Tackling chronic respiratory disease in low-resource settings

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Exploring, engaging, and leveraging local contexts to facilitate successful implementation of lung health programmes

Evelyn Brakema

Tackling chronic respiratory disease in low-resource settings – Exploring, engaging, and leveraging local contexts to facilitate successful implementation of lung health programmes

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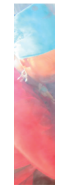
If you think you are too small to make a difference, try sleeping with a mosquito.
[African proverb]

CONTENTS

CHAPTER



GENERAL INTRODUCTION

GENERAL INTRODUCTION

A story of chronic respiratory disease in a setting where resources are limited

The story of Asel

In a mountaneous village in Kyrgyzstan, Central-Asia, lives a proud mother of three. While her husband herds the sheep, Asel takes care of the children. Every day, she keeps them by her side while she spends several hours cooking, just like her mother had done when Asel herself was a little girl. Asel cannot afford gas or electricity, but luckily dung from the sheep is a free and easily available fuel.

Asel's husband is a smoker. In combination with burning the dung for heating and cooking, the house becomes quite smoky. One day, people from the capital, or maybe even further away, had given her a special cookstove. They said this stove was better, but it was not true. The food had no taste and the stove generated less heat. The low temperatures in winter required Asel to use their traditional stove besides the new one, until at some point her husband needed the metals of that stove and now the remainders are still stored behind the house.

For the last three years, Asel notices that she feels tired and breathless more quickly than others of her age. She has a constant cough that produces sputum, especially in the mornings. It has been increasing over time, and now makes it harder to carry the dung uphill. Once the nurse had given her antibiotics, but these did not help. It's not clear what's going on, probably something with the lungs because of the cold weather.

The story of Asel is a story of chronic respiratory disease (CRD) in low-resource settings, of exposure to risk factors (already affecting health before birth), of health perceptions and behaviours, social structures, and the socioeconomic impact of chronic respiratory symptoms. It also shows the importance of aligning health interventions with their contex and the consequences of failure to do so. In this thesis, the elements of the story are studied in depth. Together, these elements form an image that shows the importance of understanding CRD in its context, and how to design and implement context-driven lung health interventions that people adhere to over time.

The burden of chronic respiratory disease is highest in low- and middle-income settings

CRD is a silent, growing pandemic. Most prevalent is chronic obstructive pulmonary disease (COPD), followed by asthma (Box 1). COPD has become the third cause of death worldwide, annually killing 3.3 million people. This accounts for 5.8% of all deaths, which is more deaths than HIV, malaria and tuberculosis combined.[1,2] Although the highest prevalence of CRD occurs in high-income countries (HICs) with ageing populations,[3] the highest burden of disease occurs in low-and middle-income countries (LMICs), where 90% of the COPD-related deaths and most of the asthma-related deaths occur.[4,5]

Unlike infectious diseases such as pneumonia and COVID-19, manifestations of CRD develop slowly and silently. Meanwhile, especially due to its chronic nature, CRD severely impacts people's lives. COPD ranks sixth for global DALYs (74.4 million) and asthma ranks 34th (21.6 million); most DALYs occur in LMICs.[3] Besides the direct burden, CRD also has a high socioeconomic impact. CRD can severely impair daily activities; patients are more likely to miss school or work, and suffer from social isolation.[6-8]

Chronic respiratory disease

The category 'chronic respiratory disease' (CRD) includes chronic obstructive pulmonary disease (COPD), asthma, pneumoconiosis, interstitial lung disease and pulmonary sarcoidosis, and others. In this thesis, 'CRD' refers to COPD and asthma, which together constitute around 90% of the global burden of CRD.[9]

COPD:

COPD is a slowly progressive, inflammatory disease affecting the airways and alveoli. COPD includes emphysema and chronic bronchitis, and is characterised by a persistent reduction of airflow. The most common symptoms are breathlessness, chronic cough, and sputum production. In time, patients can experience problems in daily activities (walking upstairs and even getting dressed). Patients can suffer from episodes of severe symptoms that last from several days to weeks. Such exacerbations can be seriously disabling, require urgent medical care including hospitalisation, and may result in death.[4]

Asthma:

Asthma is characterised by recurrent attacks of breathlessness and wheezing caused by inflammation, and hence narrowing, of the airways. Symptoms vary in severity and frequency from person to person. Triggers for the attacks include indoor allergens (house dust mites in carpets), outdoor allergens (pollens), tobacco smoke, occupational irritants or air pollution.[5] COPD and asthma cannot be cured; treatment is focused on disease control. If managed well as a chronic condition, symptoms can be relieved, quality of life improved, and risk of death reduced.[5,10]

Contributors to the high burden of chronic respiratory disease in low- and middle-income settings

High exposure to risk factors

An important reason for the high burden of CRD is the high exposure to risk factors in LMICs. First, tobacco is traditionally considered the main risk factor to CRD; for men tobacco is the leading risk factor for CRD-related disabilities.[11] Over 80% of the tobacco users live in LMICs.[12] While tobacco use is decreasing globally, in many LIMCs the rate of tobacco use is still rising.[13] Tobacco prevention and cessation policies are less in place in LMICs; even more so, marketing campaigns of tobacco companies have recently switched to target these areas.[12] Second, air pollution is now recognised as another major risk factor, and the leading cause for CRD-related disabilities among women. The process of rapid industrialisation and urbanisation in LMICs is accompanied by still rising levels of ambient air pollution, whereas levels have declined in high-income countries.[14] Furthermore, household air pollution globally affects around 3 billion people daily, predominantly from LMICs, as they rely on solid fuels as their main energy source. Burning solid fuels, such as dung, wood, and coal, generates high levels of air pollution and impacts health on many dimensions, also beyond respiratory health. Particularly at risk are women – often responsible for cooking – and their children who are kept close to their mothers.[15] Moreover, as exposure to air pollution among pregnant women impacts the lung development of their foetus, increased predisposition to CRD already starts in-utero.[16] Third, disadvantageous factors associated with poorer living conditions, such as malnutrition and a history of tuberculosis, co-occur and interrelate in LMICs. These risk factors further contribute to a higher burden of CRD.[7]

Poor access to adequate healthcare

Besides the higher prevalence of risk factors that contribute to the development and progression of CRD, access to adequate healthcare is generally more limited in LMICs than in HICs. Awareness regarding CRD and related risk factors is poor among communities and their healthcare professionals, and hence the potential benefit of healthcare is under-recognised. Additionally, there are multiple barriers to healthcare. These include fear of stigma (assuming chronic respiratory symptoms could lead to a diagnosis of tuberculosis), financial barriers, large distances to health facilities, lack of trained staff, lack of equipment, and lack of (affordable) diagnostic- and treatment options.[17] Smoking cessation support and pulmonary rehabilitation programmes are not yet widely available in LMICs.[18,19] Furthermore, research is relatively scarce for LMICs, which makes it challenging to have an evidence-based approach to CRD.[17] The poor awareness of CRD, limited diagnostic options such as spirometry and the skills needed for their interpretation, lead to an underdiagnosis of CRD.[20] This, in turn, results in an underestimation of the scale of the problem. Therefore, policymakers may be unaware of the importance and potential cost-effectiveness of prioritising CRD in their setting.

Failure to integrate evidence-based lung health programmes in routine practice

To combat the high prevalence of CRD and related risk factors in LMICs, evidence-based programmes exist, such as smoking cessation, cleaner cooking solutions to tackle household air pollution, pulmonary rehabilitation, and self-management interventions. However, many of these programmes were developed and proven effective in high-income settings with completely different health- and political infrastructures, financial options, health-related beliefs and behaviours, and cultural traditions. They cannot simply be transferred to low-resource settings without adaptations to the local circumstances. Even when developed locally, programmes often fail to translate into meaningful outcomes due to unsuccessful implementation processes.[21-23]

Implementation is a typically effortful, complex process. In this thesis, 'implementation' is defined as the act of carrying an intervention into widespread use,[24] ranging from the dissemination of an intervention to its sustained use. Particularly in LMICs, implementation failure can have dramatic consequences, as it drains resources from settings where they are scarce already while it undermines health outcomes. Therefore, the World Health Organization (WHO), global health funders and others institutions have urged for more and better implementation research, in particular for these settings.[25-28]

Numerous factors interact at multiple levels to determine implementation success or failure of health interventions.[29] A central and critical factor is the alignment of interventions and their implementation strategy with the local context.[24] The word 'context' – derived from the Latin *cum* (with) *texere* (to weave) – is often referred to as 'setting' or 'environment'.[30] In this thesis, context is interpreted broadly: a set of characteristics and circumstances that surround the implementation effort,[31] such as settings' epidemiological or anthropological characteristics (e.g. prevalence data and local health beliefs), their health- and political infrastructure, their socioeconomic aspects, and their network of relevant stakeholders. Adequate understanding of the local context is indispensable for leveraging the contextual characteristics to facilitate a successful implementation process.[32]

The Horizon 2020 FRESH AIR implementation research project

To generate evidence on how to effectively implement lung health programmes in low-resource contexts, we conducted the Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR) research project.[33] Within FRESH AIR, we studied the implementation of CRD-related interventions, ranging from preventive measures (an awareness-raising programme about CRD and related risk factors, a cleaner cooking programme, very brief advice for smoking cessation) to diagnostic measures (online spirometry training for healthcare workers, testing a phone-based application as diagnostic tool for CRD,

improving diagnosing asthma for children under five years old) to therapeutic measures (pulmonary rehabilitation) (Figure 1).

Fourteen institutions from nine countries teamed up to conduct these interrelated studies in diverse low-resource settings: in Uganda, Kyrgyzstan, Vietnam, and Greece. The settings were selected based on the high levels of risk exposure (tobacco consumption and/or exposure to household air pollution). Also, these countries presented a range of different implementation challenges for their diverse demographic-, geographic-, economic-, health system- and cultural characteristics. Furthermore, with this selection, we could build on existing collaborations, as each country was part of the International Primary Care Respiratory Group's global network.

In our approach, we focused on engaging important local and international stakeholders throughout the entire process. For example, relevant stakeholders were a Minister of Health, a district health educator, or a patient representative. Collaboratively with the stakeholders, we first mapped the CRD-related context: we assessed the prevalence of CRD, measured the socioeconomic burden and studied health beliefs and behaviours. Next, we used the findings to facilitate the design of context-driven interventions and hence increase their implementation success. The FRESH AIR project was funded by the European Commission Horizon 2020 research programme (680997) and registered in the Netherlands Trial Register (NTR5759).

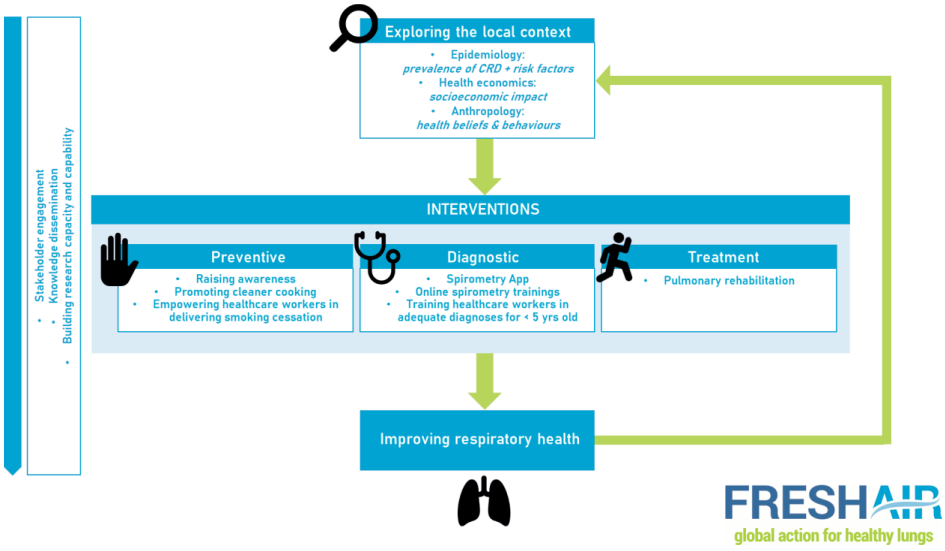


FIGURE 1. *The FRESH AIR studies; exploration of the local context served the development of the implementation strategies of the interventions. This was a dynamic, iterative process. CRD = chronic respiratory disease.*

Aims and outline of this thesis

This thesis addresses the challenge of tackling CRD in low-resource settings, and capitalises on the role of context. It is composed of two parts: the first focuses on exploring and understanding the problem in its context, the second works towards a solution. Many of the FRESH AIR substudies form the basis of the chapters in this thesis. How these studies relate to the remaining FRESH AIR studies (e.g. how a context assessment resulted in tailored implementation strategies for pulmonary rehabilitation programmes) is discussed throughout the chapters and in the General Discussion of this thesis.

