (2008) were feasibility RCTs, and study by Chau et al. (2012) was a pilot RCT. There was one study including one intervention group and two control groups. i.e., studies by Stamenova et al.(2020). Study by Türk et al.(2020) included two intervention groups and one control group.
[b] Sample size at post-intervention reported separately for the intervention group (IG) and control group (CG).
[c] The setting was used to conduct the interventions including primary care (PC), secondary care (SC) and home.
[d] Interquartile range was also reported and not the mean/SD (as this information was not reported in the publication).
[e] ____ = not reported in the study.
[f] COPD severity was classified according to GOLD classification. GOLD, Global Initiative for Chronic Obstructive Lung Disease. Asthma severity was classified by the physician diagnosis. M = moderate severity.
[g] UC = usual care

Table 2. Risk of bias judgements for randomized controlled trials

Study	Bias arising from the randomization process [a]	Bias due to deviations from intended intervention	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall
COPD						
Bentley et al. (2014)	L	S	L	S	S	H
Cameron et al. (2016)	L	S	L	S	L	S
Casas et al. (2006)	L	S	S	L	L	S
Chau et al. (2012)	S	H	L	S	L	H
Garcia et al. (2007)	L	S	L	S	L	S
Haesum et al. (2017)	L	S	L	S	L	S
Jehn et al. (2013)	S	H	L	S	L	H
Koff et al. (2009)	L	H	L	S	L	H
Nguyen et al. (2008)	L	S	L	S	S	H
Sorknaes et al. (2013)	L	S	L	L	L	S
Stamenova et al.(2020)	L	S	L	S	L	S
Wang et al. (2017)	L	S	L	S	L	S
Wang et al. (2020)	L	S	L	S	L	S
Wei et al. (2014)	L	S	L	S	L	S
Xin et al. (2016)	L	S	L	S	L	S
Asthma						
Barbanel et al. (2003)	L	S	L	S	L	S
Cao et al. (2018)	S	S	S	S	L	H
Kohler et al. (2020)	S	S	L	S	L	H
Ostojic et al. (2005)	S	S	L	S	L	H
Türk et al. (2020)	L	S	L	S	L	S
Ver der Meer et al. (2009)	L	S	L	S	L	S
Ver Gaalen et al. (2013)	L	S	L	S	L	S

[a] L = Low risk of bias; S = Some concerns; H = High risk of bias

Intervention characteristic

Category of the blended self-management intervention

In COPD studies, five blended self-management intervention combinations were discussed: (1) multiple component eHealth and an individual face-to-face intervention (n = 6) [191-195,199], (2) internet-assisted intervention and an individual face-to-face intervention (n = 5) [29,187,189,190,196], (3) multiple component plus an individual and group face-to-face intervention (n = 1) [191], (4) mobile applications and an individual face-to-face intervention (n = 2) [197,198], and (5) mobile applications and an individual plus group face-to-face intervention (n = 1) [188].

In asthma studies, three blended self-management intervention combinations were discussed: (1) mobile application and the individual face-to-face intervention (n = 3) [28,200,202] and (2) internet-assisted intervention and the group face-to-face intervention (n = 4) [167,201,203,204]. Detailed information on the interventions in the COPD and asthma studies can be found in **Table 3.**

Table 3. Description of the blended self-management interventions in COPD and asthma studies.

Study	eHealth		Face-to-face	
	Category (details)[a]	Functionality	Category (details)[b]	Functionality
COPD (Included in the meta-analysis)				
Bentley et al. (2014)	IA (Telehealth-supported service)	Guide, remind, record	Individual (Home visits)	Training
Chau et al. (2012)	IA (Peripheral devices + mobile phone)	Guide, record, remind, display	Individual (Home visits)	Education, consultation
Garcia et al. (2007)	IA (Web-based call centre)	Guide, remind, record	Individual (SC & home visits)	Assessment, education, consultation
Jehn et al. (2013)	MC (Peripheral devices + mobile)	Display, record, remind	Individual (Outpatient visits)	Training, monitoring
Koff et al. (2009)	MC (Peripheral devices + web platform+ phone call)	Record, display, instruct, guide, remind, communication	Individual (Home visits)	Education, consultation; Training, assessment
Nguyen et al. (2008)	MC (Web modules + PDA)	Guide, remind, record,	Individual (Home & PC	Education, training, assessment

		communication	visits)	
Stamenova et al.(2020)	MC (Peripheral devices + web platform+ phone call)	Display, record, remind, guide, communication	Individual (SC visits)	Assessment, consultation
Wang et al. (2017)	IA (Web platform)	Guide, record, instruct, communication	Individual (SC visit)	Monitoring
Wang et al. (2020)	MA (web-based application)	Guide, communication	Individual (SC visits)	Education
Wei et al. (2014)	MA (Phone call)	Guide, remind, record, communication	Individual (PC visits)	Education, training, assessment
Xin et al. (2016)	MC (Phone call + web platform)	Guide, record, instruct, communication	Individual (SC visits)	Education, training
COPD (Not included in the meta-analysis)				
Cameron et al. (2016)	MA (Phone call)	Guide, communication	Individual + group (Exercise guidance)	Education, consultation
Casas et al. (2006)	IA (web-based application)	Display, record	Individual (SC & home visits)	Assessment, education, consultation
Haesum et al. (2017)	MC (Peripheral devices + web platform)	Guide, record, remind, communication	Individual + group visits	Training, monitoring
Sorknaes et al.(2013)	MC (Peripheral devices + web platform)	Guide, instruct, communication	Individual (PC visits)	Consultation
Asthma (Included in the meta-analysis)				
Cao et al. (2018)	MA (Wechat application)	Guide, remind, communication	Individual (SC visit)	Education
Ostojic et al. (2005)	MA (SMS)	Guide, display, record, communication	Individual (PC visits)	Education
Türk et al. (2020)	IA (Web platform)	Instruct, record, communication	Group (Unclear)	Education, training

Ver der Meer et al. (2009)	IA (Web platform)	Guide, remind, record, communication	Group (Unclear)	Assessment, education
Ver Gaalen et al. (2013)	IA (Web platform)	Guide, remind, communication	Group (Unclear)	Education, consultation
Asthma (Not included in the meta-analysis)				
Barbanel et al. (2003)	MA (Phone call)	Guide, remind, record	Individual (Unclear)	Education
Kohler et al. (2020)	IA (Web platform)	Guide, record, communication	Group (Unclear)	Education, training

[a] eHealth categories (internet-assisted (IA), multiple component (MC), mobile application (MA)) and specific eHealth application were included. [b] Face-to-face categories and specific intervention were included. SC = secondary care, PC = primary care.

BCTs of the blended self-management intervention

In COPD studies, the number of BCTs used in the interventions ranged from three to ten, with a mean of 6.42 (SD = 1.99). "General information", "Provide feedback on performance", "Prompt self-monitoring/ tracking" and "Problem-solving/barrier" were included in fifteen studies [29,166,187-199]. "Action planning" [29,188,189,193-196,198,199] and "Motivational approach" [29,166,188,189,192-194,196,197] were included in nine studies, respectively. "Prompt review of behavioural goals" were included in seven studies [29,188,189,191,193,195,196]. "Goal setting" was used in five studies [29,188,189,193,195,196]. "Social support" was in four studies [29,189,193,197], and "Emotional control training" was used in two studies [188,193].

In asthma studies, the number of BCTs ranged from four to ten, with a mean of 6.29 (SD = 2.63). "General information", "Prompt self-monitoring/ tracking" and "Problem-solving/barrier" were used in all seven studies [28,167,200-204]. "Provide feedback on performance" was used in six studies [167,200-204]. "Action planning" and "Motivational approach" were used in four studies [28,167,203,204]. "Goal setting" and "Prompt review of behavioural goals" were used in three studies [167,203,204], "Social support" was used in two studies [203,204], and "Emotional control training" was used in one study [203]. (**Multimedia Appendix 3**).

Effects of the interventions

Systematic review

In COPD studies, the following three health-related effectiveness outcomes were reported: mortality [187,189,194], exacerbation frequency [192,199] and body mass index (BMI) [29]. On the outcome mortality, all three studies reported no effect [187,189,194]. On the outcome exacerbation frequency, both

studies found the blended self-management intervention reduced the exacerbation frequency (*RR* = 0.38, 95% CI: 0.26 to 0.56). The study with BMI reported that the blended self-management intervention had a significant effect in BMI (d = 0.81, 95% CI: 0.25 to 1.34) [29]. Eleven different process outcomes were studied: number of visits (including home visits, primary care visits and secondary care visits) (n = 3) [189,190,192], satisfaction with the intervention (n = 3) [29,166,190], medication adherence (n = 3) [29,198,199], costs (n = 2) [166,187], smoking (n = 2) [29,188], self-management ability (n = 2) [193,197], physical activity (n = 2) [29,193], nutrition (n = 1) [188], alcohol (n = 1) [188], psychosocial management (n = 1) [188] and symptom management (n = 1) [188]. Two of three studies showed moderate effect (d = 0.73, 95% CI: 0.50 to 0.96) [198,199] while the other one reported no effect on medication adherence [29]. On the outcome of self-management ability, one reported large effect (d = 1.15, 95% CI: 0.66, 1.62) [197], and the other one showed no effect [193]. No effect was found on the other process outcome indicators. In asthma studies, three health-related effectiveness outcomes were reported: admission [202], BMI [203], and exercise capacity [203]. No effect was found in admission. Large effect was found in BMI (d = 1.42, 95% CI: 0,28 to 2.42) and exercise capacity (d = 1.50, 95% CI: 0.35 to 2.50). Three process outcomes were reported: asthma knowledge (n = 2) [167,201], visits (n = 2) [167,202], adherence (therapy and medication adherence) (n = 2) [167,202]. No effect was found on process outcome indicators.

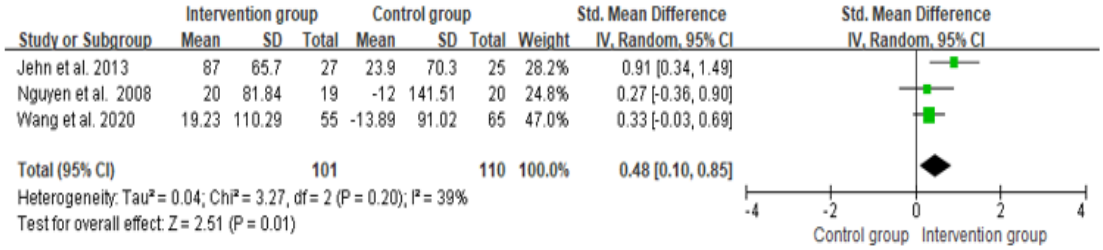
Meta-analysis

Eleven studies focusing on COPD patients were included in the meta-analysis [29,166,187,190,192,193,195-199]. The following health-related effectiveness outcomes were included: exercise capacity, dyspnea, lung function, QoL and admission rate. Three studies reported walking distance as an indicator of exercise capacity [192,193,196]. Blended self-management intervention showed a small effect on the walking distance without significant heterogeneity (SMD = 0.48, 95% CI: 0.10 to 0.85, chi-squared = 3.27, P = .20, I^2 = 39%) (see **Figure 2**). No study was identified as an outlier. Dyspnea was reported in four studies [29,190,193,196]. It was measured with the dyspnea subscale of the Chronic Respiratory Questionnaire [190,193], Medical Research Council [29] and Modified Medical Research Council [196]. Lung function was measured with FEV1% [190,192,196] and FEV1/FVC (%) [29] in four studies. No significant difference was found for dyspnea and lung function between the IG and the CG (see **Figure 2**). No study was identified as an outlier. QoL was reported in eight studies with SGRQ [29,166,187,196], CAT [192,197,199] and CRQ [193]. A large effect was found on QoL with substantial heterogeneity (SMD = 0.81, 95% CI: 0.11 to 1.51, chi-squared = 108.44, P < .001, I^2 = 94%). The standardized residual identified one study as an outlier [29]. Removal of this study resulted in an increased effect size without decreasing heterogeneity (SMD = 0.90, 95% CI: 0.15 to 1.65, chi-squared = 94.14, P < .001, I^2 = 94%) (see **Figure 3**). Furthermore, blended self-management intervention reduced the admission rate with a

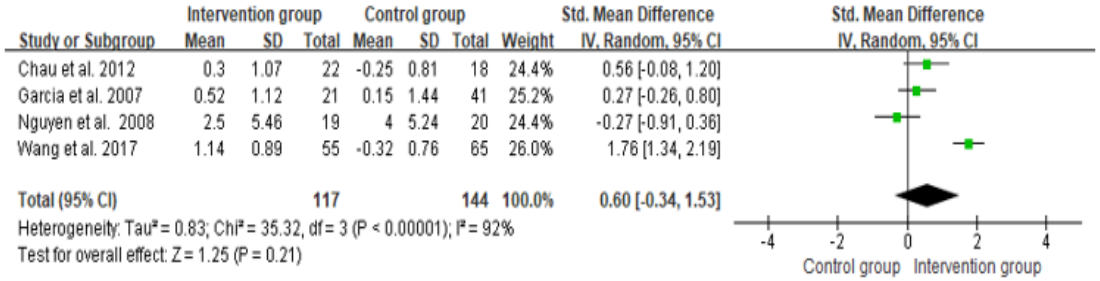
substantial heterogeneity (*RR* = 0.61, 95% CI: 0.38 – 0.97, chi-squared = 17.63, *P* = .003, I^2 = 72%) (see **Figure 4**). No outliers were identified.

Five asthma studies were pooled in the meta-analysis [167,200,202-204]. Three health-related effectiveness outcomes were included, that is lung function, QoL and asthma control. Lung function was reported with FEV1(%) [200,203] and FEV_1 [167]. Blended self-management intervention showed a small effect on lung function without significant heterogeneity (SMD = 0.40, 95% CI: 0.18 to 0.62, chi-squared = 1.48, *P* = .83, I^2 = 0%). No study was identified as an outlier. Three studies reported QoL with asthma quality of life questionnaire [167,200,204]. There was a small effect size of the blended self-management intervention on QoL without significant heterogeneity (SMD = 0.36, 95% CI: 0.21 to 0.50, chi-squared = 0.76, *P* = .68, I^2 = 0%). No study was identified as an outlier. Three studies reported asthma control with asthma control questionnaire [167,200,204]. A moderate effect was found in the blended intervention self-management group without significant heterogeneity (SMD = 0.67, 95% CI: 0.40 to 0.93, chi-squared = 2.98, *P* = .23, I^2 = 33%) (see **Figure 5**). No study was identified as an outlier.

A. Forest plot for exercise capacity



B. Forest plot for dyspnea



C. Forest plot for lung function

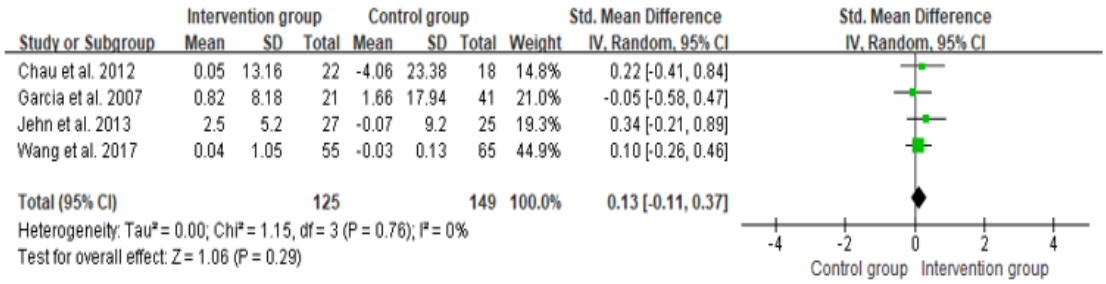


Figure 2. Forest plot for exercise capacity, dyspnea, and lung function in COPD studies.

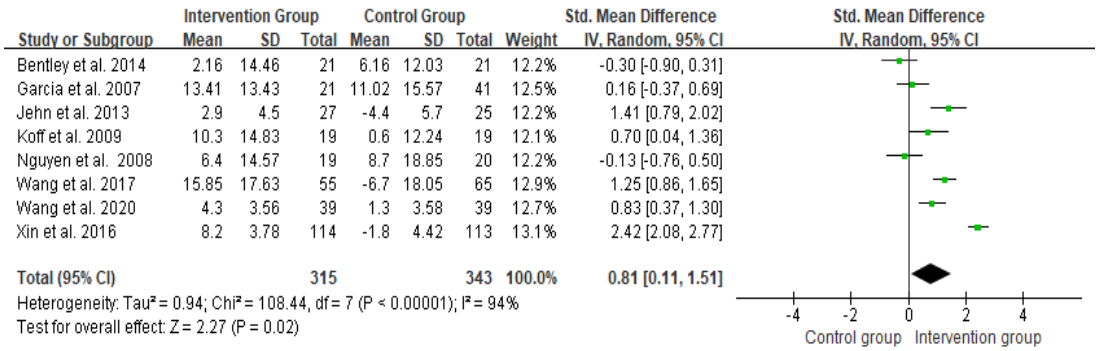


Figure 3. Forest plot for quality of life in COPD studies.

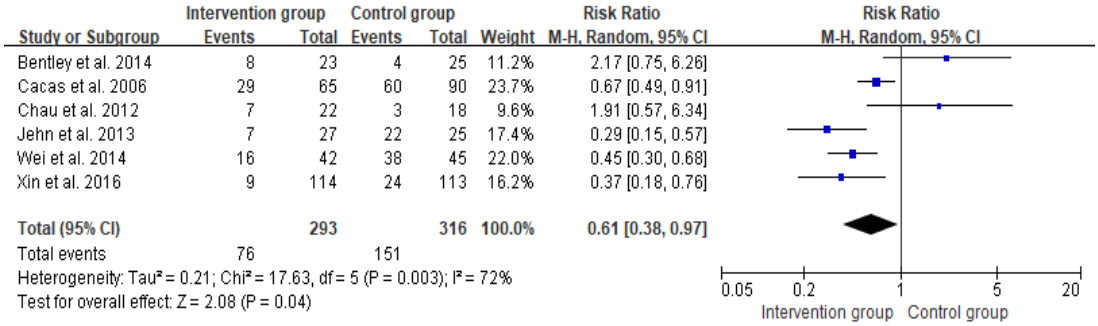


Figure 4. Forest plot for admission rate in COPD studies.

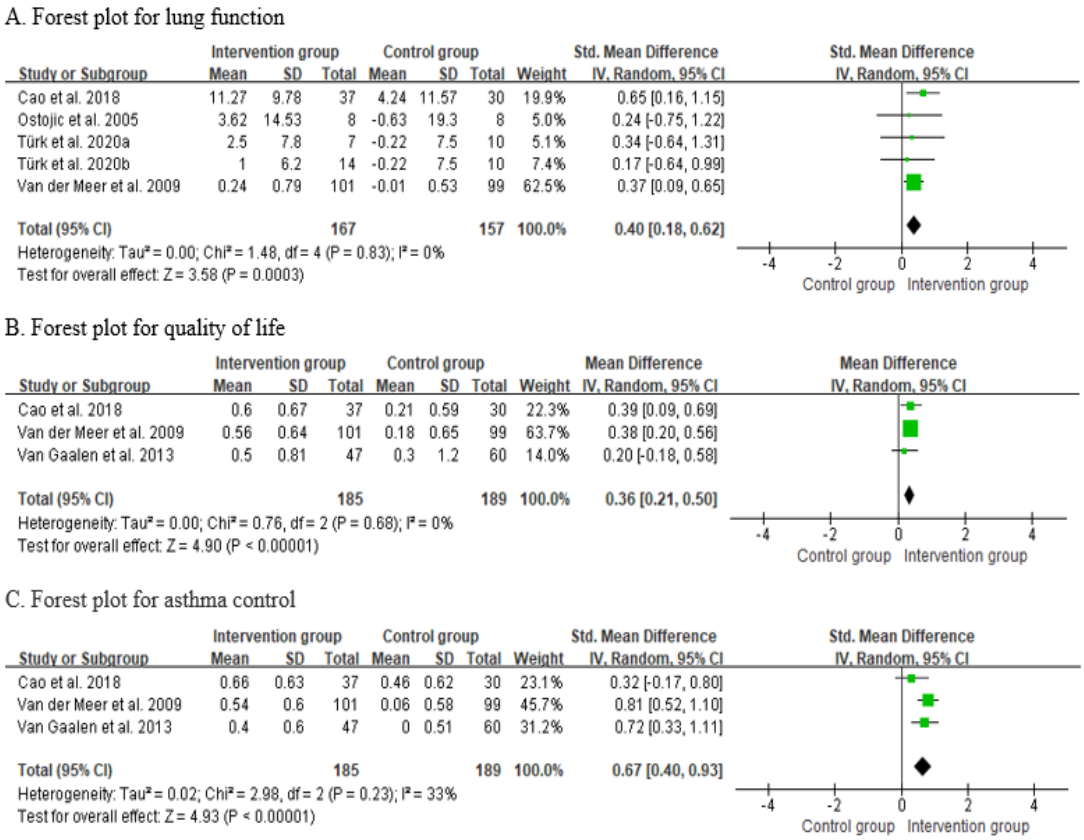


Figure 5. Forest plot for lung function, quality of life and asthma control in asthma studies.