Part I – Understanding the problem; exploring chronic respiratory disease in its local context

Chapter 2 illustrates the burden of CRD in low-resource settings in Kyrgyzstan. This epidemiological study details the prevalence of COPD and its risk factors, and demonstrates the importance of understanding different contexts even within neighbouring settings within the same country. **Chapter 3** details how the many risk factors for CRD in low-resource settings co-occur and interrelate, and elaborates on what this implies for potential solutions. Next, **chapter 4** moves beyond the direct burden and shows the socioeconomic burden of CRD in low-resource settings; this health economics study describes the impact of CRD on patients' work productivity and activity impairment in their daily lives in each of the FRESH AIR countries. **Chapter 5**, a systematic review, demonstrates through the example of smoking cessation how different contexts (such as different health infrastructures, medication availability, or cultures) can result in similarities and differences in national guidelines across the globe.

Part II – Towards a solution; facilitating implementation success of lung health programmes by engaging and leveraging their local context

To optimise the effect of health interventions, **chapter 6** details the factors that are critical to a successful implementation process for interventions targeting CRD in LMICs. The factors identified in this systematic review and meta-synthesis are translated into a hands-on implementation tool to assist implementers in practice. During this review process, an abundance of evidence on the implementation of cleaner cooking interventions was revealed. Due to the discrepancy between all the available evidence on implementation of cleaner cooking interventions on the one hand and the continued large-scale implementation failure on the other hand, **chapter 7** was written. This opinion paper calls for urgent consolidation of the fragmented evidence and translation of the evidence to practice. As a start, we engaged with other researchers in this field, the Clean Cooking Implementation Science Network and the World Bank, and conducted a systematic umbrella review to develop practical Cleaner Cooking implementation tools. This review of reviews involved a more complex methodology, and therefore we first published a protocol paper to enhance transparency (**chapter 8)** before publishing the results **(chapter 9)**. One factor identified as critical to successful implementation in both the general

lung health intervention review and the cleaner cooking intervention umbrella review (chapters 6 & 9), is ensuring compatibility between the intervention, the implementation strategy and the local context. However, to do so, no evidence was available on how to systematically map the local context first. Therefore, in **chapter 10**, we designed a systematic context-mapping tool and validated it in the four FRESH AIR countries. **Chapter 11** details the results of the application of this context-mapping methodology; in this mixed-methods approach we mapped local beliefs and behaviours across settings in Uganda, Kyrgyzstan, Vietnam, and Greece. Next, **chapter 12** brings this thesis full circle by illustrating how all the previous findings can result in a context-driven implementation strategy for a subsequent FRESH AIR health intervention; a train-the-trainer awareness programme on CRD and related risk factors was implemented, tailored to local beliefs and behaviours. Lastly, in **chapter 13**, the General Discussion, all findings are collated, and the implications and recommendations are discussed.

Overall, the aim of this thesis is to provide policymakers, healthcare professionals, and researchers with data that can contribute to reducing the burden of CRD in low-resource settings across the globe (figure 2). Evidence on how to map local contextual characteristics and leverage these throughout the implementation process of relevant interventions should facilitate implementation success. Implementation success can optimise the use of resources in settings where these are scarce already, and ultimately, improve communities' health outcomes.

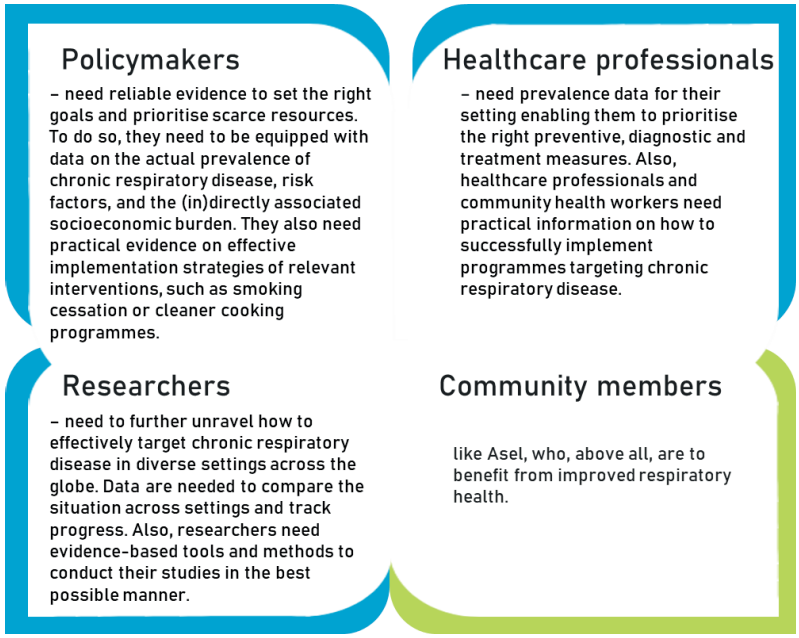


FIGURE 2. *The relevance for practice of this thesis, specified for several stakeholders.*

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PART I
UNDERSTANDING THE PROBLEM

EXPLORING CHRONIC RESPIRATORY DISEASE IN ITS LOCAL CONTEXT

CHAPTER 2

HIGH COPD PREVALENCE AT HIGH ALTITUDE: DOES HOUSEHOLD AIR POLLUTION PLAY A ROLE?

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Take home message:
High indoor PM2.5 levels could explain elevated COPD prevalence in rural, high altitude settings: prevention is key!

ABSTRACT

Studies comparing chronic obstructive pulmonary disease (COPD) prevalence across altitudes report conflicting results. However, household air pollution (HAP), a major COPD risk factor, was mostly not accounted for in previous analyses and never objectively measured. We aimed to compare the prevalence of COPD and its risk factors between low-resource highlands and lowlands, with a particular focus on objectively measured HAP.

We conducted a population-based, observational study in a highland (~2050 m above sea level) and a lowland (~750 m above sea level) setting in rural Kyrgyzstan. We performed spirometry in randomly selected households, measured indoor particulate matter with an aerodynamic diameter <2.5 μm (PM2.5) and administered a questionnaire on other COPD risk factors. Descriptive statistics and multivariable logistic regressions were used for analyses.

We included 392 participants: 199 highlanders and 193 lowlanders. COPD was more prevalent among highlanders (36.7% *versus* 10.4%; p<0.001). Their average PM2.5 exposure was also higher (290.0 *versus* 72.0 μg·m–3; p<0.001). In addition to high PM2.5 exposure (OR 3.174, 95% CI 1.061–9.493), the altitude setting (OR 3.406, 95% CI 1.483–7.825), pack-years of smoking (OR 1.037, 95% CI 1.005–1.070) and age (OR 1.058, 95% CI 1.037–1.079) also contributed to a higher COPD prevalence among highlanders.

COPD prevalence and HAP were highest in the highlands, and were independently associated. Preventive interventions seem warranted in these low-resource, highland settings. With this study being one of the first spirometry-based prevalence studies in Central Asia, generalisability needs to be assessed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the world's third leading cause of death, accounting for 5.7% of all deaths globally [1, 2]. Over 90% of COPD-related deaths occur in low- and middle-income countries, leading to a substantial clinical, economic and societal burden [3, 4]. Gaining insight into risk factors and places where the burden of disease is highest is key to a tailored approach to COPD.

Globally, around 400 million people live at high altitude (>1500 m above sea level) [5], yet it remains equivocal whether COPD prevalence is higher in these settings. Five observational studies in diverse settings reported contradictory findings [6–10]. Additionally, two studies pooled data from various prevalence studies, and while one described a lower COPD prevalence at higher altitude [11], the other observed no difference when adjusting for several risk factors [12]. However, household air pollution (HAP) was not adjusted for in either of these pooled studies. Of note, especially in low-resource settings, HAP is increasingly reported as a major risk factor for COPD [2, 3, 13–18].

HAP is caused by the indoor use of coal and biomass (e.g. animal dung, wood and crop residues), also known as solid fuels. Cooking and heating with solid fuels, as is common in 90% of rural households worldwide, leads to variably high levels of lung-damaging pollutants. The most exposed are women and their children, as women often prepare the meals above the fire in poorly ventilated houses for several hours daily, keeping their children close to them [13–15]. In 2015, HAP was estimated to be responsible for 4.2 million deaths and 103.1 million lost years of healthy life [19].

Some of the previous studies did report HAP exposure across altitudes, but used self-reported proxies (such as "solid fuel use") [7, 8, 10]. None objectively measured personal particulate matter exposure in vivo, which is needed for accurate pollution assessment [20]. Earlier studies also focused almost exclusively on urban settings, yet rural settings have more limited access to clean fuels and are consequently more severely affected by HAP [14].

Therefore, in this study we aimed to compare the prevalence of COPD and its risk factors between rural, low-resource highlands and lowlands, with a special focus on HAP. We expected that the more extreme climate conditions at high altitude increase the need for (solid fuel-based) heating and for limiting ventilation, thereby increasing the risk of COPD. We therefore hypothesised HAP exposure to be higher at high altitude and, consequently, COPD prevalence to be higher as well.

METHODS

Study design and setting

We conducted an observational, cross-sectional, population-based study in a lowland and a highland setting in rural Kyrgyzstan. This lower-middle-income country in Central Asia has a population of 5.96 million, with an average life expectancy of 71 years [21]. It has the highest respiratory mortality of all countries in the European Respiratory Society (ERS) "White Book" [22]. Kyrgyzstan offers a large contrast in altitude. Its lowest region (Chui, ~750 m above sea level) and one of its highest regions (Naryn, ~2050 m above sea level) were selected as lowland and highland settings. Chui has 756000 rural inhabitants (out of a total of 922 000) and hosts the country's capital Bishkek. Its neighbouring region, Naryn, has 245 000 rural inhabitants (out of a total of 284000) [23]. We collected data in the lowlands between February 3 and May 7, 2015, and in the highlands between July 16 and September 13, 2014. The colder measurement period in the year in the lowlands compared with the highlands was considered to involve relatively more (solid fuel-based) heating and less ventilation in the lowlands. Hence, seasonal influences would lead to an underestimation of differences in exposure to HAP and in respiratory symptoms.

This study preceded the Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR) project (Netherlands Trial Register identifier NTR5759), an implementation science project targeting chronic lung diseases in low-resource settings [24].

Participants

Given that no previous studies of COPD prevalence in Kyrgyzstan or neighbouring countries existed at the time of protocol development, we aimed for 600 participants based on a previous FRESH AIR study in Uganda [25] and on the BOLD (Burden of Lung Disease Initiative) study [26]. To this end, 50 households per setting were selected randomly through a multistage sampling approach. All permanent residents aged ≥18 years who provided informed consent were included, because people highly exposed to HAP may develop COPD even before the age of 30 years [25]. Persons with a current respiratory infection or a contraindication for spirometry [27] were excluded. We obtained written, informed consent from all participants. All field researchers were trained on ethics and the informed consent procedure. The Research Ethics Committee of the National Centre for Cardiology and Internal Medicine (Bishkek, Kyrgyzstan) approved the study (protocol 9;2014/3/1).

Demographics, COPD risk factors and respiratory symptoms

A standardised questionnaire, composed of validated questionnaires and used in the FRESH AIR study in Uganda [25], was tailored to Kyrgyzstan (supplementary appendix S1). It was

researcher-administered in the local language (Kyrgyz or Russian). It included questions on demographics, cooking and heating circumstances, COPD risk factors, and respiratory symptoms (tables 1 and 2). Household air pollution HAP was measured by the time-weighted average concentration of particulate matter with an aerodynamic diameter <2.5 µm (PM2.5) using a SidePak Personal Aerosol Monitor AM510 (TSI, Minneapolis, MN, USA). The cooks in the households were instructed to wear the device continuously on their body throughout the measurements. Measurements mostly started in the morning (median time 11:41 versus 11:48 h, respectively) and hence involved preparation of at least one warm meal. The median time of continuous measurement was 269 min in the lowlands and 284 min in the highlands (supplementary appendix S2). Of note, we initially aimed to measure 24-h indoor concentrations but this was not feasible due to the limited possibility to charge the battery of the device in the rural areas.

TABLE 1 Demographics and distribution of risk factors for chronic obstructive pulmonary disease

	Lowlands	Highlands	p-value
Subjects	193	199	
Male	100 (51.8)	87 (43.7)	0.109
Age years	44.4±13.6	50.0±16.3	<0.001
Height cm	166.3±8.9	161.1±9.6	<0.001
Weight kg	71.7±14.7	67.4±13.7	0.002
BMI kg·m^{-2}	25.9±4.7	26.0±5.6	0.793
Higher education[#]	54 (28.0)	10 (5.0)	<0.001
Profession			<0.001
Primary sector	4 (2.1)	92 (46.2)	
Secondary sector	23 (11.9)	8 (4.0)	
Tertiary/quaternary sector	90 (46.6)	13 (6.5)	
Housewife/husband	31 (16.1)	37 (18.6)	
Other	45 (23.3)	49 (24.6)	
Smoking status			<0.001
Never-smoker	110 (57.0)	140 (74.1)	
Ex-smoker[¶]	12 (6.2)	14 (7.4)	
Current smoker	71 (36.8)	35 (18.5)	
Male	58 (81.7)	30 (85.7)	0.604
Pack-years[+]	4.0 (1.6–11.5)	11.0 (2.0–24.5)	0.009
Tuberculosis (ever-diagnosed)[§]	0 (0.0)	3 (2.0)	0.086
Solid fuel			
Solid fuel use	145 (75.1)	199 (100.0)	<0.001
Nonsolid fuel use	193 (100.0)	82 (41.2)	<0.001

Data are presented as n, n (%), mean±SD or median (interquartile range). BMI: body mass index. [#]: the highest level of completed education above secondary education; [¶]: two missing values in the lowlands and 14 in the highlands; [+]: two missing values in the lowlands and six in the highlands; [§]: 46 missing values, all in the highlands.

TABLE 2 Prevalence of chronic obstructive pulmonary disease (COPD) and respiratory symptoms

	Lowlands	Highlands	p-value
Subjects	193	199	
Post-BD FVC % pred	92.0 (84.0–104.0)	100.0 (92.0–110.0)	<0.001
Post-BD FEV_1 % pred	90.0 (83.0–101.5)	92.0 (85.0–104.0)	0.091
Post-BD FEV_1/FVC %	82.0 (75.0–96.0)	76.0 (65.0–97.0)	0.003
COPD	20 (10.4)	73 (36.7)	<0.001
Male	16 (80.0)	36 (49.3)	<0.001
Moderate/severe (GOLD stage ⩾2)	14 (70.0)	18 (24.7)	<0.001
S_{pO_2} %	95.0 (95.0–96.0)	93.0 (92.0–95.0)	<0.001
Chronic cough/sputum[#]	15 (7.8)	47 (23.6)	<0.001
Severe breathlessness (MRC dyspnoea scale ⩾4)	6 (3.1)	22 (11.1)	0.003

Data are presented as n, median (interquartile range) or n (%). Missing outcomes for lung function were excluded from the study (figure 1); there were no other missing values. BD: bronchodilation; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; MRC: Medical Research Council. [#]: chronic is defined as having symptoms for ⩾2 months.

COPD diagnosis

A local team of medical doctors, trained by teachers from Imperial College London (London, UK), assessed lung function using spirometry (EasyOne; Medizintechnik, Zurich, Switzerland) following joint American Thoracic Society (ATS)/ERS guidelines [28]. We determined forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) before and after bronchodilation with 400 µg salbutamol using a spacer. COPD was defined as having a post-bronchodilator FEV1/FVC ratio <70% [29] and severity was classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages [30]. Subjects with complete reversibility were included as non-COPD in the analyses (an asthma diagnosis was suspected). Arterial oxygen saturation (SpO2) was measured by pulse oximetry (YX302 Fingertip Pulse Oximeter; Timago International Group, Bielsko-Biała, Poland).

Data analysis

SPSS version 23 (IBM, Armonk, NY, USA) was used for the analysis. Baseline characteristics, COPD prevalence and HAP exposure across altitudes were compared with independent t-tests for normally distributed continuous variables, Mann–Whitney U-tests for nonnormally distributed variables and Chi-squared or Fisher's exact tests for categorical variables. Univariable and forced-entry multivariable logistic regression models, adjusting for clustering within households by generalised estimating equation analyses [31], were used to assess the independent association between risk factors and COPD. HAP and other known COPD predictors (age, sex, education level and pack-years of smoking) [12] and altitude were included as predictors. Tuberculosis (ever-diagnosed) was not included in the model due to the limited number of cases. Working in the primary or secondary sector was included as a predictor due to the assumed higher occupational exposure compared with the tertiary/quaternary sector [32]. HAP was categorised into tertiles (supplementary appendix S4), given the nonnormal distribution

with high values (in this high range we did not assume linearity of HAP with the logit of the outcome). Multicollinearity was not evident in the model. p-values <0.05 and odds ratios with a 95% confidence interval excluding 1 were considered statistically significant.

Handling of missing data

Inadequate registration of several households and residents resulted in various duplications and uncertainty about these residents' PM2.5 measurements. To guarantee data quality and enable adjustment for a clustering effect within households, we discarded both these original and duplicate measurements from the analysis. Participants with missing PM2.5 and/or spirometry values were also excluded.

RESULTS

Study population

All 599 invited individuals consented to participate in the study. After exclusion, 193 lowlanders and 199 highlanders from 41 households per setting remained for analysis (figure 1).

Demographics and distribution of risk factors for COPD

Highlanders were significantly older, and had lower height and weight (table 1). They had a lower level of education, and worked more often in the primary sector and less frequently in the secondary sector. The highland population consisted of significantly fewer smokers, although their pack-years were significantly higher. Highlanders were (nonsignificantly) more frequently ever-diagnosed with tuberculosis.

Household air pollution across altitudes

The time-weighted average PM2.5 concentration per household in the highlands was significantly higher than in the lowlands (median (interquartile range (IQR)) 290.0 (123.5–703.5) versus 72.0 (31.0– 167.0) μg·m–3; p<0.001) (figure 2). Furthermore, higher maximum PM2.5 concentrations were measured in the highlands (median (IQR) 5822.0 (2308.0–9152.5) versus 272.0 (140.0–901.5) μg·m–3; p<0.001). In both areas these maxima were mostly reached at the beginning of the afternoon (median time 13:42:04 versus 13:05:40 h). Measurement duration is specified in supplementary appendix S2. The highlanders' cooking and heating circumstances were also more at risk of generating HAP. For example, highlanders significantly more often had higher-risk types of fuel use (e.g. dung versus gas), stoves (e.g. open fire versus improved cookstove), ventilation (e.g. eaves spaces versus open door), and cooking locations and durations. Details on these factors across the settings are provided in supplementary appendix S3.

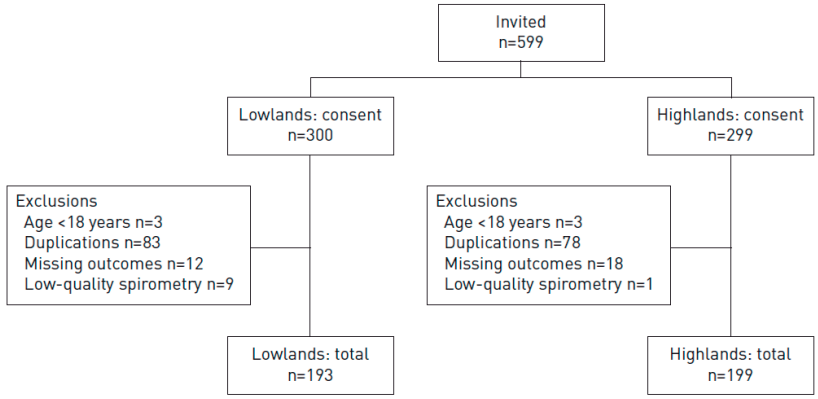

FIGURE 1. Flowchart of participants

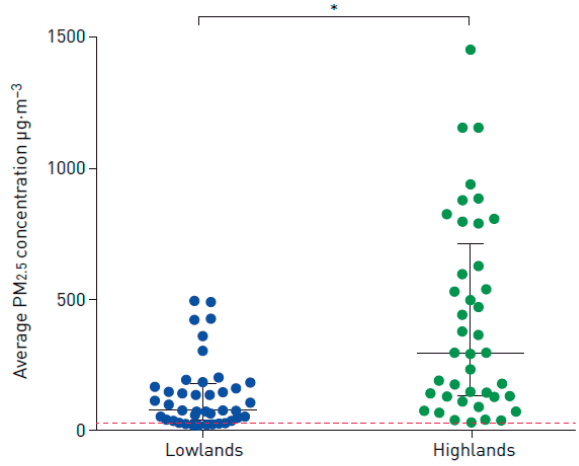

FIGURE 2 Levels of particulate matter with an aerodynamic diameter <2.5 µm ($PM_{2.5}$) in the lowlands *versus* the highlands (measured as time-weighted average concentration per household). The median and interquartile range are indicated. The dashed line is the maximum average 24-h $PM_{2.5}$ concentration of 25 µg·m^{-3} as stated in the World Health Organization indoor air quality guideline [33]. Missing values were excluded from the study (figure 1). *: difference is statistically significant (p<0.001).

COPD prevalence across altitudes

COPD was more prevalent in the highlands (36.7% versus 10.4%; p<0.001), although severity was lower (GOLD stage ≥2: 24.7% versus 70.0%; p<0.001) (table 2 and figure 3). COPD was equally distributed among males and females in the highlands, while in the lowlands the vast majority of patients were male (49.3% versus 80.0%; p<0.001). COPD patients in the highlands

were significantly less frequently smokers and were exposed to significantly higher PM2.5 levels compared with lowlanders (figure 4 and supplementary appendix S4). Additionally, oxygen saturation was significantly lower among highlanders (SpO2: 93.0% versus 95.0%; p<0.001).

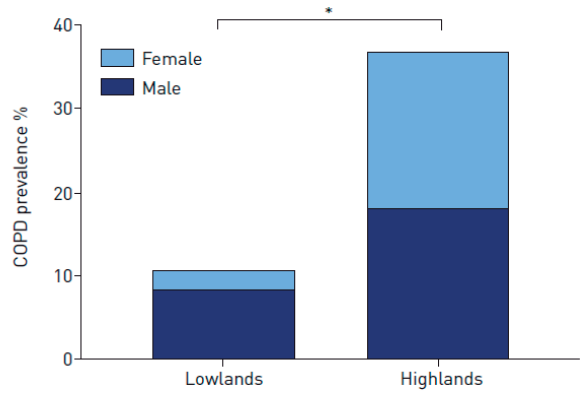

FIGURE 3 Chronic obstructive pulmonary disease (COPD) prevalence in the lowlands *versus* the highlands. *: difference is statistically significant (p<0.001).