Discussion

Principal Findings

This systematic review and meta-analysis assessed the effectiveness of blended self-management interventions on health-related effectiveness and process outcome indicators in people with COPD or

asthma. Twenty-two studies were included in the systematic review, of which fifteen were about COPD and seven were about asthma.

The studies focusing on COPD patients included three different health-related effectiveness outcome indicators, and mixed effects were observed. No effect was found on mortality. A positive effect was found on exacerbation frequency and BMI. Eleven different process outcome indicators were studied (e.g., medication adherence, self-management ability). Two of the three studies found a moderate effect on adherence. A positive effect was found in one of two studies on self-management ability. No effects were found on the other process outcomes. Eleven of the COPD studies were included in the meta-analysis. Blended self-management interventions did not have a significant effect on dyspnea and lung function. Still, they did result in a small improvement in exercise capacity and a moderate improvement on QoL and decreased the admission rate. Overall, the majority of studies had some concerns about the risk of bias assessment.

The asthma studies included four health-related effectiveness outcomes. Large effects were found in BMI and exercise capacity. There was no effect on the admission rate and exacerbation frequency. Three process outcomes were studied (i.e., visits, intervention and medication adherence and asthma knowledge). No effect was found on all the process outcomes. Five asthma studies were included in the meta-analysis. Blended self-management intervention showed a small effect on lung function and QoL, and a moderate effect was found on asthma control. Half of the studies reported some concerns, and others showed high risk in the risk of bias assessment.

The meta-analysis suggested that blended self-management interventions can effectively improve COPD patients' exercise capacity. This result was in line with another systematic review that examined the effect of COPD disease-management programs, including eHealth and face-to-face components [30]. However, this finding was not consistent with the systematic review of the effect of telehealth in COPD patients [206]. That may be because the blended programs, contrary to the telehealth programs, were likely to promote exercise capacity using various BCTs, including providing information and instruction on the behavior, self-monitoring, and providing feedback on performance by eHealth and face-to-face intervention [30]. This meta-analysis also showed that there was a positive effect of blended self-management interventions on QoL, which was in line with the findings of a meta-analysis that investigated the effect of COPD self-management interventions, including various self-management programs [207]. Blended self-management intervention significantly decreased the admission rate. This finding was consistent with the previous meta-analysis [208], where the effect of integrated care from healthcare providers with or without eHealth was identified. That might be because patients increased self-management ability and acted on exacerbations more promptly if they received self-management intervention with multiple BCTs [209]. However, the blended self-

management interventions included in this meta-analysis did not improve dyspnea and lung function, and this was consistent with earlier systematic reviews, which investigated the implementation of eHealth or manual therapy in COPD patients [210,211].

Blended self-management intervention showed an inconsistent impact on process outcomes in COPD patients. To illustrate, internet-assisted eHealth and individual face-to-face intervention showed a positive effect on self-management ability [196], while no effect was found in the blended intervention, including multiple eHealth components and individual face-to-face intervention [193]. The findings in this study may show that certain combinations within the blended interventions may be more effective in some outcomes; however, more large-scale studies using different combinations are needed to provide insight into this. There are several potential explanations for the lack of effects in the COPD studies included in the systematic review. First of all, the length of the blended interventions varied in the included studies (i.e., ranged from 4 to 48 weeks). The short intervention duration might have been problematic because patients with mild to very severe COPD were included in the studies. Airway obstruction is usually irreversible in those patients, and the duration of the blended interventions might have been too short or not have encompassed enough training session to accommodate a change in health [212]. Furthermore, it appeared that patients did not sufficiently adhere to blended interventions [29]. This lack of adherence might be because eHealth applications were unfamiliar to use for some patients [213]. We recommend that future studies educate patients on how to use eHealth because eHealth positively improved medication adherence.

In asthma studies, in line with other systematic reviews focusing on integrated asthma management (i.e., the cooperation of community pharmacist and general practitioner or eHealth and face-to-face intervention), the blended interventions had a positive effect on QoL and asthma control [214,215]. A previous review focusing on face-to-face interventions in asthma patients showed that face-to-face intervention could not improve QoL and asthma control [216]. The possible reasons for this improvement could be attributed to the integrated care provided by healthcare providers. Healthcare providers could update and refer patients for education, counselling, and guidance with eHealth and face-to-face intervention [214,215]. Unlike face-to-face interventions, blended interventions or integrated asthma management - where healthcare providers could refer patients for additional education, counselling, and guidance with eHealth and face-to-face intervention – are more effective. A positive effect was found on lung function. This finding was consistent with the meta-analysis focusing on aerobic exercise on asthma patients [217]. That may be because adequate exercise training was beneficial to lung function. However, due to limited studies included in the meta-analysis, more studies are needed to identify the effect. In this systematic review, limited studies investigated the effect of the

blended intervention for asthma patients. The findings should, therefore, be interpreted cautiously, and future studies with larger sample sizes are needed.

Strengths and limitations

Several strengths of this review are worth mentioning. First, a detailed description of the interventions was provided, and a wide range of outcomes was included. The detailed information might provide a helpful direction for the development of effective blended self-management interventions. Second, GRADE was used to assess the quality of evidence about the true effect of the blended intervention on COPD and asthma patients. This quality of evidence assessment could provide a clear and pragmatic interpretation of the recommendations for clinicians and policymakers. And finally, we followed a strict study design and precise data analysis steps. By using a strict and precise process, we wanted to ensure the quality of the systematic review and meta-analysis.

Nevertheless, several limitations also needed to be addressed. First, there was a diversity in the intervention and outcome measurements, which made it difficult to compare the findings. As a consequence, there might be statistical heterogeneity in the true effect size. The significant heterogeneity potentially diluted the intervention effect [218]. Second, only a small number of studies reported the same outcome measure, and studies with a small sample size were included. These studies may be underpowered to detect a true effect, and this negatively impacted the validity of these studies. Third, the quality of the evidence ranged from very low to high on all the outcomes. The various quality of evidence in the outcomes may weaken the recommendation level for clinicians and researchers because the high heterogeneity among studies downgraded the quality of evidence. Fourth, we were not able to assess the risk of publication bias in the meta-analysis because few studies reported the same outcome [181]. There might be a potential risk for publication bias. Fifth, not all studies reported a follow-up. The lack of this reporting made it impossible to examine the long-term intervention effect in a comprehensive way. The results should be interpreted with caution due to the mentioned limitations. Larger RCTs are required to provide more insights, especially RCTs examining the effect of blended interventions in asthma patients. Moreover, data reporting should be performed in an exact, standardized format to enable reliable extraction for future meta-analysis studies.

Conclusions

The studies focusing on COPD found mixed effects of blended self-management interventions on health-related outcomes, with the strongest evidence found for exercise capacity, QoL and admission rate. In asthma studies, small to moderate effects were found on asthma control, lung function and QoL. Overall, blended self-management interventions potentially improve health-related outcomes in COPD and asthma patients, and more studies are needed to evaluate their effectiveness.

Chapter 4

Illness perceptions and self-management among people with chronic lung disease and healthcare professionals: a mixed-method study identifying the local context

Song XY, Hallensleben C, Li BB, Zhang WH, Jiang ZL, Shen HX, Gobbens R JJ, Chavannes NH, and Versluis A, "Illness perceptions and self-management among people with chronic lung disease and healthcare professionals: a mixed-method study identifying the local context," Healthcare, vol. 10, no. 9, pp. 1657, 2022. doi: 10.3390/healthcare10091657.

Abstract

Background

Self-management intervention (SMI) may fail if they misalign with the local context.

Objectives

To optimize the implementation of SMIs in Chinese people with chronic lung disease (CLD), the local context was identified in Chinese primary care (PC) and secondary care (SC).

Methods

A mixed-method study using semi-structured interviews and quantitative surveys was conducted on people with CLD and healthcare professionals (HCPs). The qualitative data was collected until data saturation was reached, and participants were invited to complete the survey after the interview. The qualitative data—analyzed with the framework approach—was triangulated with the quantitative data.

Results

A total of 52 participants completed the interviews, and 48 also finished the survey. Four themes were identified; (a) illness perceptions (e.g., patients had poor CLD knowledge and SM, inadequate resources lead to suboptimal disease control in PC); (b) self-management skills (e.g., most patients delayed exacerbation recognition and action, and some were admitted at the crisis point); (c) factors influencing self-management skills (e.g., (in)adequate disease knowledge and medical expenditure affordability); and (d) needs for self-management (e.g., increased disease knowledge, individualized self-management plan, eHealth, (healthcare insurance) policy support).

Conclusions

Identified themes were dependent on each other and should be leveraged when implementing SMIs. Ultimately, such SMIs can optimize patient health outcomes.

Introduction

There is a high prevalence of CLD in low- and middle-income countries, such as China [7,8]. Specifically, more than one-fourth of CLD patients are in China; over 144 million Chinese people are affected by CLD [7,8]. The high disease burden for CLD (mainly chronic obstructive pulmonary disease [COPD] and asthma) is due to ineffective intervention [12,219].

There is evidence that (blended) self-management interventions (SMIs) could significantly improve patients' quality of life and reduce emergency department visits [220]. Self-management (SM) is defined as an individual's ability to manage symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent to life with a chronic illness [154]. In China, CLD SM is suboptimal [221,222]. Specifically, people with CLD in China take late action resulting in exacerbations, which indicates the need for effective SMIs [221,222]. Exacerbations are defined as sustained worsening of a patient's condition beyond normal day-to-day variations that are acute in onset, which may also require a change in medication with or without hospitalization [14].

Implementing effective SMIs in China may help to reduce the disease burden in people with CLD [223]. Many factors need to be considered when implementing SMI; the critical factor is the compatibility between SMI and the local context [224,225]. Local context is defined as the set of characteristics and circumstances surrounding the implementation effort, such as local beliefs, local health behaviours, and socioeconomic aspects [42]. Identifying the local context, e.g., local illness perceptions and experience with and needs for SM, is essential to facilitate the alignment between SMI implementation and local context [226].

Illness perceptions involve the illness's identity, causes, consequences, length (timeline), and whether it can be cured or controlled [227] [61]. Determining what illness symptoms are present can help identify how patients cope with or self-manage the disease [228]. This study aims to gain insight into two SM skills, i.e., exacerbation recognition and action. Both skills are essential because they help to reduce recovery time and decrease disease burden [229,230].

The current study aims to map the local context of CLD in China. People with CLD and healthcare professionals (HCPs) in Chinese primary care (PC) and secondary care (SC) will be included. HCPs are included because of their essential role in helping patients manage their diseases. Since patients and HCPs may hold different views in PC and SC, this study will be conducted in both settings. Altogether, we aimed to identify the local context, including illness perceptions, experience with, and needs for SM in people with CLD and HCPs in Chinese PC and SC.

Methods

Design

A mixed-method study involving semi-structured interviews and a survey was used [231].

Settings and Participants

The study was conducted in people with CLD and HCPs working with CLD—from November 2019 to May 2020—in PC and SC in Zhengzhou and Kaifeng. The inclusion criteria of patients were: (1) ≥18 years old, (2) diagnosed with CLD or repeated persistent cough lasting longer than eight weeks in the past two years [232], and (3) fluency in spoken and written Chinese. People with mental disabilities, as diagnosed by the physician, were excluded. HCPs were included when they worked in PC or the respiratory department of SC. Recruitment of participants was carried out through random and purposive techniques [233].

Measurements and Outcomes

Qualitative Interview

An interview topic list focused on illness perceptions towards CLD, experience with, and the needs for SM. Two vignettes—one focusing on COPD and one on asthma—introduced CLD to patients and HCPs. Both vignettes were checked by the CLD nurse specialist (CH) to ensure their validity and feasibility before being used. Interviews lasted between 45 and 70 min. The interview topic list can be found in Appendix A.

Quantitative Survey

In patients, demographic and clinical characteristics were collected: age, gender, years with disease or symptoms, and the exacerbation frequency in the last year. Illness perceptions were measured with the 8-item Brief Illness Perceptions Questionnaire (BIPQ) [234]. The BIPQ helps identify patients' opinions on their disease: identification (symptoms experienced), illness coherence (understanding of disease), consequences, emotional responses, illness concern, timeline, and personal and treatment control. Each item is scored from 0–10, with higher scores indicating a more threatening view of the illness [234]. Items on personal control, treatment control, and emotional response were reverse scored. The total score on the BIPQ ranged from 0 to 80. The items and their implications can be found in **Table 1**. The BIPQ has good internal reliability and has been used with various illness groups [234]; the Chinese version of BIPQ has acceptable test-retest reliability, with a Cronbach's alpha of 0.54 to 0.76 [235]. Participants had to select the three most important causes of their illness from 18 possible causes. Next, there were questions on smoking behaviours used in other studies [236,237]. Ex-smokers were asked about the number of years they had smoked. Current smokers were asked the following eight questions: the number of years they smoked, the number of cigarettes smoked daily, type of smoking

products, opinion on smoking damage, history of trying to stop smoking, the longest period managed to stop smoking, and interests and confidence to stop smoking.

For HCPs, the demographic characteristics included gender and years of work. An adjusted version of the BIPQ was used to identify HCPs' perception of the patients' disease with the mentioned eight illness representations [234]. Next, HCPs had to select the three most important causes of illness from the exact 18 causes shown to patients. Furthermore, HCPs' perceptions of CLD guideline recommendations and confidence in implementing guideline recommendations were assessed [238]. Respondents were asked to indicate their level of agreement using a five-point scale (frequency ranged from 'never' to 'always'; confidence ranged from 'not at all confident' to 'extremely confident'). The quantitative questionnaires for patients and HCP can be found in Appendix A.

Table 1. Interpretation of the Brief Illness Perception Questionnaire.

Items	**A Higher Score Implies:**
Consequences	Greater perceived influence of the illness
Timeline	A stronger belief in a chronic time course
Personal control	Greater perceived personal control
Treatment control	Greater perceived control of the treatment
Identity	Greater experience of severe symptoms as a result of the illness
Concern	Greater feelings of concern about illness
Coherence	A better understanding of the illness
Emotion	A stronger emotional response to the illness

Data Collection

Before the interview, the researcher (XYS) provided detailed study information and asked for written consent. After obtaining written consent from the participants, the researcher (XYS) used the topic list to guide the interview. Interviews were audiotaped, and notes were made if necessary. Then, participants were asked to complete the quantitative surveys. The data were collected at the healthcare settings or the participant's home.

Data Analysis

The framework approach guided the qualitative analysis [239]. Two researchers (XYS, ZLJ) transcribed and read all the interviews. In the first three transcripts, codes were made in the margin of the transcripts. Next, the two researchers discussed and agreed on 52 codes to apply in subsequent transcripts. Codes were defined and grouped into categories to form a working analytical framework. Emerging codes from subsequent interviews continuously improved the framework. The categories and codes were applied to index the interviews. A separate sheet, with one row (per interview) and one column (per code), was used for each category. The codes and the quotations (i.e., sentences indexed with the codes) from each interview were summarized for each category. Researchers systematically identified themes based on the study. Atlas. Ti 7.5 software and Excel were used to store and manage the qualitative data.

Quantitative data were entered by the researchers (XYS and ZLJ) and analyzed using the IBM SPSS software package version 23.0. Descriptive analyses (e.g., mean, standard deviation [SD], N, percentages) were used to summarize the quantitative data (e.g., demographic, clinical characteristics, BIPQ data). The mean BIPQ score was compared between groups using an independent t-test (i.e., patients from PC versus SC settings, HCPs from PC versus SC settings, and all patients versus all HCPs). All statistical tests were two-sided, with the significance at $p \leq 0.05$.

Validity and Reliability

XYS conducted the first interview, and three researchers checked the transcripts (CH, AV and RG) to ensure sufficient interview quality. Furthermore, two interviewed HCPs read their transcript to ascertain that the interviewer represented their perspectives accurately. These two participants did not suggest any changes. The self-developed questions, including smoking behaviors, perceptions of guideline recommendations, and confidence in implementing guideline recommendations, were based on the previously applied questionnaire with proven feasibility and acceptability.

Two Chinese researchers independently coded all interview transcripts (XYS and ZLJ). The Chinese researcher (XYS) translated the initial English analytical framework and checked it by the XYS and English-speaking researchers (CH and AV) to ensure validity. In the quantitative data analysis, two researchers independently entered the data into the SPSS software (XYS and ZLJ) to ensure data consistency after checking.

Results

Descriptive Statistics

A total of 27 patients and 25 HCPs participated in the interviews; 25 patients and 23 HCPs completed the quantitative survey. Reasons for not completing the survey were: having a health check-up or treatment (patients) and having an emergency meeting or insufficient time (HCPs). Detailed descriptive statistics on patients and HCPs are in **Table 2a** and **Table 2b**.

Table 2a. Descriptive statistics of patients and healthcare professionals (HCPs).

Data about Patients	N	Data about HCPs	N
Location		Location	
Primary care	14	Primary care	13
Secondary care	11	Secondary care	10
Disease diagnosis		Gender	
COPD	18	Male	4
Emphysema	3	Female	19
Asthma	2	Years of working experience	
Chronic bronchitis	2	<5	2
Age (years)(mean ± SD)	69.60 ± 13.07	5–10	19
Years with disease		≥10	2
<5	5		
5–10	7		
≥10	13		
Number of exacerbations in the last year			
0	2		
1	10		
≥2	13		
Smoking status			
Current smokers	5		
Ex-smokers	16		
Never smoked	4		
Mean years of smoking			
Current smokers	33.75 ± 14.24		
Ex-smokers	48.80 ± 13.07		

COPD: chronic obstructive pulmonary disease; SD: standard deviation.

Table 2b. Descriptive statistics of patients and healthcare professionals (HCPs).

Data about Patients	N
Current smokers' cigarette situation	
Mean daily smoking (cigarettes)	9.40 ± 3.78
Duration of quitting smoking (months)	
<6	2
6–12	3
≥12	0
Frequency of quitting smoking	
<2	1
≥2	4
Interest in quitting smoking	
Not at all	1
A little	1
Somewhat	2
Much	0
Very much	1

COPD: chronic obstructive pulmonary disease; SD: standard deviation.

Theme 1: Illness Perception

The qualitative data on illness perceptions were categorized using subthemes; see headings below. The quantitative data on illness perceptions is shown in **Table 3**.

Table 3. Comparison of Brief Illness Perception Questionnaire scores between patients and healthcare professionals (mean(SD)).