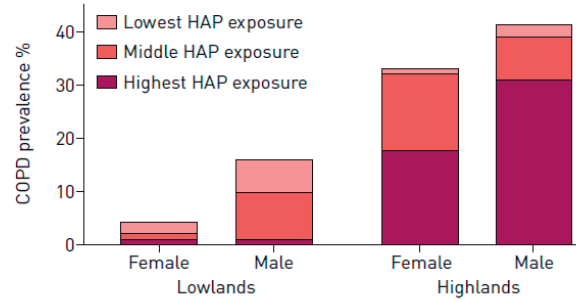

FIGURE 4 Chronic obstructive pulmonary disease (COPD) prevalence in the lowlands and highlands by sex and household air pollution (HAP) exposure. HAP exposure was categorised into tertiles, with time-weighted average concentrations of particulate matter with an aerodynamic diameter <2.5 µm of ⩽72, >72–293 and >293 µg·m^{-3}.

Predictors for COPD

Across the two altitudes, a total of 93 participants met COPD criteria. In the univariable logistic regression model, age, sex, pack-years, altitude and HAP were positively associated with COPD (figure 5 and supplementary appendix S4). In the multivariable logistic regression model, age, pack-years, altitude and the highest HAP exposure remained significantly positively associated with COPD. The decline in lung function along with an increase in PM2.5 exposure is depicted in supplementary appendix S4.

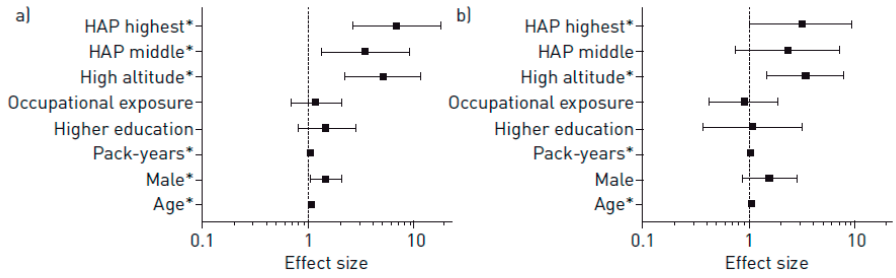

FIGURE 5 Potential predictors for chronic obstructive pulmonary disease (COPD): a) univariable analyses and b) multivariable analysis. HAP: household air pollution. COPD (n=93) *versus* no COPD (n=299). Generalised estimating equation analyses adjusted for a clustering effect within households. Age per year increase. Higher education means the highest level of completed education is above secondary education. HAP exposure was categorised into tertiles, with time-weighted average concentrations of particulate matter with an aerodynamic diameter <2.5 µm of ⩽72, >72–293 and >293 µg·m^{-3}. The lowest category is the reference category. Data are presented as OR (95% CI). Note that with a COPD prevalence >10%, OR no longer approximates relative risk. *: difference is statistically significant (95% CI of the OR excluding 1; p<0.05).

DISCUSSION

In this study, we compared the prevalence of COPD and its risk factors between the highlands and lowlands in rural, low-resource settings in Kyrgyzstan, with a special focus on objectively measured HAP. Both COPD prevalence and HAP exposure (peak and average PM2.5 concentrations) were significantly higher among highlanders. In addition to living at high altitude and being exposed to high HAP concentrations, more pack-years and higher age were also independently associated with COPD (and more common in the highlands). Our results highlight the particular vulnerability of rural highlanders to COPD and confirm the increasingly acknowledged impact of HAP on respiratory health.

Overall COPD prevalence in both Kyrgyz settings was high considering our relatively low age inclusion criterion (≥18 years). Our lowlands prevalence was similar to the global prevalence of ~10%, yet the prevalence observed in the highlands was more than 3-fold higher [26]. Our definition of COPD might have contributed to this high prevalence, especially among highlanders who were slightly older (a fixed FEV1/FVC ratio is known to overdiagnose COPD in the elderly [34]). Also, we used Caucasian reference values (rural, high-altitude, Central Asian values do not exist), while a Kyrgyz study at middle altitude (~1000–2000 m) reported larger FVC values among their population [35]. Larger physiological FVC values may result in smaller FEV1/FVC ratios and hence in overdiagnosis. A recent Kazakh population-based study found a prevalence of 6.7% [36]. The authors only studied a lowland, adult (≥18 years) population, used the same definition of COPD, but studied an urban rather than a rural setting. Given the lower use of solid fuels in urban settings, the latter factor may explain the lower COPD prevalence they observed.

In accordance with our hypothesis, along with a higher COPD prevalence in the highlands we observed significantly higher HAP exposures. It seems plausible to observe more HAP at higher altitude in rural areas, because more extreme climate conditions increase the need for (solid fuel-based) heating and for limiting ventilation. Furthermore, highlanders more commonly worked in the primary sector where dung is both cheaper and more easily available than clean fuels. Hence, particularly in the highlands, our HAP measurements dramatically exceeded the average 25 μg·m–3 as stated in the WHO 24-h PM2.5 air quality guideline [33]. These measurements are consistent with PM2.5 concentrations in other households using predominantly biomass fuels [13]. Our findings support the assumption that HAP plays a substantial role in explaining a high COPD prevalence at high altitude. This assumption is furthermore consistent with the relatively more (nonsmoking) female patients in our highland population, like in other settings where women are highly exposed to biomass fuel smoke [13–15, 17, 25, 37]. Although the pathogenic mechanisms of the harm of HAP are not yet fully uncovered, HAP is considered to alter the innate immune response, enhance pulmonary and systemic inflammation, and promote an oxidative stress state. This may cause macromolecular cell damage, including DNA changes [38]. Nevertheless, BOLD results remind us to remain alert for causes other than HAP for airflow obstruction [39].

In addition to the strong and significant relation between COPD and PM2.5 concentrations, altitude itself was another independent predictor in the multivariable analysis, also after adjusting for age and pack-years. Altitude might directly impact COPD prevalence as it is associated with an increase in both airways and total lung capacities. However, evidence remains inconclusive if this increase is proportional (hence, if and how FEV1/FVC ratios are affected [40–42]). Alternatively, altitude could relate to COPD prevalence indirectly via (unmeasured) factors. These could be a more frequent history of pneumonia/ tuberculosis, lower level of physical activity [43, 44], higher occupational exposure [32] or more (childhood) poverty/lower sociodemographic development (as again a mediator for other factors) [2, 45].

Remarkably, prevalence of moderate/severe COPD (GOLD stage ≥2) appeared to be lower in the highlands. This could be due to down-migration of the severely ill for higher ambient oxygen levels [46], for better access to advanced healthcare in the Kyrgyz capital or to a potential relation between severity and solid fuel smoke versus tobacco smoke [37]. The lower highland oxygen saturation levels we observed seem plausible due to lower ambient oxygen levels in the highlands. Furthermore, a double exposure of tobacco and biomass fuel smoke among COPD patients is associated with lower oxygen saturation levels [47]. However, although the number of COPD patients with a double exposure was significantly higher in the highlands, the total number of participants with a double exposure was the same.

As mentioned earlier, the seven other studies covering COPD prevalence across altitudes reported conflicting findings [6–12]. We argue that these conflicting results can be partly explained by differences in HAP exposure, which these studies either did not measure, or measured by proxy, or did not adjust for in the analyses. HAP exposure, associated COPD prevalence and the difference across altitudes may have differed substantially between the study settings. The settings were almost exclusively urban, sometimes in a high-income country, meaning more extreme high-altitude climates could be less influential on HAP exposure due to better access to clean fuels [14]. Furthermore, ethnicity often differed between the highand low-altitude settings within a study, hampering proper comparison of lung functions.

We corrected for objectively measured HAP in our analyses, compared consistently between rural, low-resource settings and between people of the same ethnicity. Altitude remained an independent predictor for COPD. The conflicting results between all present studies, performed in different settings, may indicate COPD prevalence might not be attributable to altitude itself. Instead, it could be mainly mediated through (unmeasured) factors expressed by altitude, with HAP being one of them.

A major strength of this study is the objective, personally monitored PM2.5 exposure combined with spirometry according to ATS/ERS guidelines [28], other than self-reported presence of risk factors or symptoms. This method precisely answers a recent call for objective measurements on the association between HAP and COPD [20]. This study also benefited from a high participation rate. Participants indicated they were eager to receive extra medical attention as access to healthcare is generally limited in these rural areas. This high rate impedes selection bias and enhances generalisability to other settings. Lastly, we present one of the first spirometry-based COPD prevalence studies in Central Asia [2].

Some limitations must also be noted. Due to organisational difficulties during data collection, we had to exclude various participant and household measurements in both settings. Differences between the two settings were, however, still statistically significant, and we were not able to identify any differences between excluded and included participants. Also, due to the limited battery and charging capacity in the rural areas, we could not perform 24-h PM2.5 measurements. We therefore measured each household for ~4 h and at the same hour during the day, including the preparation of at least one warm meal. Hence, 24-h PM2.5 concentrations are likely to be lower as those contain a longer period without meal preparations. Lastly, given that the data in the lowlands were collected in a relatively colder period of the year, with a relatively higher need for (solid fuel-based) heating and limiting ventilation, differences in HAP and respiratory symptoms might be underestimated.

In conclusion, we observed a substantially higher COPD prevalence in high-altitude areas compared with low-altitude areas in rural Kyrgyzstan. HAP exposure was high in both settings, but particularly in the highlands. There was a strong, significant relation between COPD and HAP that remained significant when adjusted for other risk factors. Although generalisability to other rural, low-resource highlands remains to be assessed, our results call for an increased focus on COPD awareness, diagnosis and treatment. Moreover, policy makers, healthcare workers and highlanders in these settings should focus on prevention by increasing awareness on HAP and by reducing it (e.g. by the implementation of clean cooking stoves). This could not only benefit chronic lung health, but also target other PM2.5-related diseases such as ischaemic heart disease, cerebrovascular disease, lung cancer, low birthweight and pre-term birth, type 2 diabetes, and lower respiratory infections [16].

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Author contributions: T. Sooronbaev and A. Tabyshova adapted the FRESH AIR study to the Kyrgyz settings and coordinated data collection. E.A. Brakema, A. Tabyshova, M.J. Kasteleyn and E. Molendijk analysed and interpreted data. E.A. Brakema wrote the first draft of this report. All authors provided comments and E.A. Brakema revised the report. All authors gave input to the final version. All authors had full access to all the data. E.A. Brakema and N.H. Chavannes had the final responsibility for the decision to submit the study for publication.

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CHAPTER

COPD'S EARLY ORIGINS IN LOW-AND-MIDDLE INCOME COUNTRIES: WHAT ARE THE IMPLICATIONS OF A FALSE START?

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OPINION PAPER

The Global Initiative for chronic Obstructive Lung disease (GOLD) guideline of 2018 describes COPD as 'the result of a complex interplay of long-term cumulative exposure to noxious gases and particles, combined with a variety of host factors including genetics, airway hyper-responsiveness and poor lung growth during childhood'.1 Tobacco smoking is traditionally viewed as the main contributing factor to the development of COPD. However, COPD also occurs among non-smokers, especially in low-income and middle-income countries (LMICs).2,3 Notably, more than 90% of COPD-related deaths occur in LMICs.4 For these countries, other risk factors, such as ambient, occupational and household air pollution play a significant role in the development of COPD.1,2,5–7 Does COPD in these settings have a different pathophysiological trajectory compared to COPD in high-income countries, and if so: what does this imply?

In normal lung development, airway branching is completed by the 17th week of gestation, after which airways increase in volume until young adulthood. Alveoli are present at birth and develop further during childhood. Lung volume and airflow continue to increase as the thorax grows, influenced by age, sex, and ethnicity, reaching a peak at young adulthood. Lung function then remains constant for about 10 years (the plateau phase), after which it gradually declines.8 In the 'classic' COPD patient, the decline in lung function is more rapid than in healthy individuals. However, in a considerable proportion of COPD patients, lung function does not decline rapidly, but reaches a lower plateau phase in early adulthood instead. For these patients, a completely different pathophysiological trajectory seems to lead to the diagnosis of COPD: the decline in lung function follows a normal pattern, yet they seem to have a 'false start' by attaining a lower maximum lung function.8–11

Several factors can contribute to a lower maximum lung function. There is increasing evidence that different environmental factors (such as tobacco smoke, household air pollution caused by burning solid fuels or kerosene lamps), maternal factors (malnutrition, asthma, diabetes), and gene–environment interactions can impact lung growth. Additionally, childhood factors (low birth weight, prematurity) and other diseases during childhood (lower respiratory tract infections, asthma, tuberculosis, HIV) may all contribute to a decline in lung function.1–3,5,8,9,11–14 (Mal)nutrition additionally plays a vital role in lung development.15 Unfortunately, many of these factors commonly interrelate and co-occur in LMICs. A low socioeconomic status can furthermore deteriorate the situation, as this is not only independently associated with a lower lung function, but also with other health risks (poor access to healthcare, poor nutrition, low birth weight, exposure to indoor and outdoor pollution, poor living conditions and water supply/sanitation).16–18 Overall, populations in LMICs are particularly vulnerable to such risk factors for a lower maximum lung function.16,18

Our knowledge about reduced maximum attained lung functions caused by 'early life disadvantage factors' in LMICs seems humble compared to the knowledge generated by extensive research on tobacco-related COPD, often conducted in high-income countries.5,11,13,19 The question is whether these early life, disadvantageous factors cause different COPD phenotypes with their own pathophysiology, diagnostic approach, rate of lung function decline, response to treatment, and potential reversibility. 3,9,13,19 The paucity of data indicates differences may exist, and that those with a lower forced expiratory volume in one second in early adulthood are also exposed to an increased prevalence and earlier incidence of other non-communicable diseases and premature death.5,12,20,21 Additionally, COPD related to biomass fuel smoke was demonstrated to be commonly present among young, non-smoking women,6 whereas 'classic' COPD patients are elderly, smoking men. Such difference could be attributed to differences in risk exposure between men and women, yet potential differences in sensitivity to COPD between men and women per phenotype could play an additional role. Furthermore, as rates of lung function decline vary according to the underlying cause of COPD, the approach equally differs. For tobacco or biomass fuel smoke exposure the decline may decelerate once removed from the exposure, whereas a normal decline within patients with a lower plateau phase seems harder to influence.

COPD caused by a false start has several implications. First, COPD caused by early life disadvantage factors should be tackled at much earlier stages. Prevention is key, and must start before birth, continue throughout childhood and then be combined with the 'regular' preventive measures targeting an accelerated decline. As early life disadvantage factors are diverse, prevention addressing these factors should be equally diverse. We argue that raising awareness on COPD is therefore crucial. COPD, the third cause of death worldwide, is often completely unknown to local community members, including their healthcare professionals and policy makers.22 Local curricula for healthcare professionals (doctors, nurses, midwives) thus need to increase focus on COPD and on its early origin. Moreover, community health workers should be trained on a national scale to facilitate COPD awareness programmes in their communities. Raising awareness among policy makers is also essential. The diverse early life risk factors require COPD interventions to be embedded in a wide, intersectoral approach to facilitate a socioeconomic upliftment (targeting amongst others poverty, education, infrastructure, health literacy).

Increased awareness on the early development of COPD and on the existence of COPD in general could enhance early diagnosis and timely action. Increased awareness is particularly important considering the widescale underdiagnosis of COPD. This raises the question how to best diagnose the disease (affordably, easy to learn), and how to do so at an early stage.6,23 Although affordable medications to treat COPD in LMICs are rare, non-pharmacological approaches, such as pulmonary rehabilitation and patient education can impact COPD symptoms

and disease progression. Particularly in LMICs, these approaches seem cost-effective (if not, cost-saving).24

The second implication is related to research. As outlined earlier, more research into a lower maximum lung function and its clinical implications is needed. Furthermore, a false start implies a different perspective on how to study the effect of interventions targeting household air pollution on lung function. For decades, clean cook stove programmes fail to demonstrate consistent positive effects on lung function.25

Often this is attributed to flawed implementation of such interventions, or to crosscontamination of air pollution within the community. However, even after successful adoption of clean cook stoves, the lungs in this generation could remain irreversibly damaged. Instead, should we not measure effects on lung function among children and adolescents, or even among the next (unborn) generation?

To conclude, COPD development generally starts early in life due to a complex interplay of disadvantageous factors. Many of these factors particularly occur in LMICs. To address the silent growing epidemic of COPD in LMICs, lung health should be optimised even before birth and in early childhood. Prevention is key, and focus should be on creating large-scale awareness— beyond the healthcare system only, involving all stakeholders. More research is needed to explore the implications of early life disadvantage factors for COPD in LMICs. This should lead to an evidence-based approach for those with a false start—those (at risk of) having a lower maximum lung function.

Author contributions E.A.B. wrote the first version and subsequent versions of this manuscript in close collaboration with F.v.G. R.v.d.K., M.P., S.S., and N.C. gave input throughout the entire process.

Competing interests The authors declare no competing interests.

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CHAPTER

THE SOCIOECONOMIC BURDEN OF CHRONIC LUNG DISEASE IN LOW-RESOURCE SETTINGS ACROSS THE GLOBE – AN OBSERVATIONAL FRESH AIR STUDY

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ABSTRACT

Background: Low-resource settings are disproportionally burdened by chronic lung disease due to early childhood disadvantages and indoor/outdoor air pollution. However, data on the socioeconomic impact of respiratory diseases in these settings are largely lacking. Therefore, we aimed to estimate the chronic lung disease-related socioeconomic burden in diverse low-resource settings across the globe. To inform governmental and health policy, we focused on work productivity and activity impairment and its modifiable clinical and environmental risk factors.

Methods: We performed a cross-sectional, observational FRESH AIR study in Uganda, Vietnam, Kyrgyzstan, and Greece. We assessed the chronic lung disease-related socioeconomic burden using validated questionnaires among spirometry-diagnosed COPD and/or asthma patients (total N = 1040). Predictors for a higher burden were studied using multivariable linear regression models including demographics (e.g. age, gender), health parameters (breathlessness, comorbidities), and risk factors for chronic lung disease (smoking, solid fuel use). We applied identical models per country, which we subsequently meta-analyzed.

Results: Employed patients reported a median [IQR] overall work impairment due to chronic lung disease of 30% [1.8–51.7] and decreased productivity (presenteeism) of 20.0% [0.0–40.0]. Remarkably, work time missed (absenteeism) was 0.0% [0.0–16.7]. The total population reported 40.0% [20.0–60.0] impairment in daily activities. Breathlessness severity (MRC-scale) (B = 8.92, 95%CI = 7.47–10.36), smoking (B = 5.97, 95%CI = 1.73–10.22), and solid fuel use (B = 3.94, 95%CI = 0.56–7.31) were potentially modifiable risk factors for impairment.

Conclusions: In low-resource settings, chronic lung disease-related absenteeism is relatively low compared to the substantial presenteeism and activity impairment. Possibly, given the lack of social security systems, relatively few people take days off work at the expense of decreased productivity. Breathlessness (MRC-score), smoking, and solid fuel use are potentially modifiable predictors for higher impairment. Results warrant increased awareness, preventive actions and clinical management of lung diseases in low-resource settings from health policymakers and healthcare workers.

BACKGROUND

Low- and middle-income countries account for more than 90% of the global COPD mortality and 80% of the asthma mortality [1]. Also regarding the socioeconomic burden, low-resource settings seem disproportionally affected [2–4]. In these settings, increased predisposition to chronic lung diseases (CLDs) already starts in-utero due to high exposure to environmental risk factors (such as excessive indoor and outdoor air pollution) and poorer living conditions (e.g. undernutrition) [3, 5–12]. Hence CLDs develop in a younger, primarily working age, population [5, 13–15]. Furthermore, the patient burden is particularly high in low-resource settings, because CLDs manifest themselves more severely due to suboptimal (access to) care, including diagnostic- and treatment options [2–4, 16]. Severe CLDs can impact patients' daily activities substantially [17]. With often limited or non-existent social security systems, families are left in severe trouble when their breadwinner can no longer support them financially [2, 18]. Paradoxically, most studies on the CLD-associated socioeconomic burden have been performed in high-resource settings. The urgency of evaluating outcomes specifically in low-resource settings was therefore underlined recently [19]. In particular, the need for social, economic, and policy research was highlighted as crucial for diminishing the burden of CLD in LMICs [12].

An important form of the social burden of CLD is impairment of patients' daily activities [17]. On top of that comes the direct economic burden (such as medication and hospital visits) and indirect economic burden (such as productivity loss at work) [20, 21]. While widely available in high income countries, data on the social and indirect economic burden in low-resource settings remain especially scarce [2, 22, 23]. One study reported on an indirect burden, unemployment, for both high- and low-resource settings [24]. It observed a relation between chronic airflow obstruction and unemployment only for high-resource settings. However, as employment was a dichotomized outcome, disease-related hours missed from work (absenteeism) were not taken into account. In addition, while being at work, symptoms of CLD can seriously impact productivity (presenteeism). Presenteeism is more responsive to asthma control than absenteeism and is a vital source of preventable burden [20]. Hence, the actual socioeconomic impact of CLDs in low-resource settings has yet to be uncovered.

Gaining more knowledge on the actual socioeconomic burden is of critical importance to adequately inform policymakers, healthcare professionals, and community members on the impact of CLDs [12]. Evidence on the burden can raise awareness and encourage prioritization of the use of scarcely available resources for CLDs, so that these can be approached with highly (cost-) effective interventions [2, 3]. Furthermore, there is a need to identify (modifiable) risk factors for impairment [25], which may allow targeted interventions. Therefore, the aim of this study was to estimate the socioeconomic burden of CLD in diverse low-resource settings across the

globe. To inform governmental and public health policy, we focused on work productivity and activity impairment and its modifiable clinical and environmental risk factors.

METHODS

This study was part of the FRESH AIR project (Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups; trial registration number: NTR5759), targeting (implementation of) the prevention, diagnosis, and treatment of CLDs in low-resource settings [26]. An online supplement provides additional information on the methods (Additional file 1: Appendix 2).

Design and setting

This observational, cross-sectional study was performed between July 2016 and March 2018 in Uganda, Vietnam, Kyrgyzstan, and rural Greece. The study sites were sampled purposefully to represent four distinct low-resource settings in terms of geography, ethnicity, risk factor exposure, and healthcare- and political system. At these sites, we selected healthcare centers routinely using spirometry to diagnose CLDs (asthma, COPD, or asthma-COPD overlap (ACO)). The exact selection method of settings and participants was designed in close collaboration with the local teams to meet their daily clinical routine, typical patient population, and available resources (Additional file 1: Appendix 2; Table E1).

Participants

We recruited participants consecutively during visits to the selected health centers (Additional file 1: Appendix 2 Table E1). We included patients ≥15 years with a spirometry-confirmed diagnosis of COPD [27], asthma or ACO [28]. We did not deploy additional inclusion criteria for COPD (age, tobacco use), as patients in low-resource settings may develop COPD earlier in life due to disadvantage factors such as household air pollution [5, 6, 10, 13]. Patients with a disability hampering communication, too severely ill to participate, or with missing outcomes on activity impairment, were excluded.