Domains	**Patients (n = 25)**			**HCPs (n = 23)**		
	PC (n = 14)	**SC (n = 11)**	**Total (n = 25)**	**PC (n = 10)**	**SC (n = 13)**	**Total (n = 23)**
Con-sequences	5.21(0.80)	5.91 ± 0.94	5.52 ± 0.92	5.90 ± 0.74 *[b]	4.46 ± 0.97	5.09 ± 1.12
Timeline	8.07(2.53)	9.18 ± 0.40	8.56 ± 1.96	9.40 ± 0.52	9.08 ± 0.49	9.22 ± 0.52
Personal control	5.29(0.61)	5.45 ± 0.69	5.36 ± 0.64	4.10 ± 0.88 *[b]	3.38 ± 0.51	3.70 ± 0.76 **[c]

Treatment control	6.71(1.07)	7.36 ± 1.21	7.00 ± 1.15	2.60 ± 0.52	3.08 ± 0.64	2.87 ± 0.63 **[c]
Coherence	6.64(0.84)	7.19 ± 0.75	6.88 ± 0.83	5.30 ± 1.42 *[b]	6.39 ± 1.04	5.91 ± 1.31 **[c]
Concern	7.27(1.10)	7.36 ± 0.93	7.32 ± 0.99	5.60 ± 1.17 **[b]	2.92 ± 0.28	4.09 ± 1.56 **[c]
Identity	6.27(0.79)	5.79 ± 0.80	6.00 ± 0.82	5.60 ± 0.52	5.77 ± 0.73	5.70 ± 0.63
Emotional response	7.45 ± 0.69	8.21 ± 0.80 *[a]	7.88 ± 0.83	4.54 ± 1.51 *[b]	3.30 ± 0.48	4.00 ± 1.31 **[c]
Total score	53.29 ± 3.99	56.09 ± 3.05	54.42 ± 3.81	41.80 ± 2.57 *[b]	39.62 ± 1.39	40.57± 2.23 **[c]

Notes: *a: significantly different compared with patients in PC, $p < 0.05$; *b: significantly different compared with HCPs in SC, $p < 0.05$; **b: significantly different compared with HCPs in SC, $p < 0.001$; **c: significantly different compared with patients, $p < 0.001$. Abbreviations: SD = standard deviation; HCP = healthcare professional; PC = primary care; SC = secondary care

Theme 1a: Coherence and Identification

Most patients in PC and all patients in SC reported that the last exacerbation was a difficult time for them. That is because they suffered physical and psychosocial function deterioration. Yet two patients in PC felt the last exacerbation was not a problem because they experienced regular exacerbations during the winters. Patients in different healthcare settings described different symptoms, i.e., patients in PC experienced coughing, wheezing, and chest tightness while those in SC underwent dyspnea (**Table 4**, Q1).

After reading vignettes on COPD and asthma, patients and HCPs identified the diseases differently (see **Figure 1**). Moreover, HCPs in PC diagnosed diseases by their working experience and those in SC using spirometry equipment (**Table 4**, Q2, Q3).

Table 4. Themes presented from patients and healthcare professionals (HCPs) of illness perceptions and self-management (SM) skills with quotes.

Data From Patient			Data from Healthcare Professionals	
Quotes	**Category**	**Theme**	**Category**	**Quotes**
Q1: "It felt like a plastic bag on my face, and I could not breathe in the oxygen at that moment." (Patient 15, SC).	Illness coherence	1a. Illness coherence and identification	Illness coherence	Q2: "It is easy to diagnose it from my experience." (HCP1, PC) Q3: "We always recommend that patients have a spirometry test." (HCP 14, SC)
Q4: "Eating fried sunflower triggered my episode." (Patient 2, PC) Q5: "When I moved the goods, I was out of breath and fainted." (Patient 15, SC)	Illness disease	1b. perceived causes	Disease cause	Q6: "Air pollution is the most important reason." (HCP 23, SC)
Q7: "I used to participate in square dancing." (Patient 4, PC)			Physical limitation	Q10: "Patients work less after the exacerbation due to decreased physical function." (HCP1, PC)
Q8: "When I cough in public, people cover their mouths with their hands and go away from me. Their actions depress me." (Patient 19, SC)	Reduced social interaction	1c. perceived consequences and emotional response	Decreased lung function	Q11: "A new exacerbation accounts for the decreased lung function." (HCP10, PC)
Q9: "I can't work now. I am like a burden to my family." (Patient 16, SC)			Indifference on patient complains	Q12: "I do not have time to explore patients' feelings." (HCP6, SC)
Q13: "No episodes disturb my daily life. I am just as healthy as those who do not have COPD or other chronic diseases." (Patient 17, SC)	Asymptomatic equal to cured	1d. curable possibility and perceived duration	Incurable and chronic	Q14: "Chronic lung disease will accompany the patients for a lifetime." (HCP6, PC) Q15: "It could not be cured." (HCP16, SC)
Q16: "I cannot manage the	Poor self-	1e. identified disease	Poor patient	Q18: "SM is helpful to

disease by myself." (Patient 7, PC)	management control	self-management	control the disease, but few patients can make it due to limited disease knowledge." (HCP17, SC)
Q17: "Doctors are the professionals. I do what they asked me to do." (Patient 20, SC)	Passive role with doctors	Guideline use in practice	Q19: "Patients' symptoms were more complicated than described in the guidelines." (HCP19, SC) Q20: "Few of us know the guidelines." (HCP9, PC)
Q21: "Well, when I had the early symptoms, I thought I had a cold. (Patient 8, PC)	Late exacerbation recognition	2. identified SM skills Patient delayed action	Q25: "Some patients do not visit us until their family members force them." (HCP10, PC)
Q23: "If my symptoms worsen, I will ask my daughter to contact my doctor immediately." (Patient 13, PC) Q24: "Early action can reduce the risk of being sent to the hospital." (Patient 14, PC)	Early exacerbation action	Patient prompt action	Q26: "Patients did not contact us until they reached a crisis point leading to hospitalization." Q27: "He sends a message or dials a voice call to me via Wechat when he feels uncomfortable." (HCP16, SC)

Q: quotes; SC: secondary care; PC: primary care.

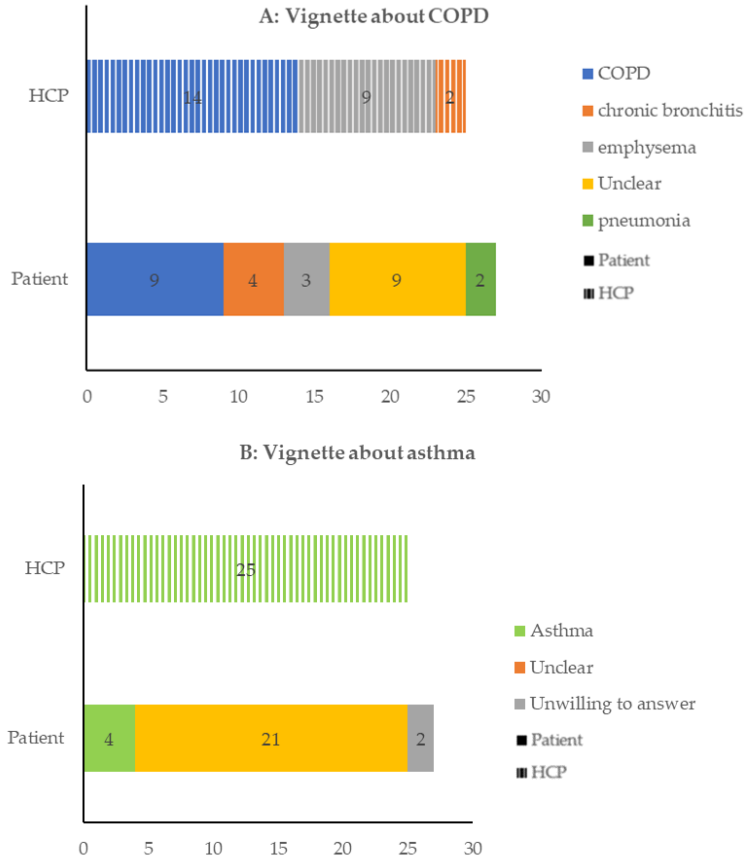


Figure 1. Identification of the chronic obstructive pulmonary disease (COPD) and asthma vignette from patients and healthcare professionals (HCPs).

Theme1b: Perceived Causes

When patients discussed the disease's cause, most attributed it to age, air pollution, and smoking. Because the Chinese term 'cause' can also mean 'to provoke'', food and physical activity were mentioned as cause/triggers (**Table 4**, Q4, Q5). HCPs noted that air pollution, age, smoking and seasonal changes from fall to winter contributed to the exacerbations (**Table 4**, Q6). Quantitative data showed that patients and HCPs perceived air pollution, smoking, and age as the prevailing disease causes, and patients additionally perceived weather as the disease cause. The distribution of the perceived causes are in Appendix B.

Some participants identified the vignette as chronic lung disease without specific names; some patients reported that it was not their obligation to recognize a disease name unfamiliar to them.

Theme 1c: Perceived Consequences and Emotional Response

Patients mentioned that the exacerbations gradually deteriorated health-related quality of life. Some 15 patients' physical function was affected by the symptoms, and 5 of them experienced a negative

impact on their sleep quality. The lack of a restful night's sleep and the morning battle of coughing and mucus expulsion left patients feeling exhausted, and the symptoms affected their mood the following day. Two patients said their daily life was limited. A total of 23 patients experienced reduced social interaction (**Table 4**, Q7, Q8). The misunderstanding from other people, for example, that the symptoms are contagious, pushed the patients away from social activities. Patients also frequently felt guilty due to their productivity losses (**Table 4**, Q9).

HCPs reported that physical limitation and decreased lung function were significant consequences of the diseases (**Table 4**, Q10, Q11). Moreover, most HCPs mentioned not paying enough attention to patient complaints (**Table 4**, Q12).

Theme 1d: Curable Possibility and Perceived Duration

A total of 20 patients believed that the disease was incurable and chronic after being informed by their HCPs, while 7 patients in SC stated that their disease was curable and acute, and they were cured when asymptomatic (**Table 4**, Q13). All HCPs highlighted that CLD was incurable and chronic (**Table 4**, Q14, Q15).

Theme1e: Identified Disease Control

Patients believed they were powerless to control the disease, while HCPs were sufficiently professional to help them manage it (**Table 4**, Q16, Q17). Therefore, they commonly perceived that they would SM the disease well when following medical advice. HCPs admitted that SM was helpful in managing diseases, but their patients showed poor SM (**Table 4**, Q18). Additionally, HCPs in PC mentioned that limited CLD medications were available in their settings. Moreover, all HCPs were encouraged to adopt the CLD guidelines in practice. Despite broad familiarity with the guidelines in SC, knowledge about guidelines in PC was suboptimal. In addition, HCPs did not always adhere to CLD guidelines for different reasons (**Table 4**, Q19, Q20). Moreover, most HCPs in PC sometimes or never applied the guideline recommendations, while those in SC always or often used the recommendations (see **Figure 2**).

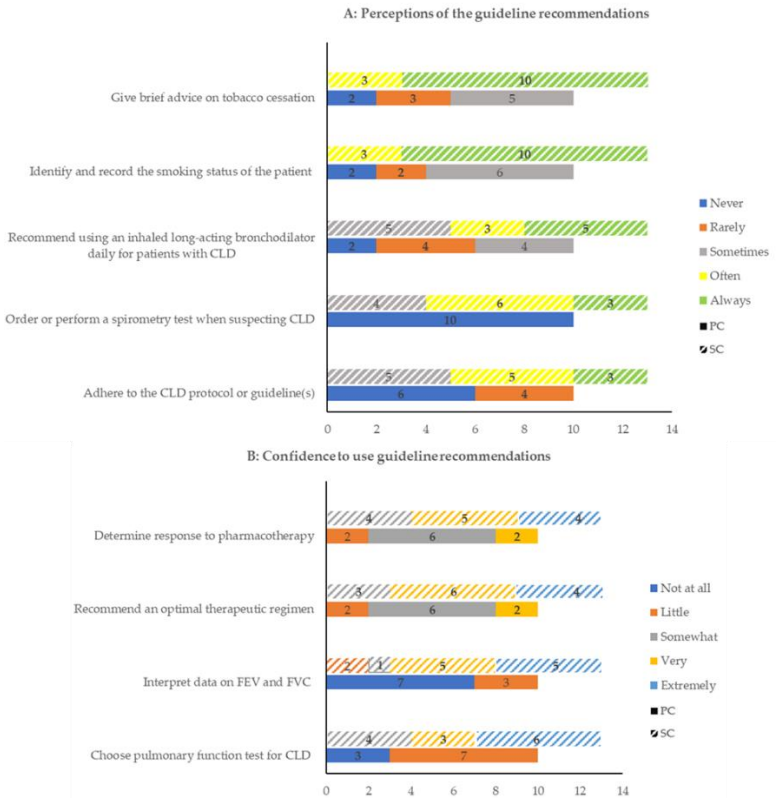


Figure 2. Perceptions of and confidence in using the guideline recommendations in practice by healthcare professionals (HCPs) in primary care (PC) and secondary care (SC).

Theme 2: Identified SM Skills

Most patients struggled to use SM skills, i.e., exacerbation recognition and action, while some patients recognized and took action on exacerbations early (**Table 4**, Q21–24). The distribution of identified SM skills in patients between PC and SC can be found in Appendix B. Most HCPs noted that patients postponed exacerbation actions, yet two HCPs from PC observed that some patients went to them early (**Table 4**, Q25–27).

Theme 3: Factors Influencing SM Skills

Three generic factors were identified to influence exacerbation recognition and actions, including disease knowledge, former experience with exacerbations, and family support. Moreover, one specific factor influencing the ability to recognize the exacerbations was identified (i.e., perceived illness severity), and three specific factors influencing the performance of SM skills were identified (i.e., self-empowerment, Chinese herb, and medical expenditure affordability). These factors—with the facilitating and barrier aspects —were dependent on each other; details on how these factors influence SM skills can be found in **Table 5**, Q28–41.

Table 5. The theme presents factors influencing self-management (SM) skills with quotes.

Themes & Category	Explanation	Quotes
Generic factors influencing SM skills		
Disease knowledge	Sufficient knowledge facilitated patients to develop SM skills, while insufficient knowledge was the barrier.	Q28: "I know nothing about the disease or the episode so that I could do nothing about it." (Patient 2, PC) Q29: "My knowledge of the disease helps a lot." (Patient 13, PC)
Former experience with exacerbations	Realizing the importance of early detection and prompt action from past experiences were the facilitators. Habituation to the disease from the former experience was the barrier.	Q30: "After my previous painful experience in the hospital, I realized that attention to the different symptoms (exacerbation) and visiting doctors early was essential." (Patient 15, SC) Q31: "…However, I frequently did nothing about the worsening symptoms because I learned to live with it." (Patient 16, SC)
Specific factors influencing the exacerbation recognition		
Family support	Helpful family support was the facilitator. In contrast, insufficient family support when patients were at home was the barrier.	Q32: "My daughters sent me to the hospital and covered the diagnosis cost. Their actions are warm and helpful." (Patient 14, PC) Q33: "Family members regarded patients as well-functioned labor and expected them to do higher intensity household chores than the patient could endure. Such patients went on with the housework with all exacerbations." (HCP 23, SC)
Perceived illness severity	Perceiving the exacerbation as usual was a barrier. The perception that the exacerbation was a hazardous event facilitated recognizing exacerbations early.	Q34: "I must pay attention to my disease carefully. Otherwise, I will be published by the worsened exacerbations." (Patient 23, SC) Q35: "Some patients would not think breathlessness or coughing was a problem unless these symptoms disturb their eating and drinking." (HCP 23, SC)

Self-empowerment	High self-empowerment facilitated the patients' act on the exacerbations and vice versa.	Q36: "For the early symptoms, I can control them myself effectively. I will contact my daughter for the ambulance for symptoms out of my control." (Patient 13, PC) Q37: "I always try to avoid the medicine or the doctors, even if I know my symptoms get worse." (Patient 14, PC)
Chinese herb	Patients perceived the Chinese herb as facilitators, while HCPs perceived patients should take these medications with their suggestions.	Q38: "Chinese herb relieved aggravation." (Patient 4, PC) Q39: "Patients take the Chinese herbs by themselves without informing us. To make sure the medicine works well, they should ask our advice before taking unprescribed Chinese medicine from us." (Patient 5, PC)
Medical ex-penditure affordability	The higher medical expenditure affordability, the more likely the patient is to see a doctor early.	Q40: "Visiting the doctors means paying money, which is the last thing I want to do." (Patient 4, PC) Q41: "My retirement pension and medical insurance can cover all the medical costs. When I am uncomfortable, I just visit the doctors." (Patient 12, PC)

Q: quotes; PC: primary care; HCP: healthcare professional; SC: secondary care.

Theme 4: Needs for SM

The needs for SM addressed the expected facilitators, e.g., increased disease knowledge and the strategy to support the SM, e.g., eHealth use and individualized SM plan. The other details on the needs for SM are included in **Table 6**, Q42–51.

Table 6. The theme presents needs for self-management (SM) with quotes.

Categories	Quotes
Increased disease knowledge	Q42: "The doctor told me I was diagnosed with COPD and left…I expected to know more about this disease." (Patient 15, SC) Q43: "With more information on disease and medications, patients will be more familiar with the seriousness of their condition, manage risk factors and change behavior, and then take action to meet their own needs for disease management." (HCP 23, SC)

Individualized SM plan	Q44: "I need one intervention to help me recognize the episode early and act on it early." (Patient 10, PC)
Nurse specialist	Q45: "A nurse specialist experienced in dealing with patients will be helpful to deliver SM information." (HCP 17, SC)
eHealth use	Q46: "eHealth will help us deliver SM information to patients, e.g., Wechat." (HCP 21, SC)
	Q47: "If we could remotely monitor patients' diseases, we could provide more care to more patients." (HCP 21, SC)
Sufficient family support	Q48: "When I forgot to take medicine, my family members remaindered me about it immediately. Family support can help me a lot." (Patient 10, PC)
Policy support	Q49: "With the economic policy support from the government, we will have more resources to provide SM." (HCP 2, PC)
	Q50: "If public medical insurance can cover more medical costs, more patients will choose to visit the doctors earlier." (HCP 22, SC)

Q: quotes; PC: primary care; HCP: healthcare professional; SC: secondary care.

Discussion

This mixed-method study identified the local context of people with CLD and HCPs in Chinese PC and SC. Four themes were identified, namely, (a) illness perceptions; (b) identified SM skills; (c) factors influencing SM skills; and (d) needs for SM. These themes were dependent on each other and should be addressed when implementing SMIs.

Most patients could not identify the CLD correctly; this finding was evidenced by a previous study showing that patients had limited disease knowledge [222]. Moreover, the disease decreased patients' physical and psychosocial functioning. Most patients believed the disease was chronic, yet a few believed it would not be long-term, possibly due to their limited understanding. Age, air pollution, and smoke were the leading disease causes in interviews, and the survey identified the weather as an additional cause. The weather was mentioned as the temperature variability can trigger exacerbations [240].

Compared with those in PC, patients in SC showed a more severe emotional response to the illness. This finding is not surprising because patients in SC suffer more severe exacerbations, which leads to more negative emotions [59]. Notably, no difference was found in total illness perception scores from patients between PC and SC, which could be due to the chronic nature of CLD. Most patients in this study had CLD for more than five years and went to PC and SC for mild and severe exacerbations; therefore, patients with long-term CLD may hold similar illness perceptions. Interestingly, no other existing studies have compared illness perceptions - in people with CLD - between PC and SC.

Most patients delayed exacerbation recognition and actions. It is likely that these patients had difficulties with exacerbation recognition and had limited knowledge of potential actions they could undertake. A few patients, mainly in PC, showed early exacerbation recognition and action. Their early response to the disease was because they applied their disease knowledge and former experience to identify the exacerbation and take prompt action. Early presenters were mostly from PC because of the accessibility, e.g., the location was closer to the patient's home, and the treatment cost was lower [241]. The identified illness perceptions among people with CLD were in line with the previous study [222].

Most HCPs correctly identified the CLD. HCPs agreed that CLD was chronic and could affect physical and psychosocial functioning. This finding complies with one previous study [38]. HCPs agreed that patients showed poor SM skills.