Procedures

Eligible participants were identified and informed about the study by their physicians during a routine visit. After consent, participants filled out a questionnaire. Their physician added the clinical data from existing medical history files. In three hospitals in Kyrgyzstan, well-organized patient registries allowed research-assistants to recruit participants per telephone to administer the questionnaire (Additional file 1: Appendix 2 provides further details on the procedures).

Instruments

The questionnaire was composed of several validated [29, 30], structured questionnaires with additional open-ended questions, assessing demographic, socioeconomic, and health factors (Additional file 1: Appendix 3). The outcome work- and other activity impairment was assessed using the recommended Work Productivity and Activity Impairment (WPAI) questionnaire [30–32]. The WPAI-questionnaire assesses CLD -related absenteeism, presenteeism, overall work impairment (absenteeism and presenteeism combined), and impairment of regular activities during the preceding 7 days [30]. All items are calculated into percentages (Additional file 1: Appendix 3), with higher numbers indicating greater impairment and less productivity. When available, we used official, validated WPAI-translations [33]. All questions were asked in the local language (English, Vietnamese, Russian, Greek). In Uganda, where several local languages are spoken, the involved research-team represented all major language groups. We piloted the questionnaire and improved the translation and contextual adaptations accordingly. For example, as many patients were unaware of the name of their disease, we added clarifications on CLDs before asking about the impact of their 'COPD' and/or 'asthma'.

Sample size

With a total covered population of +/– 146 million (Uganda: 40; Kyrgyzstan: 6; Vietnam: 90; Greece: 10 million), an estimated global CLD-prevalence of 5% [22, 34], a number of 1040 participants resulted in a 99% confidence level and a 4% error margin. Notably, CLD-prevalence is mostly unknown in our diverse low-resource settings. Therefore, the sample size was not calculated to compare between countries and not weighted based on country-size or differences in prevalence.

Statistical analysis

Population characteristics and the WPAI were analyzed using descriptive statistics (SPSS version 25; IBM, Armonk, NY, USA). The relation between predictors and activity impairment was first assessed per country, using univariable and forced-entry multivariable linear regressions. An identical regression model was used for each country, based on known risk factors for impairment (Additional file 1: Appendix 2) [35–37]. We added solid fuel use for cooking/heating, as besides smoking this is another major risk factor for CLD in low-resource settings [1, 8, 10, 38]. There were no indications for multicollinearity. The unstandardized coefficients of each country with their 95% confidence intervals (CI) were then meta-analyzed (Comprehensive Meta-Analysis version 3; Biostat, Englewood, NJ, USA). We generally used a fixed-model. Only for 'comorbidity' we used a random-effect model, as for this variable there were indications for heterogeneity of effect between the countries. Because our Kyrgyz population had no asthma patients, we performed a separate meta-analysis without this country to check for any differences (Additional file 1: Appendix 4 Table E4). Coefficients with 95%CI excluding 1 were considered statistically significant.

RESULTS

Clinical and demographic characteristics

We included a total of 1040 participants (Fig. 1); most were recruited in Vietnam and Kyrgyzstan. Almost half of the total population was male, and the median age was 60.0 [IQR 48.0–70.0] (Table 1). The Ugandan population consisted of more female and younger participants, whereas the other countries' populations consisted of somewhat more male participants of older age. A slight majority of the participants was diagnosed with COPD (55.1%), followed by asthma (38.5%), and a small number with ACO (6.4%). Breathlessness severity was generally moderate (median MRC-score 3.0; IQR 2.0–4.0). Having at least one comorbidity was common (34.7%), with heart disease being most prevalent (Additional file 1: Appendix 4 Table E1). Risk factors for developing CLD were highly prevalent, such as having ever smoked daily (43.9% of whom 91.7% male), solid fuel use (54.0%) and occupational exposure to dust or fumes (59.4% of the 401 workers). The distribution of risk factors differed across the countries. For example, in Uganda, smoking prevalence was extremely low (3.5%) compared to solid fuel use (98.8%), whereas in Greece this was the other way around (68.9 and 49.4% respectively). Clinical and demographic details are reported in Additional file 1: Appendix 4 Table E1.

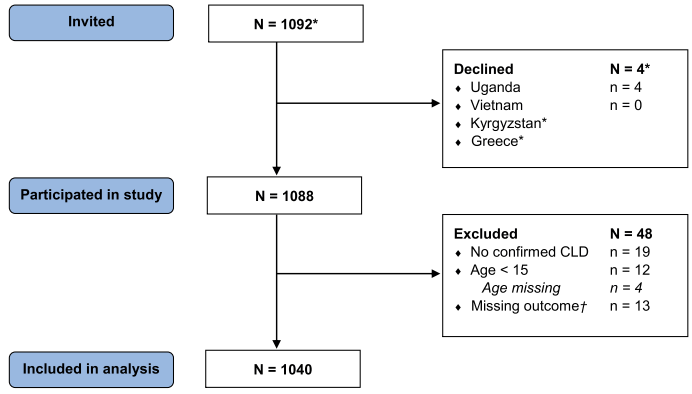

Fig. 1 Recruitment of study participants. CLD = chronic lung disease. *In Greece and Kyrgyzstan, the exact number was not registered during the process. †Participants were excluded from the analysis if the outcome 'activity impairment' was missing

Work productivity and activity impairment

Locally, 533 participants (51.2%) were considered to be of working age (Additional file 1: Appendix 4 Table E1). Although 401 identified themselves as 'working', 270 (67.3%) of those worked for a salary at an employer. WPAI-scores were generally very similar across the countries. However, in Kyrgyzstan, all scores were higher (Fig. 2, Table 2). Still, a similar pattern was visible in each country: while CLD-related absenteeism was (relatively) very low among those employed, presenteeism was relatively high, leading to a substantial overall work impairment. Activity impairment was considerably high, particularly in the total population. To facilitate in-

Table 1 Clinical and demographic characteristics

	Uganda *N* = 173 (16.6%)	Vietnam *N* = 471 (45.3%)	Kyrgyzstan *N* = 306 (29.4%)	Greece *N* = 90 (8.7%)	Total *N* = 1040 (100%)
Demographic characteristics					
Male	39 (22.5)	274 (58.2)	188 (61.4)	55 (61.1)	556 (53.3)
Age (yrs.), median [IQR]	35.0 [22.5–47.0]	62.0 [52.0–72.0]	62.0 [55.0–70.0]	72.0 [63.8–79.0]	60.0 [48.0–70.0]
BMI (kg/m^2), median [IQR]	23.8 [20.4–28.3]	21.9 [19.5–24.4]	25.8 [23.7–29.4]	28.0 [24.7–31.5]	23.9 [20.8–27.3]
Higher education[a]	46 (26.7)	156 (33.1)	291 (95.1)	4 (4.4)	497 (47.8)
Working status					
Working	93 (53.8)	193 (41.1)	92 (30.1)	23 (25.6)	401 (38.6)
Employed (for payment)	*81 (87.1)*	*134 (69.4)*	*40 (43.5)*	*15 (65.2)*	*270 (67.3)*
Not working	41 (23.7)	153 (32.6)	34 (11.1)	13 (14.4)	241 (23.2)
Student	36 (20.0)	5 (1.1)	0 (0.0)	0 (0.0)	41 (3.9)
Retired	3 (1.7)	119 (25.3)	180 (58.8)	54 (60.0)	356 (34.2)
Having child (ren)	117 (67.6)	417 (88.5)	302 (98.7)	79 (87.8)	915 (88.0)
Ever smoker	6 (3.5)	251 (53.3)	138 (45.1)	62 (68.9)	457 (43.9)
Pack years, median [IQR]	*3.8 [2.0–19.9]*	*29.0 [15.5–44.0]*	*27.0 [14.2–40.8]*	*57.0 [26.1–74.0]*	*30.0 [15.1–45.0]*
Male	*4 (66.7)*	*234 (93.2)*	*134 (97.1)*	*47 (75.8)*	*419 (91.7)*
Current smoker	*6 (100.0)*	*92 (36.7)*	*37 (26.8)*	*40 (64.5)*	*175 (38.3)*
Solid fuel use	170 (98.8)	130 (27.6)	218 (71.5)	44 (49.4)	562 (54.0)
Occupational exposure[b]	87 (93.5)	104 (53.9)	37 (40.2)	10 (43.5)	238 (59.4)
Health characteristics					
Diagnosed as:					
COPD	11 (6.4)	190 (40.3)	305 (99.7)	67 (74.4)	573 (55.1)
Asthma	161 (93.1)	223 (47.3)	0 (0.0)	16 (17.8)	400 (38.5)
ACO	1 (0.6)	58 (12.3)	1 (0.3)	7 (7.8)	67 (6.4)
Breathlessness severity (MRC-scale), median [IQR]	2.0 [1.0–2.0]	3.0 [2.0–4.0]	4.0 [3.0–4.0]	2.0 [2.0–4.0]	3.0 [2.0–4.0]
Exacerbation(s) in past year	0 (0.0)	102 (21.7)	35 (11.4)	9 (10.0)	146 (14.0)
Comorbidity (any)	27 (15.6)	228 (48.4)	62 (20.3)	44 (48.9)	361 (34.7)

Data are in numbers (%) unless stated otherwise. *ACO* asthma-COPD overlap, *BMI* body mass index, *IQR* interquartile range, *MRC* medical research council. Text in italics means category within category above. [a] Above secondary education. [b]Regards only those working. Missing values N (%) for BMI 6 (0.6) in G; education 1 (0.1) in U; working status 1 (0.1) in V; pack years 13 (1.2) 1 in G, 2 in V, 10 in K; solid fuel use 3 (0.3) 1 in U, K, and G; MRC-score 1 (0.1) in U; exacerbation 1 (0.1) in G

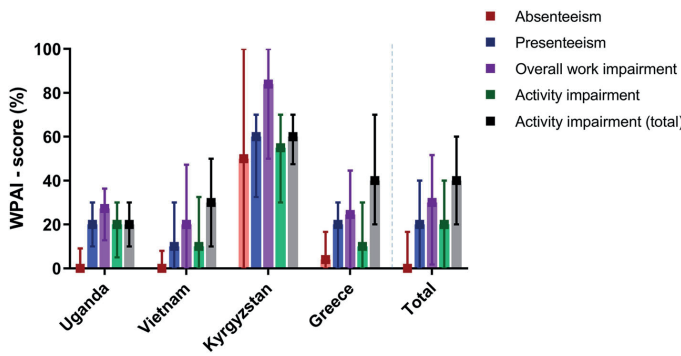

Fig. 2 Work productivity and activity impairment due to CLD. CLD = chronic lung disease; WPAI = work productivity and activity impairment in median [interquartile range] %. 100% means maximum impairment. Total number of participants (numbers of employed population): Uganda *N* = 173 (81), Vietnam 471 (134), Kyrgyzstan 306 (40), Greece 90 (15), and total 1040 (270). Due to different population characteristics per country, data should be interpreted within the country's context and not be used to directly compare between countries

terpretation of the outcomes within their country,WPAI-scores and their 95% CIs are provided in Additional file 1: Appendix 4 Table E2. The proportion of patients that suffered from any degree of impairment due to their CLD during the past seven days was also high for all four

Table 2 CLD-related work productivity and activity impairment (WPAI)

WPAI item	Uganda	Vietnam	Kyrgyzstan	Greece	Total
Employed population					
Absenteeism					
% work time missed due to CLD	0.0 [0.0–9.1]	0.0 [0.0–8.0]	50.0 [0.0–100.0]	4.0 [0.0–16.7]	0.0 [0.0–16.7]
% of the people who missed any work due to CLD, mean (95%CI)	46.8 (35.6–58.1)	31.5 (23.3–39.7)	70.0 (55.2–84.8)	50.0 (20.0–80.0)	43.0 (36.9–49.1)
Presenteeism					
% impairment while working due to CLD	20.0 [10.0–30.0]	10.0 [0.0–30.0]	60.0 [32.5–70.0]	20.0 [0.0–30.0]	20.0 [0.0–40.0]
% of the people whose productivity was affected, mean (95%CI)	77.2 (67.8–86.7)	62.2 (53.7–70.8)	100.0 (100.0–100.0)	71.4 (44.4–98.5)	72.9 (67.4–78.3)
Overall work impairment					
Absenteeism and presenteeism combined	27.3 [12.9–36.7]	20.0 [0.0–47.3]	84.0 [50.0–100.0]	24.5 [0.0–44.6]	30.0 [1.8–51.7]
% of people who suffered from any work impairment, mean (95%CI)	79.7 (70.7–88.8)	65.4 (57.0–73.7)	100.0 (100.0–100.0)	71.4 (44.4–98.5)	75.2 (69.9–80.5)
Activity impairment					
% impairment of activities due to CLD	20.0 [5.0–30.0]	10.0 [0.0–32.5]	55.0 [30.0–70.0]	10.0 [0.0–30.0]	20.0 [0.0–40.0]
% of the people whose daily activities were affected, mean (95%CI)	75.9 (66.3–85.6)	61.4 (52.8–70.0)	100.0 (100.0–100.0)	53.8 (22.5–85.2)	71.5 (66.1–76.9)
Total population					
Activity impairment					
% impairment of activities due to CLD	20.0 [10.0–30.0]	30.0 [10.0–50.0]	60.0 [47.5–70.0]	40.0 [20.0–70.0]	40.0 [20.0–60.0]
% of the people whose daily activities were affected, mean (95%CI)	80.3 (74.4–86.3)	80.5 (76.9–84.1)	98.0 (96.5–99.6)	90.0 (83.7–96.3)	86.4 (84.4–88.5)

Data are in median [interquartile range] unless stated otherwise. *CI* confidence interval; *CLD* chronic lung disease. Total number of participants (numbers of employed population): Uganda *N* = 173 (81), Vietnam 471 (134), Kyrgyzstan 306 (40), Greece 90 (15), and total 1040 (270). Due to different population characteristics per country, data should be interpreted within the country's context and not be used to directly compare between countries

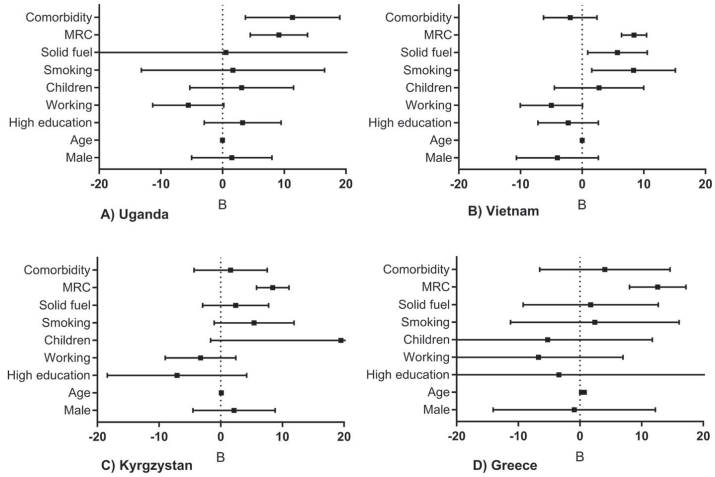

Fig. 3 Multivariable regressions per country. Mean unstandardized B (95%CI). MRC = medical research council breathlessness scale (ranging 1-5). Age (years). **a** Uganda, **b** Vietnam, **c** Kyrgyzstan, **d** Greece

WPAI outcomes. Although many patients missed any amount of work time (43.0%), the work time they missed was very low. On the contrary, the proportion of patients who suffered from activity impairment was much higher (86.4%) and also the level of activity impairment was high.

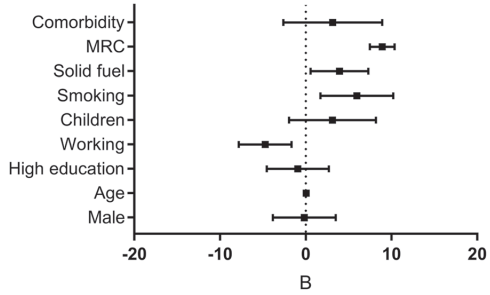

Fig. 4 Total multivariable regression. Mean unstandardized B (95%CI). MRC = medical research council breathlessness scale (1-5). Age (years)

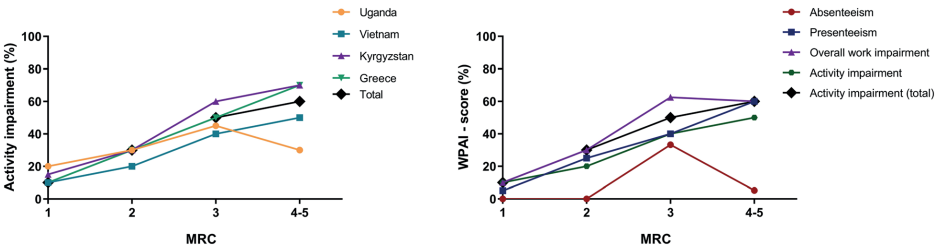

Fig. 5 WPAI and MRC-score. MRC = medical research council breathlessness scale (ranging 1-5). WPAI = work productivity and activity impairment in median %. Left: Activity impairment per MRC-score per country; Uganda *N* = 172 (1 missing MRC value), Vietnam *N* = 471, Kyrgyzstan *N* = 306, Greece *N* = 90, and total *N* = 10. Due to different population characteristics per country, data should be interpreted within the country's context and not be used to directly compare between countries. Right: WPAI per MRC-score; Absenteeism *N* = 260, presenteeism *N* = 268, overall work impairment *N* = 259, activity impairment (270), total activity impairment *N* = 1039

Risk factors for activity impairment

For data-orientation, univariable regressions are presented in Additional file 1: Appendix 4 Table E3. In each of the individual country multivariable analyses and in the meta-analysis, breathlessness severity (MRC-score) was identified as a robust predictor for activity impairment (Fig. 3, 4, 5, Additional file 1: Appendix 4 Table E4). Other significant predictors in the meta-analyses were working (inversely related), smoking, and solid fuel use. The results were similar for both meta-analyses (i.e. regardless of excluding Kyrgyzstan from the analysis). Besides activity impairment, MRC-score was identified as a predictor for both presenteeism and overall work impairment. In contrast, absenteeism remained relatively low, independent of MRC-score (Fig. 5b).

DISCUSSION

We have evaluated the socioeconomic burden of CLD in low-resource settings across the globe, with a specific focus on work- and activity impairment and its risk factors. Our findings demonstrate substantial disease-related productivity impairment, overall work impairment, and activity impairment. Remarkably, absenteeism consistently remained relatively low. Severity of breathlessness, smoking, and solid fuel use were modifiable predictors for impairment.

The patterns of absenteeism and presenteeism we have identified are similar in high-resource settings [23]. However, in our study, absolute WPAI-scores were considerably higher for all outcomes but absenteeism. Possibly, absenteeism remains low in low-resource settings, because limited or non-existent social security systems [2, 18] 'force' employees to show up at work, at the expense of a decreased productivity. Note that all WPAI-data should be interpreted within their context. The different sample sizes and diverse population characteristics would not allow for direct comparison of WPAI-scores between countries. Although participants were included using similar methods, countries and settings were selected based on diversity. The diversity-based selection resulted, for example, in differences in proportions of COPD-patients and breathlessness severity. To illustrate, Kyrgyz WPAI-scores were high compared to scores in the other countries; breathlessness severity (a strong predictor) was high in Kyrgyzstan too. Breathlessness severity could be high because of lower ambient oxygen levels in the mountains. Absenteeism could particularly be impacted by the extreme temperatures (– 20 °C in winter) and rough Kyrgyz terrains in the Kyrgyz setting, forming barriers to travelling to/from work. Hence, only considered within this context, Kyrgyz WPAI-outcomes provide meaningful information, based on real-world data on CLD-related impairment [39].

Severity of breathlessness was already reported as a predictor for impairment for higher-resource settings [36, 40, 41]; we are the first to confirm this for low-resource settings. Besides activity impairment, also presenteeism and overall work impairment increased linearly with MRC-scores.

Meanwhile, absenteeism consistently remained remarkably low despite severe breathlessness. This seems plausible, as most people with severe breathlessness have stopped working (severe breathlessness was significantly more common in our non-working population). Yet, if employed, again they ensure not to miss worktime as social security is limited.

We argue severe breathlessness may be inherent to low-resource settings, because access to healthcare and adequate equipment is limited in low-resource settings [2, 3, 16]. Therefore, a) possibly only the more severely ill patients receive a spirometry-confirmed CLD-diagnosis (one of our inclusion criteria) and b) undertreatment is common and could trigger severe symptoms. Second, low-resource settings have higher and earlier exposure to behavioral and environmental risk factors [3, 5–7, 10, 14, 42] (45% of our Kyrgyz population smoked, and the entire rural population relies on solid fuels for cooking and heating) [8]. This can result in more severe disease and hence, more breathlessness. Interestingly, higher and earlier exposure to risk factors in lower-resource settings also lead to earlier onset of disease. In combination with lower life-expectancies in lower-resource countries, this explains why the age of the patient population in Uganda was generally lower than in Vietnam and Kyrgyzstan, where in turn it was lower than in Greece.

In addition to breathlessness, both tobacco- and solid fuel use were identified as modifiable risk factors for impairment. Tobacco use was already known to predict CLD-related impairment in high-resource settings, whereas solid fuel use is newly identified and typical for low-resource settings. Furthermore, 'working' was a protective factor for activity impairment. Similarly, higher activity impairment for part-time compared to fulltime employees was reported in a high-resource setting [35]. Of note, age was a significant predictor in univariable regression analyses but turned insignificant in the multivariable analyses. We assume the effect of 'age' diminished in the multivariable model because of the presence of the more accurate predictor 'breathlessness severity' (and commonly, like age, breathlessness severity increases over time).

Comparison of CLD-related impairment to impairment due to other chronic diseases in low-resource settings is difficult due to a paucity of data. A large systematic review reported on more than 80 studies assessing WPAI due to chronic disease, yet the settings described were almost exclusively in high-income countries. The handful of studies that also included low-income countries did not report their results separately for the low-income countries [23].

To our knowledge, this is the first large (N > 1000) study to focus on the socioeconomic burden of CLDs in low-resource settings across the world providing data from validated and well-accepted instruments (WPAI, MRC-scale). This paper furthermore answers the call for robust studies identifying modifiable predictors for CLD-related impairment [25]. While some predictors were previously reported for high-resource settings [35– 37, 40], we have identified a predictor specifically relevant to low-resource settings: solid fuel use. Another strength of our study is the use of identical, yet contextually tailored, methods across four diverse settings, (Additional file 1: Appendix 2 Table E1) improving the fit with the local situation.

Some limitations should also be noted. The inclusion of only spirometry-confirmed CLD-patients might lead to selection bias; in low-resource settings patients possibly seek costly healthcare when more severely-ill, and when more severely-ill, impairment scores are higher [17, 43]. Yet given frequent CLD-misdiagnosis in the absence of spirometry [44], particularly in low-resource settings, we valued this criterion. On the one hand, misclassification due to variable spirometry interpretation or other causes for airflow obstruction (post-tuberculosis, childhood respiratory infections) cannot be fully ruled out. On the other hand, other causes would result in the need for similar interventions: reduction of occupational and household air pollution, smoking cessation, pulmonary rehabilitation, etc. Also, we had no control group in our study while socioeconomic data in low-resource settings are scarce; this made it difficult to compare our results to a healthy population. Besides, the actual population-based socioeconomic impact may be underestimated in our study. People frequently missing work might be forced to leave, particularly in more physically demanding jobs as is common in low-resource settings. Unfortunately, we cannot derive the number of early-retirements due to CLD

from our data. Lastly, following the WPAI questionnaire in its validated form, we only assessed absenteeism and presenteeism for those working for an income. We recommend future studies to apply all relevant questions not only to those "currently employed (working for pay)", but also to those self-employed or working for subsistence, as is common in LMICs.