In general, HCPs in PC - compared with HCPs in SC - held a more threatening view of the CLD. The difference was possibly related to the healthcare service setup in China. HCPs in SC are better equipped with medical skills and more patient experience, contributing to their positive attitudes [242]. Compared with patients, HCPs held a less threatening view of CLD. It could be explained that HCPs had more disease knowledge after their medical training, which led to a better understanding of how to control CLD.

Unlike patients diagnosed with a spirometry test in SC, CLD was diagnosed based on disease history and clinical symptoms in PC due to the lack of test facilities. All HCPs (strongly) agreed with but did not adhere to the guideline recommendations for different reasons; namely, HCPs in SC considered the symptoms of people with CLD more complicated than described in the guidelines, while in PC, there was limited guideline knowledge. The lack of confidence in disease treatment in PC could be explained by a lack of spirometry tests and lower professional knowledge [243].

Many generic factors were found to influence patient SM. The first factor was disease knowledge. Patients who had more disease knowledge showed a higher SM ability. The second was the former experience with exacerbations. Some patients showed prompt action due to unwillingness to suffer the adverse outcomes of the delayed exacerbation action. Nevertheless, with the former exacerbation experience, some patients took late SM actions. That is possibly because they were used to living with the symptoms, making it difficult to recognize the exacerbation and take prompt action. The third was family support; it helped patients self-manage exacerbations, yet family members expected them to do housework beyond their physical ability. A lack of disease knowledge among family members is a potential explanation [244].

One specific factor influencing exacerbation recognition was identified as the perceived illness severity. Different factors were found to influence SM actions on exacerbation. The first was patient self-empowerment. The second was Chinese herbs. Patients used such herbs to reduce the

exacerbations, while HCPs perceived that patients should take these herbs with their suggestions. The finding on the Chinese herbs was not reported in other studies. The worry from HCPs was likely because patients taking the Chinese herbs without professional guidance may decrease the SM on exacerbations. The third was the medical expenditure affordability; the higher affordability, the earlier action on the exacerbations. The identified third factor aligns with the other study [245].

The needs for SM reflected the strategies to improve SM and expected facilitators to optimize patient SM. Both patients and HCPs expressed the need for increased disease knowledge, which was the facilitator for the SM. Moreover, public healthcare insurance was needed to cover medical expenditures for the CLD. In addition, the need for an individualized SM plan, eHealth use, and independent CLD specialist reflected effective strategies to deliver SMIs easily accessible and not restricted to certain places and times. The identified needs correspond with the previous study [222]. Notably, the HCPs further pointed out that obtaining (healthcare insurance) policy support from the government was necessary. Such a finding is not surprising as optimal SMIs have been more easily adopted with support from the government in China [246].

Several limitations need to be addressed. First, less detailed information could be obtained from participants because, during the study, there was a coronavirus outbreak in China. Some participants did not elaborate much on their SM experiences because they feared the risk of becoming infected if they talked to the interviewer for too long. Second, four participants did not participate in the survey. The missing quantitative data may underpower the triangulation. Third, the small sample size in the quantitative survey may be underpowered to triangulate the qualitative data, which may negatively impact this study's validity. Therefore, the results should be interpreted cautiously due to the mentioned limitations.

Conclusions

This study presented a comprehensive view of the local context—on the identified illness perceptions and experience with and needs for SM—in China. The identified findings addressed the importance of increasing disease knowledge, developing the strategies to deliver the SMI, and gaining (healthcare insurance) policy support during the SMI implementation. Ultimately, such SMIs can help to improve patient health outcomes and reduce the disease burden. Furthermore, this study provided that the local context should be emphasized and leveraged to ensure the SMI meets local needs. A large-scale quantitative study is needed to support the findings.

Chapter 5

Factors influencing REducing Delay through edUcation on eXacerbations implementation: a stakeholder analysis

Submitted

Abstract:

Background

Self-management interventions may fail when implementers neglect contextual factors.

Objectives

This study aimed to identify what factors may influence the implementation of the intervention – REducing Delay through edUcation on eXacerbations (REDUX) – proven-effective in the Netherlands – in China.

Methods

A stakeholder analysis design was used; specifically, a qualitative approach was applied to identify the level of support for the intervention, factors influencing the support, and the preferred mode of program delivery in chronic lung disease patients, healthcare professionals, and policymakers. A quantitative approach was used to identify the necessary conditions to develop and implement a digital-version program in Chinese app developers and cyber-security officers.

Results

Thirty-five participants finished the interviews and 88 app developers and cyber-security officers completed the survey. Most patients, healthcare professionals, and policymakers were highly supportive of the interven-tion. Multiple facilitators (e.g., patient-provide interaction and involvement of doctors) and barriers (e.g., patient's inability to afford the medicine and lack of policy support) were identified to influence the support. The preferred mode of intervention delivery varied due to different reasons. For example, a digital REDUX was preferred when participants had positive previous experiences with digital health or received guidance on how to use/implement digital health applications. The quantitative data showed that the work process of developing the health apps about the app development process, design, and technical issues and protecting the users' security and privacy, such as access control, authentication, data transfer and retention, security, and confi-dentiality, aligned with the related international guideline recommendations.

Conclusions

The identified factors can assist in the successful implementation of the intervention. The method used in this study could serve to develop culturally-tailored self-management interventions.

Introduction

The prevalence of chronic lung diseases (CLD) is high in low-income and middle countries, including China [36,37]. More than 145 million people in China are diagnosed with CLD [7,8]. The CLD in China have resulted in excessive health resource consumption, i.e., the annual medical cost for CLD is more than $156 billion [12,13], and exacerbations account for much of these costs [247,248]. Exacerbations are sustained worsening of a patient's condition beyond normal day-to-day variations, which are acute in onset and often require a change in medication and hospitalization [14]. Evidence shows that Chinese people with CLD are often unaware of the early onset signs of an exacerbation. Furthermore, late responders recognize the exacerbations but choose to wait before taking action [39,221]. To reduce the burden caused by exacerbations, it is necessary to identify effective interventions to help patients recognize and address exacerbations early.

There is evidence that (digital) self-management interventions (SMIs) can help people with CLD manage their exacerbations at home effectively, which expedites recovery days and reduce the disease burden [51,249]. Such interventions aim to increase patients' involvement and control in their treatment, which could be helpful for people with CLD in China [22,27]. It is currently unknown to what extent such interventions can be helpful in China, as previous research has primarily been conducted in high-income countries [51,249]. Such SMIs may be inappropriate for patients in China due to contextual differences.

It is necessary to tailor effective (digital) SMIs to the Chinese context, which can improve the alignment between the (digital) SMI and the local context. It is essential to identify the factors that influence SMI implementation [16,75,250]. Specifically, it is vital to assess the local perceptions about the (digital) SMI in local stakeholders because they are involved in the implementation process and can help optimize the implementation effect [251]. There is a lack of evidence of factors influencing SMI implementation in the Chinese context, especially regarding interventions developed in high-income countries. This study aims to identify the factors that influence the implementation of an SMI in China. A SMI developed in the Netherlands is exampled in this study, i.e., REducing Delay through edUcation on eXacerbations (REDUX).

Background

REDUX aims to help patients self-manage their exacerbations using a paper-version action plan. The intervention was designed and tested in the Netherlands [51]. A pilot study showed that REDUX helped COPD patients reduce the number of days between exacerbation onset and their actions on exacerbations [51]. Given the positive findings of non-digital REDUX, it can be valuable to implement it in China for people with CLD [51]. Evidence has shown that digital interventions for people with COPD, i.e., digital health, can effectively improve quality of life and reduce hospital admissions [73]. A meta-

analysis has also shown that blended SMIs can help reduce the disease burden of CLD [27]. However, it still needs to be determined which modes of delivery are preferred and the necessary conditions to implement a digital SMI in the Chinese context.

To address the gap, stakeholder analysis will be applied in this study. A stakeholder analysis is a process of systematically gathering and analyzing qualitative information to determine which factors and conditions should be taken into account when developing and/or implementing a policy or program [252]. A qualitative approach is undertaken in patients, healthcare professionals (HCPs) (e.g., doctors and nurses), and policymakers. These stakeholders are included because of their essential role in the REDUX implementation (**Figure 1**). Involvement of these stakeholders can help to identify their level of support for REDUX, the factors influencing their support, and their preference for the mode of delivery [86-88,253-255]. To gain insight into the requirements to develop and implement a digital-version REDUX, a questionnaire will be administered in the Chinese app developers and cyber-security officers (their roles in the REDUX implementation are specified in **Figure 1**) [81,163,256,257].

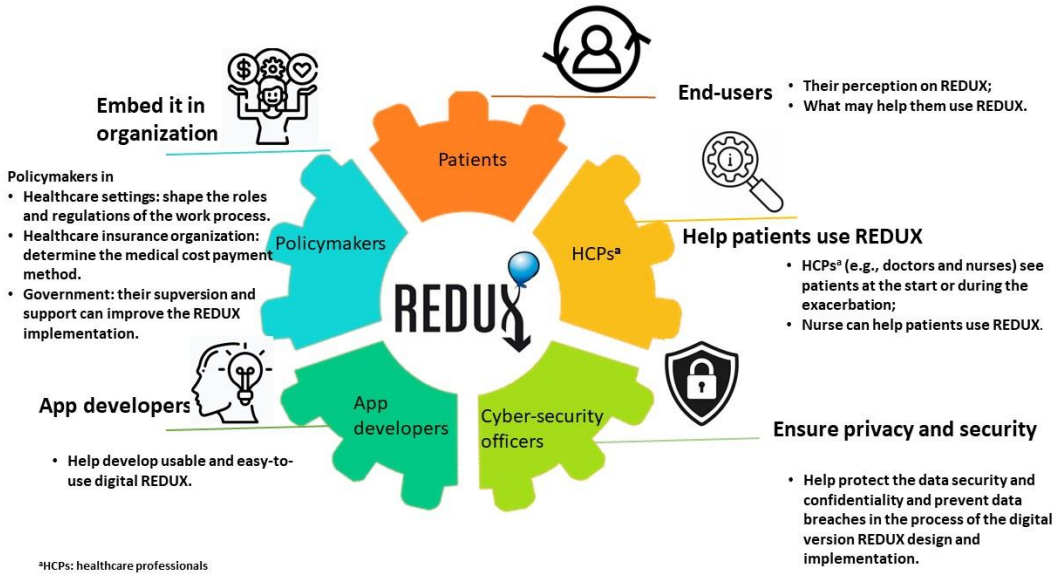


Figure 1. The roles of different stakeholders in REducing Delay through edUcation on eXacerbations (REDUX) implementation.

In sum, this study aims to identify the factors influencing the implementation of REDUX in China by identifying: (a) the level of support, factors influencing the support, and the preferred mode of REDUX delivery from patients, HCPs, and policymakers, and (b) the necessary conditions to develop and implement a digital-version REDUX from app developers and cyber-security officers.

Method

Study design

The study was designed and executed using the stakeholder analysis guidelines (see Box 1) [252]. The data was collected from September 2021 to January 2022.

Study population

Patients were included if diagnosed with a CLD (COPD or asthma, or COPD overlapping with asthma) and aged ≥ 20 years old (without a maximum age) [36,37]. Patients were excluded if they could not read or were diagnosed with mental disabilities by a doctor. HCPs who worked for the respiratory department in secondary care (SC) or with CLD patients in primary care (PC) were included. Policymakers, including the managers at the executive management level in Chinese PC and SC, government, and healthcare insurance institutions, were eligible for inclusion. Software engineers, project managers, and other positions involved in developing health app(s) were included in the group of app developers. Cyber-security officers were individuals who worked as privacy or safety officers, dealing with internet information security or digital health users' privacy [258].

Sample size calculation

Qualitative interviews were conducted until data saturation was reached [259]. The sample size estimation for app developers was based on the response rate of app developers from a previous study (i.e., 57%) [78]. To be conservative, we expected a response rate of 33%; that is, the average response rate for online questionnaires [260]. Therefore, the required sample size of app developers was 32 (5% alpha and 80% power) [261]. The sample size estimation for cyber-security officers was based on the response rate of a previous study (i.e., 33.3%) [262]. To be conservative, we set the response rate at 10%. Using this, the required sample size of cyber-security officers was 24 (5% alpha and 80% power) [261].

Stakeholder analysis process

The stakeholder analysis process was designed using the Schmeer model, which consisted of six general phases (Box 1) [252]. The stakeholder characteristics and level of support for REDUX were measured with the elements of awareness, power, position, and interest in using REDUX [252]; the definition and relevance of these elements can be found in Appendix A. The location of the stakeholders was categorized into national- and regional-level [84]. The national locations are those organizations responsible for policy-making, and the regional locations are mostly delegated to implement a new policy [84].

Instruments

Qualitative interview

The semi-structured qualitative interviews with patients, HCPs, and policymakers were guided by a topic list, focusing on perceptions and factors influencing the implementation of REDUX in China (Appendix B). The interview started with a brief introduction about REDUX and the objective of the interview. The introduction was followed by a question to identify their general understanding of self-management (SM). Next, the REDUX action plan was shown and explained to the stakeholder. Furthermore, there were questions to identify stakeholders' perceptions of REDUX and the factors influencing the implementation. The specific questions asked varied for stakeholders based on their role in the intervention.

Quantitative data

Two separate questionnaires were developed, including one for app developers and one for cyber-security officers. The questionnaires were based on previous studies [78-80]. To ensure the validity of the questionnaires, two app developers and one cyber-security officer checked the questionnaire for their field.

Both questionnaires started with a brief introduction about REDUX, the questionnaire's objective, and several socio-demographic questions. The app developers completed 18 questions about the app development process, which involved the ditigal health development guideline recommendations related to the app development process and cyber-security and privacy readiness, market, design, and technical issues during the app development. Cyber-security officers answered 24 questions about protecting the user's security and privacy in China and the conditions they needed to consider during the health app development and implementation. The questions involved the perspective on access control, authentication, data transfer, data retention, security and confidentiality, integrity, informing patients, body area network communication, and breach notification. The questionnaires are attached in Appendix B.

Box 1 Process of the stakeholder analysis for the REducing Delay through edUcation on eXacerbations (REDUX) implementation

1. **The process to select and define a policy was planned.**
   - The aim of the stakeholder analysis, the timeline to collect and analyze the data, and the targeted stakeholder categories were determined.
   - The policy, i.e., REDUX, was determined [51].
2. **Identifying key stakeholders**
   - Random and purposive techniques were used to include patients, HCPs, and policymakers[a].
   - A questionnaire was administered in app developers and cyber-security officers. They were identified by posting the questionnaire on research websites, i.e., Wenjuanxing and Dingxiangyuan.
3. **Adapting the tools**
   - The topics in the questionnaire and the interview list (see 3.5 Instruments) were defined. The stakeholder characteristic was defined, and the location category was added (see Appendix A).
4. **Collecting and recording the information and filling in the stakeholder table**
   - Written informed consent was obtained before the online semi-structured interviews. Interviews were conducted through Wechact or VooV (i.e., Chinese social media applications). After finishing the interviews, XYS and BBL copied the responses from the interview to the stakeholder characteristic table.
   - Participants gave their informed consent before participating in the quantitative questionnaire. Next, XYS and QZ copied the data from the completed questionnaires to SPSS 'IBM SPSS Statistics for Windows, version 25.0 for analysis.
5. **Analyzing the stakeholder information**
   - Resource scores for each stakeholder were averaged with integer numbers, resulting in a power score between 1 (low power) to 3 (high power). The number of perceived benefits or disadvantages of REDUX was counted to assess the interest in REDUX. Interest was scored between 1-3; 1 = low interest (i.e., perceived more disadvantages), 2 = medium interest (i.e., an equal number of perceived benefits and disadvantages), and 3 = high interest (i.e., perceived more benefits). The position was determined by participants' self-reported level of support and interest, ranging from 1 (low support) to 3 (high support). The score was averaged across stakeholders with integer numbers, resulting in a position score between 1 (low position [low support]) and 3 (high position [high support]). The awareness of REDUX was assessed with the knowledge of REDUX. The level of awareness was rated from 1 (no knowledge) to 3 (a lot of knowledge). Discrepancies between XYS and BBL were discussed to achieve agreement.
   - XYS divided the data on socio-demographical characteristics into three groups, i.e., patients, HCPs, and policymakers. Next, XYS categorized the stakeholders in a matrix where power was in the row (n = 3) and position was in the column (n = 3).
   - To identify the factors influencing support, deductive content analysis of transcripts was used by XYS and BBL using the CFIR [16], which comprises 39 specific constructs within five major domains, i.e., domains of the intervention characteristics, inner and outer setting, the individuals involved, and the process. Discrepancies in the codes were discussed to reach an agreement. Atlas.ti Web (Version 9.0) was used to store and manage the qualitative data.
   - Descriptive analyses (e.g., N, percentages) were used to summarize the quantitative data.
6. **Using the information**
   - Identifying the support for the REDUX implementation and the factors influencing it can help improve the implementation success of REDUX. The knowledge of the development of health apps in China can help determine what conditions are necessary when developing a digital version of REDUX.

HCP: healthcare professional; CFIR: Consolidated Framework for Implementation Research. [a] XYS sent invitation emails and messages to HCPs and policymakers who published publications on chronic lung disease self-management or showed nterest in this topic. When the HCPs or policymakers showed interest in our research, they were invited to participate in the research and/or were asked to refer other people who would be interested in it. in response to the invitation from a recruited policymaker, an online public presentation – presenting chronic lung disease management in the Netherlands – was given to employees of one hospital in Zhengzhou, China. The online presentation helped recruit HCPs and policymakers.

Ethical considerations

The study's objective and requirements were explained to the participants, and all participants provided written informed consent. This study received ethical approval from Zhengzhou University in September 2021 (ZZUIRB202187).

Result

Descriptive statistics

Interviews

Thirty-five stakeholders participated in the interviews (response rate = 83.3%); eight patients, 19 HCPs, and eight policymakers. Four people did not participate due to a busy schedule, and four did not respond to the invitation.

All patients showed low power; the majority scored low on position (5/8) and high on interest in the intervention (5/8). Moreover, the majority scored middle to high on awareness of the intervention (6/8). Nearly half of the HCPs showed high power (8/19) and a medium level of position (10/19). In addition, most reported high interest in (13/19) and awareness of (12/19) the intervention. Furthermore, all policymakers showed high power, and most had a high interest in (6/8) and awareness of (7/8) the intervention. The position of policymakers varied from low to high. Most patients (5/8), HCPs (14/19), and policymakers (5/8) were from regional locations. The power and position in specific locations are detailed in **Table 3**. All patients - in regional and national locations - showed low power and varied position. Most HCPs in national locations (4/5) had high position and power, whereas the position-power relationship varied for HCPs in regional locations. Most policymakers (4/5) from regional locations showed high power with middle position, whereas most policymakers in national locations had high power with a high position (2/3). Detailed stakeholder characteristic data are specified in Appendix C.

Online questionnaire

Sixty-one app developers participated in the questionnaire, with sixty completing the questionnaire. Respondents included software engineers (n = 44), project managers (n = 9), and others (n = 7). The other category included three backend developers, one quality assurance engineer, and three user experience designers. The majority worked on the health apps for 1-5 years (n = 41), and the minority for over five years (n = 19). The number of apps they had developed was 1-5 (n = 57), and over five (n = 3). Twenty-seven cyber-security officers completed the questionnaire. They worked on IT security-related tasks (n = 4) and privacy/data protection related tasks (n = 23).

Table 2 Characteristics of patients, healthcare professionals (HCPs), and policymakers in REducing Delay through edUcation on eXacerbations (REDUX) implementation (n = 35)

	Position*	Power*	Interest*	Awareness*	Location (NL/RL)
Patient (n = 8)	1/2/5	0/0/8	5/2/1	3/3/2	3/5
HCPs (n = 19)	10/7/2	8/11/0	13/4/2	12/6/1	5/14
Policy-makers (n = 8)	3/4/1	8/0/0	6/1/1	7/1/0	3/5

*:category of the variable: high/middle/low; NL: national location; RL: regional location.

Table 3 Estimation of position and power of patients, healthcare professionals (HCPs), and policymakers in REducing Delay through edUcation on eXacerbations (REDUX) implementation

	Power		
	Low	Medium	High
Position			
High	Patient in RL (n = 1)	HCP in RL (n = 2)	HCP in RL (n = 3) HCP in NL (n = 5) Policymaker in NL (n = 2) Policymaker in RL (n = 1)
Medium	Patient in RL (n = 1) Patient in NL (n = 1)	HCP in RL (n = 7)	Policymaker in RL (n = 4)
Low	Patient in NL (n = 2) Patient in RL (n = 3)	HCP in RL (n = 2)	Policymaker in NL (n = 1)

NL: national location; RL: regional location.

Factors influencing stakeholders' support for the REDUX implementation

Factors, including 14 facilitators and eight barriers, across the CFIR domain of intervention, the individual characteristics, inner and outer settings and process were identified. Specifically, three facilitators (i.e., high adaptability, low complexity, and patient-HCP interaction) and two barriers (i.e., unclear content, external entity) were identified in the intervention characteristics domain. Three facilitators (i.e., perceived intervention benefits, positive experience with SM and high level of self-efficiency) and one barrier (i.e., lack of knowledge) were identified in the domain relating to individuals involved. Regarding the inner setting domain, five facilitators (i.e., regular interaction with colleagues, involvement of physicians, active commitment from leaders of HCPs, sufficient time and human resources, and access to databases or resources) and three barriers (lack of commitment from

leaders of HCPs, increased workload, and lack of staff) were identified. In the outer setting, policy support for intervention was a facilitator. In contrast, the inability to afford the medicine and lack of support for the intervention by national guidelines or policy were the barriers. Empathy and the appropriate time to deliver the intervention were the facilitators in the process domain. These factors depended on each other; details on how they influenced the support for REDUX are specified in Appendix C.

Preferred mode of livery: qualitative data from patients, HCPs and policymakers

Patients, HCPs, and policymakers showed different preferences regarding the mode of REDUX delivery (Appendix C). A digital REDUX was considered feasible by some patients (4/8) and HCPs (6/19) and most policymakers (5/8) if these participants had positive previous experiences with digital Health or they had received guidance on how to use/implement digital health application. Yet, a paper-version REDUX was preferred by a part of the patients (1/8) and HCPs (4/19). Various reasons were given, i.e., the older patient preferred to receive the information/education in a face-to-face interaction with HCPs, and HCPs preferred to use the paper-version REDUX to collect additional relevant health data from patients during the face-to-face consultation. Furthermore, blended care was regarded as a solution to integrate digital- and paper-version advantages by some patients (3/8), HCPs (8/19), and policymakers (2/8). One HCP and one policymaker showed indifference to the delivery model because they showed low interest in REDUX.

Necessary conditions for the implementation of a digital REDUX: quantitative data from app developers and cyber-security officers

The app developers reported that the most frequently mentioned functionalities in the developed Chinese health apps were disease education (n = 32), health monitoring using sensors (n = 35) or self-report (n = 26), making (nationwide) doctor's appointments (n = 24), or medical consultation (n = 26). In the app development process, the following stakeholders were frequently involved: researchers (n = 42), doctors (n = 38), and patients (n = 22). The potential target population of health apps were researchers (n = 42), patients (n = 31), policymakers (n = 25), doctors (n = 27), and nurses (n = 27). Regarding the guidelines for developing health apps, control objectives for information and related technologies (n = 27) were regularly used. Structured threat information expressions were usually used to measure cyber-security and privacy readiness (n = 23). While, 11 health app developers did not use guidelines to measure their cyber-security and privacy readiness. The Android system (n = 49) and IOS (n = 37) were the most frequently used mobile platform to publish health apps. Furthermore, Windows was the most frequently used operating system to publish health software. Most app developers (strongly) agreed with the guideline recommendations about the app development process, design, and technical issues. Moreover, most cyber-security officers

(strongly) agreed with protecting the users' privacy and security in the international guideline recommendations such as access control, authentication, data transfer, data retention, security and confidentiality, integrity, informing patients, body area network communication, and breach notification. Yet, some cyber-security officers disagreed with such guideline recommendations. The specification about how to develop and implement Chinese health apps and ensure data security and privacy in China are included in Appendix C.

Discussion

This stakeholder analysis study identified the level of support for REDUX, factors influencing the level of support and the preferred model of intervention delivery according to the patients, HCPs, and policymakers. Additionally, Chinese app developers and cyber-security officers provided data on the necessary conditions to develop and implement the digital-version of REDUX. The patients, HCPs, and policymakers had various levels of power, awareness, and interest in REDUX. Most patients, HCPs, and policymakers were highly supportive of REDUX for its potential positive effect on improving patients' SM. Yet some patients, HCPs and policymakers showed a lower level of support potentially because it would be difficult for them to implement a new SMIs with insufficient resources and/or inadequate awareness of the intervention. Such a finding is in line with earlier stakeholder analysis studies in implementation science [82,84]. Multiple factors, covering facilitators and barriers within the CFIR domains, were identified that influenced their support (see Box 2).

Box 2. Factors – positioned within the consolidated framework for implementation research (CFIR) - influencing the implementation of REducing Delay through edUcation on eXacerbations (REDUX).

Domain I: Intervention characteristics	
Constructs	Explanation
1. Adaptability	HCPs considered it easy to incorporate REDUX into their work processes and felt confident using it. However, the open questions in the action plan were different from what they usually ask. The questions required HCPs to provide an extra explanation to patients, which hindered them from using the intervention to the Chinese context. This finding was attributed to the different contexts. To illustrate, the HCPs - in the Netherlands – use interaction strategies with open questions to empower patients to manage their disease [51]. But Chinese HCPs chose to use paternalistic strategies in practice, in which HCPs used closed questions to get information about patients and provide education benefiting them [81,269].

2. Complexity	All patients and some HCPs believed the action plan was simple and low in complexity. However, some HCPs believed that the questions in the action plan cost them extra time and effort. To circumvent complexity issues, making some minor adjustments when using REDUX in the Chinese context is required. At the same time, adequate training of HCPs using the patient-centered intervention is required as Chinese HCPs may not be used to this way of working (e.g., they use paternalistic strategies that can limit the educational effect of the intervention).
3. Design quality and packaging	The action plan is easily accessible to patients and HCPs, which promotes its use in the Chinese context.
4. Intervention source	A concern was expressed by the HCPs that a SMI developed in the Netherlands could not help people with CLD in China as the intervention is not tailored for Chinese patients. The input from this study can provide data to tailor REDUX in the Chinese context.
5. Relative advantage	Patients, HCPs, and policymakers reported that compared with other interventions (e.g., medication intervention), REDUX could actively empower patients to SM their disease.
Domain II: Individual characteristics	
1. Knowledge and beliefs about the intervention	The perceived benefits of intervention helped to increase HCPs' desire to be involved in the REDUX implementation. This facilitator was in line with a previous study, in which stakeholders showed higher interest when they perceive the benefits of an intervention [16]. Lack of knowledge was a barrier. Of great concern is that limited knowledge of the intervention may lead to other barriers, such as low self-efficacy to implement REDUX, which may hinder the implementation of REDUX.
2. Self-efficacy	Most HCPs believed in their capabilities to execute courses of action to achieve REDUX goals, which leads to a high possibility of up-taking and implementing REDUX successfully.
3. Positive experience with SM	With the experience of benefitting from SMIs, HCPs and patients would be more willing to implement or use other SMIs. For example, the positive experience with SM can promote patient collaboration during the REDUX implementation.
Domain III: Inner setting	
1. Networks and communications	Regular interaction with colleagues (including the formal and informal nurse-nurse, doctor-nurse, and doctor-doctor communication) was a facilitator. That is because such interactions can engage more HCPs with the intervention. The involvement of physicians was also a facilitator because they have more authority – compared with Chinese nurses– over patients, which can optimize patient involvement in the SMI implementation.
2. Readiness for implementation 2a. Leadership engagement	Active engagement from leaders of HCPs was a facilitator. Their engagement in the implementation process can assign dedicated staff to perform the necessary change, which may ease the workload and the concern for increased work. The inadequate leadership sub-optimized the effect of interventions due to the lack of management.

2b. Available resources	Sufficient time and human resource is a facilitator. Sufficient time and human resources can ensure that the HCPs commit to the REDUX implementation, significantly optimizing healthcare outcomes and reducing the disease burden. The lack of staff and increased workload can be considered as barriers; these barriers were also reported in many other studies on SMIs [16,270,271]. It is essential to stimulate other facilitators, e.g., leadership engagement and regular interaction with colleagues, to address these barriers. These solutions could reduce HCPs' workload and time of adding new interventions, increasing the likelihood of successful evidence implementation in busy settings.
2c. Access to knowledge and information	Access to databases or resources was a facilitator. To illustrate, ease of access to information and knowledge about the intervention helped to incorporate it into the work process.
Domain IV: Outer setting	
1. Patient needs & resources	The inability to afford medicine was a barrier. Insufficient funds for the medicine will limit the patient's ability to follow the action plan; the action plan expects patients to increase their medicine promptly when symptoms are worsening. Inadequate use of medicine could lead to worse exacerbation, which should be targeted to improve patient outcomes. Increasing patients disease knowledge e.g., adequate use of medication, can help to prevent worsening of health outcomes.
2. External policies and incentives	With policy support, such as promoting the SMI implementation, HCPs would prioritize SMIs such as REDUX in their work practice. Policies or standards could also be essential in reaching an agreement on goals and feedback during the REDUX implementation. Without policy support, some HCPs and policymakers expressed their concerns about the return of investments of implementing REDUX. The financial benefits of the REDUX implementation – such as reduced emergency room visits and hospital stay - is difficult to measure within a short time, and the healthcare insurance cannot reimburse the implementation of REDUX without such knowledge. HCPs will put more time and effort to implement REDUX when such interventions are prioritized in the policy recommendations.
Domain V: Process	
1. Planning	The appropriate time to deliver the intervention was a facilitator. This facilitator can help patients obtain the optimal benefit from the intervention when actively attempting to change their behaviors.
2. Engaging	Empathy was regarded as a facilitator. For example, patients would be more engaged in REDUX when their voices were listened to, and their needs were considered in the intervention.

HCP: healthcare professional; CLD: chronic lung disease; SMI: self-management intervention.

The preferred model to deliver REDUX varied because of different perceived benefits or feasibility of the delivery modes Such findings aligned with the previous studies, which compared the delivery and effect of different modes of SMI delivery [27,263]. Previous studies indicate that all SMI delivery modes can have advantages; tailoring the mode of delivery to the local context could help optimize the implementation effect [27,263].

When it came to the work process to develop and implement the health apps, quantitative data showed that it was possible for the Chinese patients to make nationwide doctor appointment; this could be because there is a lack of strict referral and counter-referral system between different healthcare settings, such as SC and PC [264]. These identified findings did not align with previous studies focusing on health app development outside of China [265,26]. Considering such an appointment system allows patients to access different HCPs, which can bring difficulties to collect patient data during the REDUX implementation. Accordingly, implementing REDUX to patients who have fixed HCPs can optimize the implementation.

Additionally, Chinese app developers presented that the work process – about the health app development, cyber-security, and privacy readiness, market, design, and technical issues – is in line with other studies on health app development and implementation [78-80]. Furthermore, most app developers (strongly) agreed that their work in access control, authentication, data transfer, data retention, security and confidentiality, integrity, informing patients, body area network communication, and breach notification aligned with the requirement in the guideline recommendations. This finding is new because – to our knowledge – this is the first study to identify the necessary conditions for developing and implementing health apps from the perspective of health app developers and cyber-security officers. Yet, some app developers disagreed on a few recommendations, such as access control, authentication, data transfer, data retention, security and confidentiality, integrity, informing patients, body area network communication, and breach notification. The discrepancy could be explained by the fact that the standard of digital health use is feasible for most app developers and cyber-security officers worldwide [81,267], but some guideline recommendations were beyond the standard in their practice [268]. The data explanation in the health app development - most agreement and some disagreement response on guideline recommendations - can also explain the similar data in the field of cyber-security from cyber-security officers.

Several limitations should be addressed in the interpretation of the results of this study. First, although this study applied the stakeholder analysis, there might have been some missing information on the power. That was because the power of patients, HCPs, and policymakers might shift over time or is only be applicable in specific contexts. For example, China is in a new round of healthcare innovation [72 88], which addresses the role of HCPs, especially nurses, in helping patients improve their

healthcare outcomes. That indicated that HCPs could have a higher power in the SMI implementation. Second, selection bias could exist because the questionnaire was offered on the research websites, resulting in some missing data from app developers or cyber-security officers who are inexperienced with research.

Relevance for clinical practice

We identified that the open questions in the action plan required extra explanation to patients. To improve the adaption of REDUX in the Chinese context, it is necessary to make minor adjustments to the questions (e.g., using local norms and adding answer options). To illustrate, the second question, 'what do you do', can be adjusted to a question like ' what kinds of actions did you have'. Instead of having an open answer format, answer options could be provided. Then, patients can select the answer(s) suitable for them. Patients can also add more responses when necessary. Besides, a lack of patient-centered interaction during the REDUX implementation can jeopardize SM for patients. Therefore, it is necessary to provide training to HCPs on how to provide patient-centered interventions and help patients SM their diseases.

The REDUX implementation experience in the Netherlands has shown that the return on investment could be very quick when it saves patients' hospital admissions [51]. The different perception on the same topic was identified in this study. The divergence can be due to the lack of practice using REDUX in China. It is recommended for that Chinese HCPs to implement REDUX, which can help to measure the return of REDUX. In addition, external policies and incentives were also identified as the essential factors influencing the REDUX implementation. To improve the REDUX implementation, policymakers must develop policies or guideline recommendations prioritizing patient-centered interventions, e.g., SMIs. Besides, not all Chinese CLD patients can afford medicine, which sub-optimizes not only treatment of the CLD, but also the REDUX implementation. An adequate healthcare insurance system is an essential external force that can facilitate the REDUX implementation and ensure everyone can benefit from the intervention. For example, the healthcare insurance system should improve reimbursement to help cover the medication cost due to CLD. Additionally, HCPs and policymakers worried that their investment in REDUX would not benefit patients within a short-time. In the new round of healthcare innovation [72,88], it is necessary to address the long-term benefit of implementing SMIs, e.g., prioritize the human and resource investment in SMI implementation.

Conclusion

Most patients, HCPs, and policymakers (highly) supported the REDUX implementation in China, yet some had a lower level of support for it. Multiple factors influenced their support for REDUX; critical

facilitators are patient-provide interaction in the intervention, patients' positive experience with SMIs, and involvement of physicians in the implementation process. Yet the barriers, such as patients' inability to afford the medicine, and lack of HCPs, should be addressed. The work process to develop and implement the digital-version REDUX in China should align with the international guideline recommendations. The identified factors in this study can help leverage the local resource to ensure the REDUX implementation successfully, consequently optimizing patient health outcomes. Furthermore, the method used in this stakeholder analysis study could serve to develop culturally-tailored SMIs.

Chapter 6

REducing Delay through edUcation on eXacerbations for patients with chronic lung disease: study protocol of a single-arm pre-post study

Song XY, Hallensleben C, Shen HX, Zhang WH, Gobbens RJJ, Chavannes NH, and Versluis A, REducing delay through edUcation on eXacerbations for people with chronic lung disease: Study protocol of a single-arm pre-post study, Journal of Advanced Nursing. 2022, 78(8):2656-2663. doi: 10.1111/jan.15311.

Abstract

Background

The high disease burden in patients with chronic lung disease is mainly due to exacerbations. There is a need for effective exacerbation-management interventions. A nurse-led program, REducing Delay through edUcation on eXacerbations, helped patients self-manage exacerbations.

Objectives

This study protocol aims to examine the effectiveness and preconditions of a self-management program - named REducing Delay through edUcation on eXacerbations - in China.

Design

A single-arm pre-post study.

Methods

Fifty-four patients and 24 healthcare professionals in Chinese primary care will be included. The core element of the program is a personalized action plan. Healthcare professionals will receive training in using the action plan to help patients manage exacerbations. The intervention will start when a patient is referred to the nurse for a post-exacerbation consultation and ends when the patient presents for the second post-exacerbation consultation. During the first post-exacerbation consultation, the patient and nurse will create the action plan. The primary outcomes in patients will include the delays between the onset of exacerbation and recognition, between exacerbation recognition and action, between exacerbation recognition and consultation with a doctor, and when the patients feel better after receiving medical help from healthcare professionals. The secondary outcomes will include preconditions of the program. The ethical approval was obtained in September 2021.

Discussion

This study will discuss a culturally adapted nurse-led self-management intervention for patients with chronic lung disease in China. The intervention could help Chinese healthcare professionals provide efficient care and reduce their workload. Furthermore, it will inform future research on tailoring nurse-led self-management interventions in different contexts.

Introduction

Chronic lung diseases (CLDs) are diseases of the airways and structures of the lungs, such as chronic obstructive pulmonary disease (COPD) and asthma [147]. In China, the prevalence of CLD patients is high [7,272]. In 2018, 8.6% of the Chinese population suffered from COPD, and 4.2% were affected by asthma in 2019 [7,272]. CLD results in high healthcare costs [273,274]; the annual cost was recently measured at over $151.6 billion for COPD and $4.7 billion for asthma in China [273,274].

A considerable part of the economic burden of CLD is attributable to exacerbations [147]. Exacerbations are sustained deteriorations of a patient's condition beyond normal day-to-day variations. They are acute in onset and may also require changes in medication and hospitalization [51]. When exacerbations occur, some patients respond to them quickly (early presenters), while other patients wait longer to take action (late presenters) [275]. There is evidence that early recognition and prompt exacerbation treatment could reduce recovery times and the risks of hospitalization [51]. Studies have shown that patients with CLD in China frequently recognize the symptoms late and delay action [40,276]. In a study of patients with asthma in China, many did not use regular daily controller medications before requiring hospitalization, leading to a high prevalence of exacerbations needing treatment through high-cost medical care [40]. Therefore, it is necessary to identify effective interventions that include early recognition and prompt action in China.

Typically, patients with CLD receive a medication intervention for exacerbation management. These interventions have been shown to reduce exacerbation frequency and decrease recovery times [34,35]. However, patients take only a passive role in managing their exacerbations with medication intervention. Specifically, passive patients wait longer to take action and delay seeking medical help from healthcare professionals (HCPs), leading to longer recovery times [34,35]. This finding is not surprising, given that patients typically do not actively seek information on how to self-manage exacerbations [34,35]. Combining medical intervention with self-management could help patients treat and recuperate from exacerbation at home [34,35,277]. Self-management refers to an individual's ability to manage their symptoms, treatment, physical and psychosocial consequences, and lifestyle changes accompanying a chronic condition [17]. Self-management interventions, which often consist of education and an individualized action plan [34,35], could help to reduce the burdens of CLD and expedite recovery times by informing patients about how to take an active role in their disease management, including prompt exacerbation recognition and action [249]. Nurses play an essential role in self-management intervention by coordinating multidisciplinary teamwork and providing education in such interventions [278]. One meta-analysis that identified the effect of nurse-led self-management interventions in patients with COPD has shown that these interventions can significantly improve

patients' quality of life [278]. A nurse-led self-management intervention may thus be helpful for patients with CLD to manage their diseases.

However, research on CLD self-management interventions has mostly focused on high-income countries, whereas the CLD burden is highest in low- and middle-income countries (LMICs) [7,272]. For example, the burden of CLD is particularly high in China, where there are 144 million people with CLD [7,272]. Around one-fourth of the global burden of CLD is in China [147]. Patients face a heavy disease burden in China due to the lack of efficient care and poor self-management [40,276]. One possible solution to decrease the burden on patients with CLD in China is translating CLD self-management interventions proven effective in high-resource settings to China. An example of a potentially effective nurse-led CLD self-management intervention - from the Netherlands - is called REducing Delay through edUcation on eXacerbations (REDUX).

Background

A previous intervention study in the Netherlands – led by the nurse in PC settings – examined the effects of REDUX in COPD patients in primary care (PC) settings, focusing on time spent between exacerbation recognition and seeking medical help [51]. REDUX helped COPD patients decrease the time between exacerbation onset and recognition and between the onset of an exacerbation and the point at which a patient sought medical help [51].

REDUX includes education and an action plan using a four-fold approach: (a) determining how patients can recognize early exacerbation signs, (b) recommending specific and tailored medication advice when early symptoms emerge, (c) determining an adjusted duration and dosage levels for medication usage when symptoms decrease, and (d) laying out a time frame during which patients need to seek medical help when increasing medication dosage is not working. This action plan aims to assist patients in managing their exacerbation by themselves [51]. Before implementing the action plan in practice, general practitioners (GPs) and PC nurses received training to recognize and treat exacerbations and guide patients to use the action plan [51].

There will be some adjustments in patient inclusion criteria to make REDUX more applicable to specific circumstances in China. First, the target population will be CLD patients and not just COPD patients (as was the case in the original Dutch pilot study). That will be done because there is often a misdiagnosis of COPD as asthma in China [279]. Furthermore, COPD and asthma patients have similar exacerbations that can benefit from REDUX. In line with this adjustment for the target population, we will also add inclusion criteria regarding age. There is a high prevalence in China of COPD in people aged 40 years or older and of asthma in people of age 20 years or older [7,272]. We aim to include patients with CLD of 20 years and older in China [7,272]. Yet another criterion will be added for patients who received treatment in PC settings in the past year. This criterion will be added because patients in

China who experience exacerbation can go to different PC settings or different HCPs in the same PC setting. This criterion will help ensure that patients see the same HCP for exacerbation management during the study duration, as patients who went to the same HCPs in the last year tended to go to the same HCPs for subsequent exacerbation consultations [280]. This additional inclusion criterion could help avoid the risks of missing important study data. Finally, HCPs will be trained online instead of face-to-face to reach more HCPs without undue delays created by distance and the time it takes to deliver the training. It also complies in line with social distancing regulations due to COVID-19.

Applying REDUX in a different context - from a high-income country, i.e., the Netherlands, to an LMIC, i.e., China - can help identify its effectiveness in reducing the disease burden and potential for exacerbation management outside of the Netherlands. Furthermore, it may provide insights on tailoring international self-management intervention into other contexts.

In summary, this paper describes a study that aims to examine the effectiveness of REDUX - one nurse-led self-management intervention - in patients with CLD in China. In addition, its preconditions (i.e., feasibility, appropriateness, and acceptability) will be evaluated in CLD patients and HCPs to assess whether REDUX will be successful in China.

Method

Design

The design of the study will be a single-arm pre-post study, and the study will start in October 2022. For a patient, the intervention will start when they see the nurse for the first post-exacerbation consultation and end when they present in PC for their second post-exacerbation consultation with the nurse. The reporting in this study protocol will follow the SPIRIT checklist and TIDier framework [281,282] (Appendix A). The study was registered in the Chinese clinical trial registry (ID: 2100051782).

Participants

REDUX will be conducted in Chinese PC. Patients will be invited to participate in the study by their HCPs if they: (a) are diagnosed with CLD (COPD or asthma, or COPD overlapping with asthma), (b) are aged 20 years old or older [7,272], (c) have received treatment by the HCP in a PC setting in the past year, and (d) have had a minimum of two exacerbations in the past year. Patients with mental disabilities, as diagnosed by the physician, or patients who cannot read will be excluded.

The sample size estimation of patients is based on one of the primary outcomes (i.e., the time between the onset of the exacerbation and action). The effect size used to calculate the sample size is from a study that discussed the relationship between different treatment times and health outcomes among 128 patients with COPD [249]. The study found that there was a significant difference in the effect of different treatment delays, i.e., the time from the onset of the exacerbation to the initiation of

treatment, on the recovery time (0.57 days/day delay, 0.34 to 0.79, $p < 0.001$) [249]. With the formula calculation, σ = 1.30 (i.e., $\sigma = \sqrt{n} * (upper\ limit - lower\ limit)/3.92$ = 128* (0.79 – 0.34)/3.92 = 1.30). An effect size of .43 was calculated from this (E = Δ / σ = 0.57 / 1.30 = .43). When performing a within-group comparison, a sample size of at least 43 participants is needed to detect an effect of .43 with a power of 80% and a .05 level of statistical significance [283]. Assuming a 20% dropout rate, the required sample size of patients is 54.

The sample size estimation for HCPs is based on one of the primary outcomes (i.e., the proportion of HCPs who complete the training). The proportion is from a study that identified the adoption and implementation of one intervention in PC [284]. The study found that the proportion of providers and nurses who complete the training was 57%. To achieve the same proportion of training completion, the required sample size of HCPs is 24 with a 95% confidence level and 15% of the desired margin of error [283].

Intervention

The REDUX intervention is designed to educate patients on exacerbation management by helping them to recognize their early-onset symptoms and teaching them how to react in that case. The essential part of the intervention is a personalized action plan. The action plan includes four boxes. The first box helps patients determine how they can recognize the worsening of symptoms; patients can fill in their personal, specific early signs of an exacerbation. In the second box, personalized advice is given on what medications to use in case of worsening symptoms. The third box details how long patients need to use increased medication dosage when the medication gives relief. The fourth box provides advice about what the patient should do when the symptoms worsen, specifically indicating how long the patient should wait until contacting the GP. The action plan could be accessed via the previous pilot study [51]. The training about how to coach patients using the action plan will be delivered to HCPs. HCPs, including doctors and nurses who work with CLD patients in Chinese PC, will be invited to participate in the training. Considering that the entirety of the REDUX training lasts for around three hours, we will divide the training into three consecutive sessions, with one hour per session. Every training session will be delivered to a group of three to five HCPs per week. The training will be scheduled at a convenient time for the HCPs.

After the training, the HCPs will be asked to include CLD patients when they present with an exacerbation. Their doctors will firstly treat their first exacerbation. After recovery from this exacerbation (which takes a maximum of six weeks after onset), the doctor will refer the patient to the nurse for a post-exacerbation consultation. During this consultation, the patient will receive the intervention (i.e., education and action plan). After the patient experiences another exacerbation, the nurse will - during the second post-exacerbation consultation - discuss the action plan with the patient

(i.e., how they use the action plan, whether they have reacted to the exacerbation more promptly or not, whether the action plan works or not, and why the action plan may be useful or not, and whether their recovery time is shorter than the previous occurrence).

During the first and second post-exacerbation consultations, the nurse will use a daily registration form to register the time in days between the exacerbation onset and exacerbation recognition, the time between the exacerbation recognition and action taken on the exacerbation, the time between the exacerbation recognition and point at which medical help is sought, and the time between action and improvement and recovery after each consultation. The difference in times between both exacerbation registrations will be part of the outcomes as described below. The two post-exacerbation consultations will be delivered via individual face-to-face intervention in Chinese PC. The duration of the intervention sessions will be decided by the agreement between patients and the HCPs.

Study procedures

The Chinese researcher will contact the person responsible for the original REDUX research – one nurse specialist – to ask permission to use the REDUX training and the personal action plan [51]. The content of REDUX and the personal action plan will be translated from English into Chinese. The first step will be to recruit 24 HCPs by publishing a recruitment advertisement online and sending invitation emails or messages to HCPs. The second step will be delivering the training to the participating HCPs. Considering that the entirety of the REDUX training lasts for around three hours, we will divide the training into three consecutive sessions, with one hour per session. Every training session will be delivered to a group of three to five HCPs per week. The training will be scheduled at a convenient time for the HCPs.

After the training, HCPs will be asked to include CLD patients when they present with an exacerbation. After recovery from this exacerbation (which takes a maximum of six weeks after onset) [51], the HCP should invite the patient for a post-exacerbation consultation. During this consultation, the patient will receive the intervention (i.e., education and action plan) and usual care. After the patient experiences another exacerbation, the nurse will - during the second post-exacerbation consultation - discuss the action plan with the patient (i.e., how they use the action plan, whether they have reacted to the exacerbation more promptly or not, whether the action plan works or not, and why the action plan may be useful or not, and whether their recovery time is shorter than the previous occurrence).

Data collection

Primary outcomes

HCPs will collect the following outcomes at the first and second post-exacerbation consultation: (a) the delay between exacerbation onset and recognition, (b) the delay between recognition and action,

and (c) the delay between recognition and consultation of a doctor, and (d) the moment when the patient felt better after the action or medical help from HCPs [51].

Secondary outcomes

The secondary outcomes will be evaluations of the feasibility, appropriateness, and acceptability of REDUX. These outcomes will be assessed for both patients and HCPs. In patients, feasibility will be measured with (a) the response rate, that is, the proportion of invited patients who were willing to participate (i.e., data which HCPs will provide), (b) the four-item Feasibility of Intervention Measure (FIM) (i.e., whether the intervention seems implementable, possible, doable, and easy to use) [285], and (c) an item identifying whether patients find the action plan useful. Appropriateness will be measured with the four-item Intervention Appropriateness Measure (IAM) (i.e., whether the intervention seems fitting, suitable, applicable, and matches circumstances well) [285]. Acceptability will be measured with a four-item Acceptability Intervention Measure (AIM) (i.e., which will assess whether the intervention meets the participant's approval, is appealing to the participant, whether the participant likes the intervention, and whether the participant welcomes the intervention) [285]. The items on the three questionnaires will be answered using a five-point rating scale ranging from 'completely disagree' to 'completely agree'. HCPs will collect the response rate of patients before the first post-exacerbation consultation, and the patients will complete other outcomes at the second post-exacerbation consultation. For HCPs, feasibility will be measured by (a) the proportion of invited HCPs who are willing to participate, (b) the proportion of HCPs who complete the training, and (c) FIM. The appropriateness and acceptability of REDUX will be examined with IAM and AIM. The researcher will collect the data before- and after- the training to determine the proportion of HCPs willing to participate and complete the training. HCPs will complete the three questionnaires after finishing the second post-exacerbation consultation with the last patient. All the above outcome measurements will be included in Appendix B.

Demographic and clinical characteristics

The following demographic and clinical characteristics in patients will be collected by HCPs at the first post-exacerbation consultation: age, gender, years with the disease, and disease severity based on the global initiatives for COPD [286]. The demographic characteristics of gender and years of working experience of the HCPs will be collected by the researcher before HCPs provide the first post-exacerbation consultation.

Ethical considerations

Ethics committee approval was obtained from local ethics committees in September 2021 (ZZUIRB-2021- 87). Eligible participants will be introduced to the study, including its aim and objectives, their

rights of participation and withdrawal, and the assurance of confidentiality. Their written consent will be obtained.

Data analysis

Frequencies and percentages will be used to (a) describe the categorical variables, e.g., gender and the proportion of participation rate, (b) calculate the proportion of different responses to the feasibility, appropriateness, and acceptability assessment. Mean and standard deviation will describe the continuous variables, e.g., age, years with disease and years of working experience. Wilcoxon signed-rank tests will be performed for the outcomes on delay in days between before and after the intervention. All analyses will be performed using SPSS version 23 (IBM, Armonk, USA).

Validity and reliability

All data will be carefully checked immediately after collection, and the researcher will correct any problems which may arise. The data entered into SPSS will be cross-checked for verification. Descriptive statistics will be used for data cleaning. The researchers will also be responsible for the safekeeping of the raw data to ensure confirmability.

Discussion

A previous pilot study provided preliminary evidence that REDUX was an effective self-management intervention for COPD patients for managing their exacerbations with education and creating an individualized action plan [51]. In the study being proposed here, we aim to examine the effectiveness of REDUX for patients with CLD in Chinese PC with a single-arm pre-post study design. Furthermore, the preconditions (i.e., feasibility, appropriateness, and acceptability) of REDUX will be assessed in CLD patients and HCPs in China.

REDUX is the first nurse-led self-management intervention designed for CLD patients in Chinese PC to the best of our knowledge. Necessary changes will be made in the inclusion criteria to ensure an accurate assessment of the applicability and feasibility of the intervention. The online training for HCPs will be delivered following COVID-19 distance protocols to reach more HCPs and make the self-management intervention widely available. All these changes will help adjust REDUX intervention to the Chinese context appropriately. Considering that REDUX is a tool to support and engage patients in self-managing their exacerbations, the effectiveness of REDUX will be evaluated to assess whether the intervention is effective for patients with CLD in China. In addition, the feasibility, appropriateness, and acceptability of REDUX will be measured in patients and HCPs. These aspects are not always assessed [287]. It is, therefore, necessary to assess these measurements because they are preconditions for attaining the desired service delivery and clinical outcomes [90]. Reliable and valid assessments of these measurements are essential for monitoring and evaluating the success of the REDUX intervention in China.

Nevertheless, this study has several potential limitations. One possible limitation is that we only aim to examine the REDUX intervention in PC. REDUX was initiated by the COPD & Asthma PC respiratory group in the Netherlands [51]. The REDUX intervention in this study protocol will be conducted in Chinese PC based on the previous pilot study design [51]. Therefore, the results may not be generalizable to patients treated in secondary care because REDUX has not been tested there. Future studies are needed to assess the potential of REDUX in secondary care. Furthermore, some factors may negatively influence the implementation of REDUX in China. In PC, HCPs are known to have heavy workloads, which could lead to limited time explaining REDUX to patients or helping patients self-manage their exacerbations. These factors could result in insufficient intervention. However, using REDUX in practice does not require a large time investment and – in the end – can save time for HCPs.

Conclusion

This study will contribute evidence on the potential effectiveness of the REDUX intervention in patients with CLD in China. If this intervention is found effective, the Chinese HCPs working with CLD could be trained to help their patients effectively self-manage their exacerbations with REDUX. Furthermore, data on the feasibility, appropriateness, and acceptability of the intervention in China will provide insight into whether such personalized, nurse-led self-management intervention is appropriate for patients with CLD in China. The study will help determine the feasibility of a large-scale pre-post study to evaluate the impact of the REDUX intervention in China. The experience from this study can also be used to develop other culturally-tailored self-management interventions worldwide.

Chapter 7

General discussion

Introduction

Chronic diseases such as chronic lung disease (CLD) and hypertension pose a high chronic disease burden worldwide, especially in low-and middle-income countries [1,2,6], e.g., China. Identifying effective interventions to tackle chronic diseases in these low-resource countries is necessary. The generated evidence has shown that self-management interventions (SMIs) can help patients improve their health outcomes and reduce the disease burden [19,23]. Most studies focusing on SMIs tackling chronic diseases are in high-income countries [36,37], while patients in low- and middle-income countries – such as China – show significantly poorer self-management (SM) [38-40]. Evidence has been accumulated that it is possible to implement proven-effective SMIs – developed and tested in high-income countries – in patients from low-and middle-income countries [288,289]. Implementing such proven-effective SMIs can benefit these patients [288,289]. Also, adequate knowledge about SMIs - in high-income countries - can provide precise details to optimize patient SM behaviors, such as improved medication adherence [288,289]. However, the effectiveness of such SMIs may be sub-optimal due to the different contexts with different health, economic, and cultural backgrounds [36,37]. To address these differences, it is necessary to tailor proven-effective SMIs to ensure they align with the local context [36,37,288,289]. Yet, to our knowledge, there is a lack of evidence on tailoring a SMI tackling chronic disease – developed in a high-resource country – to the Chinese context.

The main aim of this thesis was to find evidence to tailor a SMI tackling chronic disease – proven effective in high-income countries – to the Chinese context. First, this thesis provides an overview of the burden due to hypertension. Specifically, this thesis examined the association between frailty and hypertension. Second, this thesis took CLD as an example to collect evidence on tailoring a SMI tackling CLD – proven effective in high-income countries – to the Chinese context. Compared with other diseases, such as hypertension, there was a high prevalence of CLD without adequate effective treatment [54]. A four-step process of tailoring SMI for the local context was followed: (a) identify the Chinese context, (b) select SMI and mode of delivery, (c) identify factors influencing the SMI implementation, and (d) integrate SMI into the Chinese context. This chapter summarizes the main findings of the included studies and relates them to existing literature. Additionally, the study's strengths and limitations are discussed. Furthermore, this thesis presents the implications for future research and practice.

Main findings

High chronic disease burden

Chapter 2 identified the disease burden of frailty in Chinese people with hypertension. To accomplish this, a cross-sectional survey was conducted (a) to identify the prevalence of

multidimensional frailty in people with hypertension and (b) to examine a possible relationship between general obesity and abdominal obesity to multidimensional frailty in older people with hypertension. Data from 995 community-dwelling people aged 65 years or older were analyzed. This study found a high prevalence of frailty in Chinese people with hypertension (46.5%). This finding aligned with previous studies [290,291]. The high prevalence of frailty in Chinese people with hypertension indicated increased disease burden, including decreased physical function, a lower life expectancy, and higher fragile psychology [290,291]. Interestingly, abdominal obesity could be a physical, psychological, and social-frailty concern for Chinese people with hypertension, while general obesity was positively related to physical frailty. The present study also demonstrated a high prevalence of hypertension and related risk factors among the participants. It indicated the necessity to identify effective interventions to reduce the disease burden by addressing the risk factors.

Previous reviews – focusing on chronic disease burden identification – identified the high disease burden in CLD, including the high rate of disability and morbidity [10,11]. Collective evidence has shown that CLD has resulted in high healthcare costs; exacerbations accounted for most of it [12,13]. Regardless of the high disease burden, there is poor disease knowledge and SM among people with CLD [31-33]. Identifying practical interventions to reduce the high chronic disease burden is necessary.

Self-management interventions can help to reduce the chronic disease burden

Taking CLD as an example, this thesis identified helpful interventions feasible for people with CLD in China. The systematic review (**Chapter 3**) focused on the effect of blended SMI on health-related effectiveness and process outcomes of SMIs for people with chronic obstructive pulmonary disease (COPD) or asthma. The data demonstrated that SMI could help patients manage their disease actively with(out) support from healthcare professionals (HCPs), reducing the disease burden and optimizing patient outcomes. However, most included studies in the systematic reviews came from high-income countries; this identification was in accordance with previous reviews [36,37]. Such SMIs tackling CLD – developed and tested in high-income countries – may not be feasible for patients in low-resource countries, e.g., China. The data from the systematic review also reported that the SMIs – either in the model of eHealth, face-to-face, or blended care – might fail if the intervention was not feasible for the local context. For example, eHealth was sub-optimal when local people were unfamiliar with eHealth or had inadequate eHealth literacy.

This study was the first to identify the effectiveness of (blended) SMIs in people with CLD. Besides, the systematic review identified the need to tailor SMIs for people with CLD in low- and middle-income countries.

The process of tailoring CLD SMI into the Chinese context

To align SMIs with the Chinese context, it is necessary to identify the local context before the SMI implementation [288,289]. Accordingly, this thesis identified the local context, including illness perceptions, experience with, and needs for SM (**Chapter 4**). A robust mixed-method study design was employed in people with CLD and HCPs in Chinese primary care (PC) and secondary care (SC). It was observed that Chinese patients had negative illness perception, limited disease knowledge, and poor SM skills, including the recognition and action on exacerbation. Multiple needs should be addressed when identifying effective SMIs, such as the individualized SM plan, increasing disease knowledge, and eHealth use. The identified local context topics – covering the local perceptions, behaviors and unmet needs - were independent of each other. It is necessary to tailor the SMI in the Chinese context, which consequently can help to optimize patient outcomes when implementing SMIs. It was also found that the identified local context, including factors influencing SMI implementation in the Chinese context, are the main priorities in China. Conversely, the effectiveness of health programs – like SMI implementation - can be undermined when the implementation misaligns with the local context [292].

Compared with other studies identifying the local context [250,293], our study provided a complete view from stakeholders in different healthcare settings. As far as we know, this is the first study to compare patients' illness perceptions from PC and SC. For two reasons, it was essential to compare the differences between these two healthcare settings. First, the different healthcare resources in PC and SC can lead to different perceptions of the disease and treatment [243]. Second, people with CLD in China can choose to go to PC and SC depending on their disease severity and expenditure ability [253]. This study also provided a preliminary view of how the HCPs perceived the disease and their experiences with patients, which could help provide direction to tailor a SMI. To explain, HCPs have the task of identifying the cost-effective SMIs to help patients self-manage their disease. Identifying the local experiences (poor SM) and needs regarding individualized SM plans and eHealth provided direction for selecting a suitable SMI tackling CLD in the next step.

Considering the local needs, the proven-effective SMI in high-resource countries were selected in this thesis: REducing Delay through edUcation on eXacerbations (REDUX). REDUX was developed and tested in the Netherlands, a high-income country [51]. It showed a positive effect in helping patients with COPD SM [51]. Besides, the characteristic of the intervention, e.g., an individualized and easy-to-use action plan, showed a potentially positive effect on people with CLD in China. Importantly, A key aspect of REDUX is that nurses play an important role in implementing the program [51]. Nurses can positively contribute to the SMI implementation by providing education and consultation to patients [278]. Studies have shown that nurses – in high-income countries – are capable of

fulfilling extended roles; they can offer an appropriate solution to the difficulties doctors face (e.g., an increasing workload and consequently limited consultation time) [278,294]. Also, nurses can coordinate multi-disciplinary teamwork during the SMI implementation in high-income countries [278]. In comparison, Chinese nurses deliver inadequate care to secure nursing quality due to insufficient nursing staff [295-297]. At the same time, China is ongoing a healthcare reform, in which an increased nurse staff is needed, and nurses are delegated more obligations to help patients SM their disease [298]. The healthcare reform also requires nurses to improve their professional skills to deliver care [298]. To enhance the professional skills to deliver care, the lessons learned from nurse-led SMI – in high-income countries – could help Chinese HCPs to improve their professional skills [278,294,298].

Besides, the implementation of the REDUX program should address the differences in the local context. Tailoring REDUX in the Chinese context was necessary to accomplish the goal. Accordingly, the stakeholder analysis aimed to identify factors influencing the REDUX implementation in China (**Chapter 5**). To do so, multiple stakeholders, including patients, HCPs, policymakers from the healthcare setting and healthcare insurance organizations, app developers, and cyber-security officers, were included. Specifically, qualitative interviews identified the level of support for REDUX and preferred delivery mode in patients, HCPs, and policymakers. Also, the necessary conditions to develop and implement digital health apps were identified with the quantitative survey in app developers and cyber-security officers. Collecting data from multiple stakeholders involved in developing and implementing SMI can provide a complete view of the factors influencing the REDUX implementation [77].

The findings from **Chapter 5** noted that most patients, HCPs, and policymakers supported REDUX. The factors influencing the support for REDUX – including facilitators and barriers – were identified. Addressing these factors in the REDUX implementation process can help to optimize the implementation effect. This study also indicated that engaging the local stakeholders and improving their interest in REDUX could promote implementation success. These findings can be helpful for the local stakeholders to implement REDUX in China, which consequently could help people with CLD improve their health outcomes and reduce the disease burden. The preference for the delivery mode was varied, indicating that the REDUX version to use (e.g., digital or paper-based) should be tailored during its implementation in China.

The data from **Chapter 5** also identified that it was possible for the Chinese patients to make nationwide doctor appointment; this could be because there is a lack of strict referral and counter-referral system between different healthcare settings, such as SC and PC [264]. That indicated that there is still a big room to improve the healthcare referral system. Besides, the process to develop and implement the health apps was in line with the international guideline recommendations about the app

development process, design, and technical issues. Similarly, it was mentioned by most cyber-security officers that their work process aligned with the international guideline recommendations related to access control, authentication, data transfer, data retention, security and confidentiality, integrity, informing patients, body area network communication, and breach notification. The collective data showed that it was highly possible to implement REDUX in China, yet barriers should be addressed in the implementation process.

Based on the findings from **Chapter 5**, it was recommended that factors influencing SMI implementation and the implementation strategies should be tailored. The finding was in line with other studies, which demonstrated that a context-driven SMI could improve the possibility of implementing SMI successfully and optimize local resource use [46,250,271]. The similarity was that implementing SMI in a new context depends on multiple context mediators, including individual and organizational support, healthcare resources, leadership, and organizational culture and climate [46]. For example, when the local organization was supportive of the context-driven SMI, the organizational support would improve the integration of the context-driven SMI into the local organizational daily work process [46,271]. In addition, the supportive leaders, e.g., those working in the healthcare settings (nurse leaders, physician chiefs) and healthcare insurance organizations (administration managers), could assign dedicated staff to promote the SMI implementation, which helps assist the SMI implementation [46-48].

Next, the study design – focusing on implementing REDUX in China and assessing the effectiveness and the preconditions (i.e., feasibility, acceptability, and appropriateness) - was discussed in a protocol paper (**Chapter 6**). The small-scale pilot study is designed to achieve the study objective. Implementation science identifies the need for a precondition assessment, while such an assessment is lacking in previous studies [91-95]. Identifying the preconditions is necessary before the SMI implementation for two reasons. First, it could help to examine whether the SMI is tailored to the people with CLD in China. Second, these measurements could optimize local resource use before implementing the large-scale intervention.

Overall, this thesis illustrated an entire process of tailoring SMI to design context-driven interventions and improve their uptake in a different context. Furthermore, this thesis provided an overview of the local context from different stakeholders about their prevailing perceptions of lung health and lung-related SM. The collective evidence offers a starting point for further scientific research on tailoring SMI tackling chronic disease such as CLD and hypertension.

Strength and limitations

Several strengths of this thesis are worth mentioning. First, the tailored SMI tackling CLD within the Chinese context used multiple well-designed strategies, ensuring the tailoring process's validity. The

precise design allowed us to make statements about the needs and experiences in China, which can support the implementation of SMI such as REDUX. That is important because the ultimate goal of SMI is to ensure patient-centered care and delivery mode preferred by patients. The identification of contextual information can help achieve this goal. Second, multiple stakeholders were involved, thereby increasing the validity of the evidence. Previous stakeholder analysis studies on healthcare innovations were limited to the stakeholder group of policymakers, which could not represent all voices relevant when implementing the SMIs [81,82]. This thesis involved multiple stakeholders in different study phases to provide complete insights on the same topic. For example, patients, nurses, and doctors in Chinese PC and SC were included when identifying the local context. Then, the entire map of perceptions and behaviors related to SM from different stakeholders can be overviewed. Also, when identifying the factors influencing the REDUX implementation in the Chinese context, patients, HCPs, people working in healthcare insurance, app developers, and cyber-security officers were involved, which provided complete data on developing and implementing the REDUX program in China. Third, the in-time data collection and assessment were less influenced by recall bias or other confounding factors. For example, in the data collection phase of the mixed-method study, the participants were asked to complete the quantitative surveys directly after the interviews. The consequent quantitative and qualitative data assessment improves the validity of this study. Fourth, the study design and reporting guidelines were employed in the study process of the included studies. Specifically, the preferred reporting items according to the systematic reviews and meta-analysis guideline [168] were applied when conducting the systematic review. Also, the standard protocol items: recommendations for interventional trials [299], and template for intervention description and replication [300], were applied to guide the study design of REDUX for people with CLD in China. In addition, a framework approach [239] was used to guide the qualitative data analysis in the mixed-method study. Besides, a stakeholder analysis guideline [252] was used to identify the factors influencing the REDUX implementation in the Chinese context. The guidelines used in this thesis could help provide a clear and pragmatic interpretation of the recommendations for practice and further studies. Fifth, during the study process, the local stakeholders were closely connected in the research; their involvement helped to increase the possibility of successful study conduction and optimize the local resource.

Furthermore, the cooperation of the stakeholders from the Netherlands and China could pave the way for the future development and implementation of SMI in China. Specifically, REDUX was developed and tested in the Netherlands, a high-income country with a developed healthcare system. At the same time, there is plenty of room for improvement in the Chinese healthcare system, e.g., the implementation of effective SMIs, referral and counter-referral system between the PC and SC, and delivering integrated care to patients, which can optimize the SMI implementation significantly [301,302].

The international cooperation in this thesis widens the view to help deliver targeted care to patients in the low-and middle-income countries. International cooperation is of great importance. For example, the Lancet COPD commission emphasized that it was necessary to advance COPD research on effective treatment by combining all COPD communities worldwide [54].

Besides the strengths, there are also limitations within the research process that will be described below. The first limitation lies in the recruitment method, that is, the purposive sampling during the qualitative data collection. Such a sampling method is prone to selection bias [303]. We specifically used snowball sampling, a form of purposive sampling. People tend to refer those they know and have similar traits in the data collection process. And thus, this sampling method could have a potential sampling bias and margin of error. This meant that the research may have only included a selective group and the study results must be interpreted carefully. Besides, when participants know that they have already been selected for a research project, it can initiate a change in their behaviors, e.g., they may allow the researcher to reach the expected conclusion against their perceptions. To reduce the limitation of purposive sampling, the researchers used some additional methods: (a) increased the sample size in the data collection phase, and (b) included questions initiating participants to express their perceptions regarding the interview topic lists. Yet, the data interpretation should be done carefully.

The second limitation is related to the external validity of the results. Specifically, there were only a limited number of research settings were studied and the settings varied over the study projects. Accordingly, it is possible that the generalizability of the data to the Chinese context can be sub-optimal. To explain, the mixed-method study focusing on the local context was collected in a regional location, i.e., Henan province. Whereas the data in the stakeholder analysis study was collected from eight provinces. Considering that there is significant healthcare resource inequality and diverse customs within different provinces in China, with 31 provinces including a population of over 1.45 billion, data from our included participants in this thesis (in total 1173) possibly could not represent the voice all over China. Thus, caution must be taken to translate the results nationwide.

Due to the limited time and COVID regulations in China, the REDUX implementation was planned, but the actual implementation of it was not (yet) conducted. Evaluating the effect of REDUX takes considerable time because the effect during research is measured between two consecutive exacerbations[51]. In the past four years, China has strictly followed the COVID regulations, which meant that the healthcare focus – in Chinese PC and SC - was COVID vaccination and tests with inadequate attention on chronic disease management. The delayed implementation of the intervention in practice leads to the fact that the effect and preconditions of REDUX on Chinese people are still unknown. Therefore, the thesis should be interpreted cautiously due to the mentioned limitations.

Recommendations for future research

The findings in this thesis have demonstrated that mapping the local context is essential for researchers to tailor SMI tackling CLD. The identified contextual factors can improve the possibility of implementation success and optimize local resource use. During the local context identification, we cooperated with local stakeholders. In particular, we involved the local HCPs and policymakers; they motivated other people to be involved in the research and facilitated communication with the local participants. To promote the practical relevance of the SMI, it is vital to co-cooperate with the local stakeholders. Accordingly, identifying local beliefs and behaviors is recommended before the SMI implementation. That is, the implementors should address different contexts when implementing the SMI. It can be explained that people - between China and high-income countries - have different experiences and perceptions on the same topic.

Similarly, there are different strategies for managing CLD in these countries. Before implementing SMI such as REDUX in China, the local context should be addressed. Therefore, future researchers should emphasize the type of proven-effective SMI and local context identification to observe the feasibility of implementing the SMI. Also, the facilitation for the SMI implementation should be addressed to optimize the possibility of implementation success.

As mentioned, China is undergoing a new healthcare reform [88] and has published the updated healthcare policy, i.e., Healthy 2030 [72]. Both health innovations have addressed the importance of improving patient SM and reducing disease burden. A critical reason for the high support level for REDUX was its response to the Chinese healthcare reform priority. The experience of coping with COVID within China has demonstrated the ability of humans to rapidly adapt behaviors to improve health once the sense of urgency is sufficiently high [304]. Therefore, it is recommended that the implementers focus on the SMI that responded to the policy priority. The following approaches should be addressed when implementing SMI in future research. First, it is necessary for the policymakers to address the importance of SMI when determining the Chinese healthcare policy priority [305], e.g., facilitating and training patients to acquire lifelong skills to manage their disease. Second, identifying the appropriate theories [306,307], such as social learning theory and cognitive–behavioral concepts and acceptance, underpin course design, which can help develop future research directions in SMI. Third, it is recommended to identify the factors influencing SMI implementation under the existing healthcare policy priority; this can help optimize SMI uptake and implementation.

This thesis offers a starting point for further scientific research on reducing the chronic disease burden; this is important because the identification of tailoring SMI into the local context can improve the possibility of implementing SMI successfully. Future research must demonstrate the added value of addressing the tailoring steps in practice. In addition, even though REDUX has not been validated

for settings other than PC, it may have potential in secondary or tertiary care. Hence it is proposed to examine its validity in these settings in future studies as well. Besides, it was evidenced in this thesis that positive illness perceptions were highly relative to optimized patient SM and vice versa. However, it is unclear whether the positive belief in SMI can optimize the effect of SMI. The current evidence has demonstrated that positive patient beliefs about the likely success of medication intervention have been associated with improved patient health outcomes [308]. Thus, future research is needed to identify the association between positive patient beliefs and the effect of SMI. Importantly, researchers are recommended to identify what kinds of positive patient beliefs can influence which intervention outcomes, such as health-related effectiveness and process outcomes, and the mechanisms of how the positive patient belief and intervention outcomes are related. SMI combined with eHealth can help people with CLD to manage this disease by engaging them in self-care tasks, which foster behavior change toward better health [309]. However, attrition can be problematic when neglecting individual factors, such as the value of the users, e.g., personal-psychological situation [310]. It is recognized that theory-based SMI can help to solve such problems with strategies [311,312]. For example, behavior change techniques can aid in enhancing SMI with strategies, e.g., goal setting, action planning, self-monitoring, problem-solving, and goal review [309,313]. Therefore, in future studies, it is necessary to identify whether the behavior change techniques in SMI can result in substantial positive changes in patient health behaviors and psychological outcomes.

Furthermore, this thesis specifically covered the tailoring of REDUX to the Chinese context, but the broad use of the tailoring process is unclear. From the perspective of effectiveness and efficiency, it is necessary to identify the effectiveness and preconditions of such an intervention with a pilot study in practice before the full-scale implementation and evaluation. It is also suggested to expand the tailoring process in the SMI to other chronic diseases, such as hypertension, a chronic disease with a prevalence of 27.5% in the Chinese people [314]. To apply such a process to other chronic disease management, the factors should be specific to the particular disease-related context rather than the one-to-all model [315]. It is also plausible that the tailoring process could be generalized to other low- and middle-income countries, yet this remains to be assessed. The methods and lessons in the implementation process can boost the implementation of SMI in different contexts.

Practical implications and recommendations

Enhance the knowledge of disease and awareness of SMIs

This thesis reported poor disease knowledge and sub-optimal SM in Chinese people with CLD. Targeted efforts to increase knowledge of disease and SMI will be useful to reduce the disease burden [54]. Several methods can be helpful for this. First, it is urged to educate patients on the disease, e.g., the

risk factors and development of the disease and the benefits of SMIs, including decreased admission and medication use, which can optimize the effect of SMIs. Second, for future SMIs, efforts to slow down the CLD progression should focus on early disease identification and improve treatment efficacy. Thirdly, undergraduate medical and nurse students should be trained to deliver SMIs to patients and target the SMI delivery model for different patients in their vocational training.

Enrich the SMI delivery technique and mode

In recent years, healthcare systems in many countries have invested substantial effort in developing eHealth to reduce the burden of CLD [316,317]. SMIs tackling CLD combined with eHealth can help patients SM their disease without the time and place restrictions, which will benefit patients [24]. Currently, eHealth literacy is a lack in Chinese patients. In the updated Chinese healthcare policy, it has been required to promote the use of eHealth and increase eHealth literacy in Chinese people [72]. One possible way is for HCPs to promote eHealth use to facilitate communication, stimulate the demand for services, and increase access to health information for disease management.

Additionally, it is expected to apply meta-universe technology, e.g., virtual reality and artificial intelligence, in SMI delivery. Meta-universe technology allows HCPs to share their knowledge with patients and to communicate their experience without words to their doctors, allowing for powerful and effective communication, enhanced awareness of the disease, and potential interventions [318,319]. Assessing the effect of SMI with meta-universe technology on people with CLD in practice is necessary. It is recommended to apply such technologies in SMI tackling CLD to increase patient engagement and help patients enjoy the intervention process.

Extend the networks with different stakeholders

Eliminating CLD requires consistent and coordinated action from multiple stakeholders, such as physicians, general practitioners, social workers, physiotherapists, people working on healthcare insurance, and nurses, in healthcare practice. The multiple-disciplinary collaboration has effectively delivered patient-centered care with consistent medical advice, which can improve patient health outcomes and reduce healthcare costs [320,321]. The multiple-disciplinary collaboration requires shared consultations, collaboration via referral, and counter-referral between different healthcare settings, e.g., between SC and PC [321]. Currently, the Chinese healthcare system is devoted to promoting multiple-disciplinary collaboration. Still, there is a need for more cooperation between different level healthcare settings, e.g., between SC and PC, and this is one major challenge in existing care provision [322,323]. For example, the lack of the counter-referral from SC to PC and fixed HCP barrier the multiple-disciplinary collaboration[323]. To tackle the missing coordination, multiple strategies should be developed and applied. First, the Chinese healthcare reform should put effort into advancing the referral and counter-referral system between Chinee PC and SC. Secondly, the patients must have a

physician and/or general practitioner or nurse who can help provide unified, integrated care and navigate the way of multiple disciplinary cooperation. For example, in Chinese PC, the general practitioner or doctor is the first point of contact for patients and provides access to services in collaboration with other HCPs. Thirdly, interprofessional education programs should be introduced to help provide comprehensive and continuous care. The lessons of multiple-disciplinary cooperation from high-income countries could be helpful for Chinese HCPs. Furthermore, diagnosis-related reimbursement in the SC should also be applied in PC since such healthcare settings ensure people receive quality comprehensive care - from promotion and prevention to treatment and rehabilitation - as close as feasible to people's everyday environment [324].

Leadership engagement in the Chinese context – engagement of nurse leaders and chief physicians – can also improve the SMI uptake. That is related to the hierarchical management structure in China [325,326]. The health bureau's executive leaders in healthcare institutions are appointed administratively in China. Additionally, even though institutions are endowed with a certain autonomy, coordinated by the upper government, executives are willing to take measures because the promising effect of these SMI could be seen during their tenure [327]. Therefore, leadership engagement is necessary to ensure the SMI is implemented timely. To realize this, it is advocated to cooperate with such stakeholders at the start of SMI implementation, which can help to optimize the uptake of the proven-effective SMIs and assign the prioritized resource to promote the SMI implementation.

Moreover, by collaborating with international researchers and HCPs, the context-driven approaches can be improved under the global vision. Currently, China is undergoing a round of health reform; the perspectives outside of the box can result in inventive solutions to the diploma in the healthcare field, e.g., implementing the cost-effective SMIs, proven-effective in high-income countries, coping with chronic disease in the Chinese context. Cooperating with the organization – focusing on reducing the chronic disease burden – facilitates SMI implementation in low-resource settings. For example, the World eHealth Living Lab (WeLL) was created in the Netherlands, which is the independent knowledge platform for eHealth research, development and implementation. Such a platform promotes communication and cooperation among policymakers, HCPs, researchers, and health-related companies worldwide. Within the research presented in this thesis, the research team – from WeLL, affiliated with the Leiden University Medical Center, and Faculty of Nursing and Health, Zhengzhou University, Faculty of Nursing and Health, Henan University, and Henan Provincial People's Hospital – shared insights and knowledge in the field of tailoring a SMI tackling CLD. From our experience, the collaborative effort can promote the tailoring and implementation of a SMI at an international level. Specifically, with the guidance and supervision of an experienced research group in the Netherlands, Chinese HCPs implement the SMI developed and tested in the Netherlands, which

can facilitate the widespread use of proven-effective SMIs. At the same time, Chinese researchers and HCPs can benefit from international networks and receive professional research and clinical training from high-income countries. Future cooperation between WeLL and Chinese stakeholders on the development and implementation of SMI tackling CLD will continue.

Conclusion

In conclusion, the high chronic disease burden of hypertension and CLD in China requires an urgent need to implement SMIs. This thesis mapped the four-step tailoring process – including the local context identification, selection of the SMI and mode of delivery, identification of the factors that influence the SMI implementation, and integration of SMI into the local context – before implementing the SMI into practice. Tailoring the SMI implementation was recommended to help reduce the implementation failure and optimize local resources' use. Ultimately, the tailored SMI aims to improve health outcomes and reduce the disease burden. It is plausible that the tailoring process could also be generalized to other chronic diseases, such as hypertension.

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Addendum

Summary

Chronic lung disease (CLD) and hypertension can cause significant disease burdens, and people with chronic diseases are more likely to report experiencing severe physical, psychosocial, and lifestyle consequences. In addition, the health-related costs of chronic disease represent a substantial economic burden. **Chapter 1**, the Introduction, summarizes the current evidence regarding the self-management of patients with chronic disease. This chapter also discusses the benefits of self-management intervention (SMI) for reducing the disease burden. Most research on SMIs for people with chronic diseases has been conducted in high-income countries, while low- and middle-income countries face a high chronic disease burden.

Given the high disease burden of chronic diseases in low- and middle-income countries, for example, China, it is essential to identify effective SMIs that can improve the health of these patients and reduce the disease burden. Existing SMIs have mainly been developed and studied in high-income countries, where they have shown promising effects on health. However, Implementing such intervention in China may fail if the (healthcare) context, such as cultural background and the economy, needs to be considered. To successfully implement SMIs that have shown positive effects in high-income countries in the Chinese context, it is necessary to tailor the intervention to tackle CLD in China. Therefore, this thesis aims to tailor a proven effective SMI for implementation in China. To do this, four steps are taken, namely (1) identifying the Chinese context, (2) selecting the SMI and the mode to deliver the SMI, (3) identifying factors influencing the implementation of the SMI, and (4) integrating the SMI in the Chinese context. The thesis focuses on SMIs for CLD. The method applied and the knowledge gained can also be used by researchers for other chronic conditions.

Chapter 2 examined the disease burden of Chinese people with chronic disease. It focused on the disease burden experienced by Chinese people with hypertension. The prevalence of frailty among these patients and the risk factors contributing to the high disease burden were identified. The identification was made through a cross-sectional study in Chinese primary care. Nine hundred and ninety-five participants completed the quantitative survey. It was shown that the prevalence of frailty among Chinese people with hypertension was 46.5%. Factors associated with frailty were: higher age, female gender, co-morbidity, alcohol use, and having no partner. The results showed that multiple risk factors were associated with the disease burden in Chinese people with hypertension. To address the disease burden of hypertension and other chronic diseases in China, effective interventions must be implemented to address the previously identified risk factors.

In **Chapter 3**, a systematic literature review and meta-analysis was conducted to gain insight into the effectiveness of blended interventions for people with a CLD. A total of 22 randomized controlled studies were included. These studies examined SMIs that combined face-to-face treatment

with eHealth. The results showed that these interventions could positively affect physical functioning, body mass index (BMI), and quality of life. SMIs can potentially improve health outcomes in people with a CLD, but tailored intervention strategies are needed to optimize the effectiveness of these interventions. As described in **Chapter 1**, the included studies were mostly conducted in high-income countries. In contrast, research on the effectiveness of SMIs for people with CLD in low- and middle-income countries, such as China, needs to be completed.

To successfully implement a proven effective SMI in another context (i.e., China), it is necessary to identify the local context. In **Chapter 4**, mixed-method research was conducted among people with CLD and healthcare providers in Chinese primary and secondary care. In total, 52 participants completed semi-structured interviews, and 48 of the 52 also completed a questionnaire. The results showed that Chinese people with CLD have poor disease perception. They often lack knowledge about the condition and have poor disease control. Furthermore, most participants needed better self-management skills, preventing them from promptly recognizing exacerbations and taking action. Several factors were identified that influence the self-management skills of patients in China, such as insufficient knowledge about the disease and limited ability to bear medical costs. Finally, the needs for self-management were mapped out. Increasing knowledge about the disease was an identified need among patients and healthcare providers and can help facilitate patient self-management. Additionally, eHealth and an individualized self-management plan were mentioned as possible strategies for improving skills. The findings from this chapter can be taken into account when developing SMIs. Finally, the identified factors and needs for self-management have provided information for the next tailoring step, namely selecting the SMI and the mode of delivery.

In **Chapter 5**, the REducing Delay through edUcation on eXacerbations (REDUX) program was selected as the intended SMI for two reasons. First, REDUX, as an individualized self-management plan, is easy to use and promotes interaction between patients and healthcare providers. Second, the paper version of REDUX has shown a positive effect on the self-management of exacerbations in the Netherlands. Since blended interventions can improve physical function in people with CLD, this chapter will also investigate which mode of delivery of REDUX is preferred in the Chinese context (e.g. digital or paper-based).

To tailor REDUX to the Chinese context, **Chapter 5** identifies the factors that can influence the implementation of REDUX in China. The level of support for REDUX, factors influencing support, and preferred mode of providing REDUX were identified in patients, caregivers, and policymakers. Additionally, the necessary conditions for developing and implementing a digital version of REDUX were investigated among app developers and cyber security officers. A stakeholder analysis was applied using qualitative interviews with patients, healthcare providers and policymakers (n = 35) and

a quantitative questionnaire among app developers and cyber-security officials (n = 87). Most patients, healthcare providers, and policymakers supported REDUX to a high degree. Multiple facilitators (e.g. interaction between patient and healthcare provider, involvement of doctors) and barriers (e.g. patients being unable to afford medication, lack of policy support) were identified. The preferred mode to deliver REDUX varied for different reasons. Most app developers and cyber security officers agreed that their processes for developing and implementing health apps align with related international guidelines. The identified factors can help with the successful implementation of REDUX.

To integrate REDUX in the Chinese context, a small-scale pilot study is needed to evaluate the REDUX program's effectiveness and preconditions (i.e., feasibility, acceptability, and suitability). The research protocol for the pilot study is described in **Chapter 6**. Forty-four patients and 24 healthcare providers will be included in Chinese primary care. The intervention starts when a patient, after an exacerbation, is referred to the nurse for a post-exacerbation consultation. The research ends when the patient, after a subsequent exacerbation, presents again for a second post-exacerbation consultation. The study is to identify whether the intervention reduces the time between the onset of an exacerbation and its recognition and whether it reduces the time between the onset of the exacerbation and the moment a patient seeks medical help. The preconditions will be measured to evaluate whether REDUX is sufficiently adapted to the Chinese context. The results of this pilot study can indicate whether a large-scale REDUX implementation (study) is feasible. Implementing the REDUX program in the Chinese context can help Chinese healthcare providers to provide efficient care and reduce their workload. Moreover, the proposed study will facilitate future research into tailoring SMIs in different contexts.

The general discussion, **Chapter 7**, presents the main findings of this dissertation. Additionally, future research recommendations on implementing SMIs in the Chinese context and optimizing tailoring steps are discussed. Practical implications and recommendations are also presented - on increasing knowledge of the disease and awareness of SMI, improving the technology and mode to deliver SMIs and expanding networks with different stakeholders - to support the successful implementation of SMIs. This thesis is critical for tackling CLD and tailoring SMIs, which can improve the health outcomes of patients and promote the use of local resources. This thesis is also the first to focus on tailoring SMIs for Chinese individuals with CLD. The research methods and results can be used to develop and implement culturally sensitive SMIs.

Samenvatting

Aandoeningen zoals chronische longziekte (CLZ) en hypertensie kunnen een aanzienlijke ziektelast veroorzaken. Mensen met chronische ziekten melden vaker ernstige lichamelijke, psychosociale en leefstijlgevolgen te ervaren. Daarnaast vormen gezondheid gerelateerde kosten van chronische ziekten een substantiële economische last. **Hoofdstuk 1**, de Inleiding, gaat dieper in op de actuele evidentie met betrekking tot zelfmanagement van patiënten met een chronische ziekte. Ook worden in dit hoofdstuk de voordelen van zelfmanagement interventies (ZMI) voor het verminderen van de ziektelast besproken. Veel onderzoek naar ZMIs voor mensen met chronische ziekten is uitgevoerd in hoge inkomenslanden, terwijl lage- en middeninkomenslanden juist te maken hebben met een hoge ziektelast door chronische ziekten.

Gezien de hoge ziektelast van chronische ziekten in landen met een laag- en middeninkomen, zoals China, is het belangrijk om effectieve ZMIs te identificeren die de gezondheid van deze patiënt kunnen verbeteren en de ziektelast kunnen verminderen. Bestaande ZMIs zijn voornamelijk ontwikkeld en onderzocht in hoge inkomenslanden, waar ze veelbelovende effecten op gezond hebben laten zien. Echter is de kans groot dat de implementatie van dergelijke interventies in China mislukt wanneer er geen rekening wordt gehouden met de (zorg) context, zoals culturele achtergrond en de economie. Om ZMIs, die positieve effecten hebben laten zien in hoge inkomenslanden, succesvol te implementeren in de Chinese context is het noodzakelijk om de interventie goed aan te laten sluiten bij de aanpak van CLZ in China. Daarom heeft dit proefschrift tot doel een bewezen effectieve ZMI op maat te maken voor implementatie in China. Hiervoor worden vier stappen doorlopen, namelijk (1) het identificeren van de Chinese context, (2) het selecteren van de ZMI en de wijze van aanbieden, (3) het identificeren van factoren die van invloed zijn op de implementatie van de ZMI en (4) het integreren van de ZMI in de Chinese context. Het proefschrift is gericht op ZMIs voor chronische longziekten. De methode die wordt toegepast en de kennis die hiermee is opgedaan, kan door onderzoekers ook gebruikt worden voor andere chronische aandoeningen.

In **Hoofdstuk 2** is de ziektelast van Chinezen met een chronische ziekte onderzocht. Hierbij is gefocust op de ziektelast ervaren door Chinezen met hypertensie. Er is onderzocht wat de prevalentie van de kwetsbaarheid was bij deze patiënten en welke risicofactoren bij hebben gedragen aan de hoge ziektelast. Dit is gedaan door middel van een cross-sectioneel onderzoek in de Chinese eerstelijnszorg. Negenhonderdvijfennegentig deelnemers vulden de kwantitatieve enquête in. Er werd aangetoond dat de prevalentie van kwetsbaarheid bij Chinezen met hypertensie 46,5% was. Factoren die geassocieerd waren met kwetsbaarheid zijn: hogere leeftijd, vrouwelijk geslacht, co-morbiditeit, alcoholgebruik en het hebben van geen partner. De resultaten lieten zien dat meerdere risicofactoren geassocieerd zijn met de ziektelast bij Chinezen met hypertensie. Om de ziektelast van hypertensie en andere chronische

aandoeningen in China aan te pakken, is het noodzakelijk om effectieve interventies te implementeren waarbij de eerder gevonden risicofactoren worden aangepakt.

In **Hoofdstuk 3** is er een systematisch literatuuronderzoek en meta-analyse uitgevoerd om inzicht te krijgen in de effectiviteit van ZMIs voor mensen met een CLZ. In totaal zijn 22 gerandomiseerde gecontroleerde studies meegenomen. In deze studies werden ZMIs onderzocht die face-to-face behandeling combineerde met eHealth, ook wel blended interventies genoemd. De resultaten lieten zien dat deze interventies een positief effect kunnen hebben op lichamelijke functioneren, body mass index (BMI) en kwaliteit van leven. ZMIs hebben dus potentie om gezondheidsuitkomsten te verbeteren in mensen met een CLZ, maar op maat gemaakte interventiestrategieën zijn nodig om de effectiviteit van deze interventies te optimaliseren. Zoals in **Hoofdstuk 1** beschreven is, zijn de geïncludeerde studies vooral uitgevoerd in hoge inkomenslanden, terwijl het onderzoek naar de effectiviteit van ZMIs voor mensen met een CLZ in lage- en middeninkomenslanden, zoals China, ontbreekt.

Om een bewezen effectieve ZMI succesvol te implementeren in een andere context (i.e., China), is het nodig om de lokale context te identificeren. In **Hoofdstuk 4** is daarom een mixed-method onderzoek uitgevoerd onder mensen met een CLZ en zorgverleners in zowel de Chinese eerste- als tweedelijns zorg. In totaal zijn er semi-gestructureerde interviews gehouden met 52 deelnemers en hebben 48 deelnemers de vragenlijst ingevuld. De resultaten toonde aan dat Chinese mensen met een CLD een slechte ziekteperceptie hebben. Zo hebben ze vaak gebrek aan kennis over de aandoening en een slechte ziektecontrole. Bovendien hadden de meeste deelnemers slechte zelfmanagement vaardigheden, waardoor zij exacerbaties niet tijdig herkennen en laat actie ondernemen. Er zijn meerdere factoren geïdentificeerd die zelfmanagement vaardigheden van patiënten in China beïnvloeden, zoals onvoldoende kennis over de ziekte en beperkte mogelijkheden om medische kosten te dragen. Ten slotte, zijn de behoeftes voor zelfmanagement in kaart gebracht. Het vergroten van kennis over de ziekte was een geïdentificeerde behoefte bij zowel patiënten als zorgverleners, en kan helpen om de zelfmanagement van patiënten faciliteren. Daarnaast werd eHealth en een geïndividualiseerd zelfmanagement plan benoemd als mogelijke strategieën voor het verbeteren van zelfmanagement vaardigheden. De bevindingen uit dit hoofdstuk kunnen mee worden genomen bij de ontwikkeling van ZMIs. Tenslotte, de geïdentificeerde factoren en behoeften voor zelfmanagement hebben informatie opgeleverd voor de volgende aanpassingsstap, namelijk het selecteren van de ZMI en de wijze van levering.

In **Hoofdstuk 5** is het REducing Delay through edUcation on eXacerbations (REDUX) programma om twee redenen geselecteerd als de beoogde ZMI. Ten eerste, is REDUX, als geïndividualiseerd SM-plan, eenvoudig te gebruiken en bevordert het de interactie tussen patiënten en

zorgverleners. Ten tweede heeft de papieren versie van REDUX in Nederland een positief effect laten zien op de zelfmanagement van exacerbaties. Aangezien blended interventies potentie hebben voor het verbeteren van lichamelijk functioneren bij mensen met een CLZ, zal er in dit hoofdstuk ook onderzocht worden welke aanbiedingswijze van REDUX in de Chinese context wordt geprefereerd (e.g. digitaal of op papier).

Om REDUX aan te passen naar de Chinese context, worden in **Hoofdstuk 5** de factoren geïdentificeerd die de implementatie van REDUX in China kunnen beïnvloeden. In patiënten, zorgverleners en beleidsmakers is gekeken naar het niveau van steun voor REDUX, factoren die de steun beïnvloeden, en de voorkeursmethode voor het aanbieden van REDUX. In app-ontwikkelaars en cyber-security functionarissen is onderzocht wat de noodzakelijke voorwaarden zijn om een digitale versie REDUX te ontwikkelen en te implementeren. Een stakeholderanalyse is toegepast met behulp van kwalitatieve interviews bij patiënten, zorgverleners en beleidsmakers (n = 35) en een kwantitatieve vragenlijst bij app-ontwikkelaars en cyber-security functionarissen (n = 87). De meeste patiënten, zorgverleners en beleidsmakers ondersteunden REDUX in hoge mate. Meerdere facilitators (e.g. de interactie tussen patiënt en zorgverlener, betrokkenheid van artsen) en barrières (e.g. het niet kunnen veroorloven van medicijnen door patiënten, het gebrek aan beleidsmatige ondersteuning) werden geïdentificeerd die de ondersteuning beïnvloeden. De voorkeur voor de aanbiedingswijze van REDUX varieerde om uiteenlopende redenen. De meeste app-ontwikkelaars en cyber-security functionarissen waren het erover eens dat hun werkproces bij het ontwikkelen en implementeren van gezondheids-apps in overeenstemming is met gerelateerde internationale richtlijnaanbevelingen. De geïdentificeerde factoren kunnen helpen bij de succesvolle implementatie van REDUX.

Om REDUX in de Chinese context te integreren is er een kleinschalige pilotstudie nodig om de effectiviteit en randvoorwaarden (i.e., haalbaarheid, aanvaardbaarheid en geschiktheid) van het REDUX-programma te evalueren. Het onderzoeksprotocol voor de pilot studie wordt beschreven in **Hoofdstuk 6**. Vierenvijftig patiënten en 24 zorgverleners zullen worden geïncludeerd uit de Chinese eerstelijnszorg. De interventie start wanneer een patiënt, na een exacerbatie, wordt doorverwezen naar de verpleegkundige voor een post-exacerbatieconsult. Het onderzoek eindigt wanneer de patiënt, na een opvolgende exacerbatie, zich opnieuw presenteert voor een tweede post-exacerbatieconsult. Er wordt onderzocht of de interventie de tijd verkort tussen het ontstaan van een exacerbatie en het herkennen hiervan en of het de tijd verkort tussen het ontstaan van de exacerbatie en het moment waarop een patiënt medische hulp zoekt. De randvoorwaarden worden gemeten om te beoordelen of REDUX voldoende is aangepast naar de Chinese context. De resultaten van deze pilot studie kunnen uitwijzen of een grootschalige REDUX-implementatie (studie) gerechtvaardigd is. Het implementeren van het REDUX programma in de Chinese context kan Chinese zorgverleners helpen om efficiënte

zorg te bieden en hun werkdruk te verminderen. Bovendien zal de voorgestelde studie toekomstig onderzoek naar het op maat maken van ZMIs in verschillende contexten faciliteren.

In de algemene discussie, **Hoofdstuk 7**, worden de belangrijkste bevindingen van dit proefschrift gepresenteerd. Daarnaast worden aanbevelingen voor toekomstig onderzoek - gericht op het implementeren van ZMIs in de Chinese context en het optimaliseren van de maatwerkstappen - besproken. Ook worden de praktische implicaties en aanbevelingen gepresenteerd - over het vergroten van de kennis van de ziekte en de bekendheid van ZMI, het verbeteren van de techniek en de wijze van aanbieden van ZMIs, en het uitbreiden van de netwerken met verschillende belanghebbenden - om de succesvolle implementatie van ZMIs te ondersteunen. Dit proefschrift is van cruciaal belang voor de aanpak van CLZ en het op maat maken van ZMIs, wat de gezondheidsresultaten van patiënten kan verbeteren en het gebruik van lokale middelen kan bevorderen. Dit proefschrift is ook het eerste dat zich richt op het op maat maken van ZMIs voor Chinezen met CLZ. De gebruikte onderzoeksmethode en de onderzoeksresultaten kunnen worden gebruikt om ZMIs op basis van culturele kenmerken te ontwikkelen.

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Curriculum vitae

Xiaoyue Song was born on May 1st, 1993, in Xunxian, Henan province, China. She began her undergraduate studies in nursing science at Henan University in September 2011 and obtained her bachelor's degree in July 2015. Subsequently, she pursued a master's degree in community and elderly nursing at Zhengzhou University starting in September 2015. Her master's thesis, titled "A study on the effect of a home-based exercise intervention on hypertensive patients with frailty," was completed under the guidance of Prof. dr. Weihong Zhang, and she graduated in July 2018. Xiaoyue Song was awarded the "National Scholarship" during both her undergraduate and graduate studies, as well as the titles of "Outstanding Graduate Student of Henan Province" and "Outstanding Graduate Student of Zhengzhou University."

In September 2018, Xiaoyue Song received financial support from the China Scholarship Council to pursue her doctoral research in the Department of Public Health and Primary Care at the Leiden University Medical Center in the Netherlands, under the supervision of Prof. dr. Niels Chavannes, Dr. Anke Versluis, Mw Cynthia Hallensleben, and Prof. dr. Robbert J.J. Gobbens. During her PhD, she collaborated with Prof. dr. Weihong Zhang from Zhengzhou University and Dr. Bo Li from Henan University. Her research focused on tailoring a self-management intervention for chronic disease management to the Chinese context, using a Dutch program that had proven effective. The Chinese government has funded Xiaoyue Song's PhD studies, and the results of her research are presented in this thesis.

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