Nevertheless, the substantial WPAI-scores we have observed imply a high socioeconomic burden due to CLDs in low-resource settings. Considering widescale underdiagnosis of CLD, particularly in low-resource settings, costs may be even higher than policymakers may realize [45, 46]. The risk factors we identified could provide potential leads for combatting impairment. Policymakers could introduce awareness-programs to educate populations on the risks of tobacco- and solid fuel use, and on affordable solutions (e.g. clean stoves). Furthermore, enhanced self-management and pulmonary rehabilitation programs could benefit the factor breathlessness severity [47]. Self-management could be challenging in low-resource settings due to more scarce availability of medications, limited access to healthcare, or widespread overestimations on disease control [3, 4, 48, 49]. Medications should therefore be available at economic costs [50], health infrastructures need to facilitate continuity of care [4], and healthcare workers should educate patients on disease control. Concurrently, although four diverse low-resource settings were assessed in our study, causality and generalizability of our findings should be evaluated further.

CONCLUSIONS

Our results showed that although relatively limited worktime was missed due to CLD in low-resource settings, the disease related productivity- and activity impairment was substantial. Severity of breathlessness, smoking, and solid fuel use were significant modifiable risk factors for impairment. Our results warrant increased awareness on the impact of CLD and the risk factors, preventive actions regarding tobacco and solid fuel use, and enhanced clinical management of CLD in low-resource settings by healthcare workers, policymakers, patients, and employers alike.

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Authors' contributions EB, AT, and JB designed the study, and tailored the protocol to each national situation together with all authors; AT, MA, TLN and SW coordinated the national data collection; EB and JB coordinated the overall process; TS, CL, PLA, and BK were national lead investigators, NC was the principal investigator of the overall FRESH AIR project; EB analyzed the data and wrote the manuscript. AT and JB provided feedback at each version. RK provided advice in multiple research stages and at multiple versions of the manuscript. All authors gave input to the manuscript and approved the last version. On behalf of the FRESH AIR collaborators.

Conflict of interest: None declared.

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Availability of data and materials Individual de-identified participant data and meta-data can be shared upon reasonable request. This includes the study protocol, data-dictionaries with details on data cleaning and meeting minutes describing considerations for data analysis. Within reasonable time after email request data will be shared via a secure webbased system.

Ethics approval and consent to participate Participants provided written, informed consent. In the three Kyrgyz hospitals where we administered the questionnaire per telephone, verbal consent was provided instead. The study was approved by each local research ethical review board: the 7th Health Region of Crete (protocol 6951;05/27/2016), National Center of Cardiology and Internal Medicine in Bishkek (5;03/03/ 2016), Mulago Research and Ethics Committee (971;05/24/2016), and Ho Chi Minh City University of Medicine and Pharmacy (188/DHYD-HD;06/27/2016).

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CHAPTER

NATIONAL GUIDELINES FOR SMOKING CESSATION IN PRIMARY CARE: A LITERATURE REVIEW AND EVIDENCE ANALYSIS

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ABSTRACT

National guidelines for smoking cessation in primary care can be effective in improving clinical practice. This study assessed which parties are involved in the development of such guidelines worldwide, which national guidelines address primary care, what recommendations are made for primary care settings, and how these recommendations correlate with each other and with current evidence. We identified national guidelines using an online resource. Only the most recent version of a guideline was included. If an English version was not available, we requested a translation or summary of the recommendations from the authors. Two researchers independently extracted data on funding sources, development methodologies, involved parties, and recommendations made within the guidelines. These recommendations were categorised using the pile-sort method. Each recommendation was cross-checked with the latest evidence and was awarded an evidence-rating. We identified 43 guidelines from 39 countries and after exclusion, we analysed 26 guidelines (22 targeting general population, 4 targeted subpopulations). Twelve categories of recommendations for primary care were identified. There was almost universal agreement regarding the need to identify smokers, advise them to quit and offer behavioural and pharmacological quit smoking support. Discrepancies were greatest for specific recommendations regarding behavioural and pharmacological support, which are likely to be due to different interpretations of evidence and/or differences in contextual health environments. Based on these findings, we developed a universal checklist of guideline recommendations as a practice tool for primary care professionals and future guideline developers.

INTRODUCTION

Tobacco smoking is a major preventable risk factor for the development of non-communicable diseases, including cancers, cardiovascular and respiratory diseases.1 Consequently, 12% of all adult deaths worldwide are attributable to tobacco use.2 Overall, among those aged 15 years and over, the worldwide prevalence of tobacco use is 22%. Smoking prevalence is, however, substantially higher among males (36%) than females (8%) (ref. 3), with large variation across countries ranging between 22% (Brazil) and 60.6% (Russia) among males, and between 0.6% (Egypt) and 28.7% (Bangladesh) among females.3,4

Long-term smoking cessation substantially reduces health risks5,6 and leads to a decrease in the risk of early mortality.7 Nationally implemented services for smoking cessation support, such as face-to-face support8 and quit lines,9 have been found to be effective in helping smokers to quit. Easy access to such smoking cessation treatment and support has also shown to increase quit rates.10

In many countries, smokers are most often identified, advised and offered quit support in a primary care setting.11 In countries with established specialist cessation services (e.g., face-to-face services and/or quit lines), general practice is the optimum environment for the identification and referral of smokers to take place. For example, in the UK almost 300 million smoking cessation consultations a year and around 90% of all National Health Service contacts take place in a general practice setting.12 Evidence for the effectiveness of interventions in this setting is well established13; rates of smoking abstinence are increased when health professionals identify smokers, prompt quit attempts,13 and provide assistance to quit smoking, including pharmacotherapy.14,15

Guidelines in which this evidence is communicated to health professionals can be effective in improving clinical practice,16 although the effects depend upon factors such as guideline quality, context and professional experience.17,18,19 Guidelines also offer an opportunity for raising the profile of smoking cessation and facilitate the implementation of the WHO Framework Convention on Tobacco Control.20

This study aims to assess the nature and extent of the current national guidelines available for the treatment of tobacco dependence in primary care. As such, the objective of the study is threefold and includes an assessment of: (1) the parties involved in the development of these guidelines, (2) the recommendations made within these guidelines for primary care and (3) how these recommendations correlate with each other (consistency) and with the state-of-the-art evidence of what is effective (validity).

METHODS

Search methods and inclusion criteria

To identify national guidelines for smoking cessation, we used an independent online resource which hosts a compilation of national treatment guidelines from across the world (www.treatobacco.net). Additional search methods included the consultation of international colleagues within the field of tobacco dependence treatment. The initial search was performed in December 2014 and was updated in September 2015. Only the most recent version of each available national guideline was included. If multiple guidelines for specific subpopulations (e.g., pregnant women) were available for one country, all those guidelines were included.

Only English-language guidelines were eligible for analyses. If guidelines were not available in English, we contacted the lead authors of the guideline and asked if they could provide an English-language version. If unsuccessful, we then asked if they were willing to provide details on the key recommendations made within the guidelines (section 'Guideline recommendations'). In case the communication with an author resulted in the availability of a more recent version of the guideline or to a version with a more specific focus on primary care, this version of the guideline replaced the initially included guidelines of this country.

We excluded guidelines where smoking cessation was only part of a guideline on a different topic (e.g., a paragraph on tobacco treatment within a guideline for asthma or COPD).

Data extraction

From each country's guideline we extracted information regarding the lead authors, the year of publication, and the lead organisation(s) involved in commissioning and/or producing the guideline (e.g., Ministry of Health). We also extracted information on funding sources for guideline development and on the development methodology. We classified the country as a high-, middle- or low-income country based on the information from the World Bank income group (http://data.worldbank.org/about/country-and-lending-groups).

Guideline recommendations

In order to identify the recommendations made, we extracted the main recommendations put forth in each country's guideline. For each included guideline, we created a coding framework consisting of the recommendations within the guideline. A segment of text was extracted as a recommendation if it met the following criteria: (1) the text was explicitly specified as a recommendation and (2) the recommendation was made specifically for a primary care setting or primary healthcare practitioner, or was relevant to either one of these. Recommendations were extracted in their smallest, irreducible form. For example, a recommendation might state that "pregnant women should only be offered NRT if they are unable to quit otherwise, and

intermittent forms of NRT are preferable to patches in this population". We recorded this as two separate recommendations: (1) "pregnant women should only be offered NRT if they are unable to quit otherwise" and (2) "intermittent forms of NRT are preferable to patches for pregnant women". Recording the recommendations in this way facilitated the comparison of recommendations across guideline documents.

To ensure consistency in the extraction of recommendations, two researchers (K.S. and G.A.) independently extracted the recommendations from two pre-selected guidelines. These two researchers discussed any discrepancies in their extraction and resolved them through discussion or through arbitration with the third researcher (A.Mc.). After having agreed upon a consistent approach to extraction, K.S. and G.A. extracted both 50% of the remainder guideline recommendations.

Consistency of guideline recommendations

To establish how consistent the recommendations were internationally, we compared each of the individual national recommendations and contrasted them against all others. Those recommendations that were identical, or very similar, were assigned to categories (e.g., 'give all smokers brief advice to quit' or 'record and update tobacco use status for all patients'). We used a 'pile-sort' method in order to establish this categorisation. Each individual recommendation was printed out on a separate piece of card along with a unique identifier. The cards were sorted independently by two researchers (K.S. and G.A.) into piles of identical/very similar individual recommendations. Each researcher assigned a category label to individual piles, and subsequently met to discuss the categorisations. Disagreements in categorisation were discussed with the third author (A.Mc.) until resolved, with category labels being finalised and agreed upon at this stage.

Validity of guidelines recommendations

To establish how well the recommendations in each of the guidelines correspond to state-of-the-art evidence, recommendations were cross-checked against the most recent English Service and Delivery Guidance for local Stop Smoking Services.21 This publication makes recommendations for how stop smoking services in the UK should be commissioned, delivered and monitored. Most importantly, it includes an updated evidence review of a number of recommendations for the treatment of tobacco dependence, including behavioural support, pharmacotherapy and the treatment among specific subpopulations.

Each recommendation within the included national guidelines was assigned an evidence rating using the SIGN rating system.22 The SIGN system includes five ratings: "A" (the recommendation is supported by good/strong evidence), "B" (the recommendation is supported by fair/reasonable evidence, but there may be minimal inconsistency or uncertainty), "C" (the recom-

mendation is supported by published expert opinion only), "I" (there is insufficient evidence to make a recommendation) and "✓" (good practice point in the opinion of the guidance development group).

Checklist of smoking cessation intervention components

We developed a checklist of components as a practice tool for primary care professionals based on: (1) the analysis of recommendations in the identified national guidelines, (2) the consistency and validity of these recommendations and (3) experts' opinions from the International Primary Care Respiratory Group.

RESULTS

Guideline inclusion

We identified a total of 43 guidelines from 39 countries. After initial review, we excluded three guidelines. Reasons for exclusion were that they either merely presented minimum specifications for a national smoking cessation service (Northern Ireland and Spain), or they focused on treatment of asthma and chronic obstructive pulmonary disease (COPD) other than on smoking cessation (Greece). Of the remaining 40 guidelines, only 16 guidelines were initially available in English. Authors of another 10 guidelines were willing to complete our coding framework on the key recommendations made within the guidelines, resulting in a total of 26 guidelines that were fully assessed for this review (Fig. 1). Table 1 provides a detailed overview of the final inclusion.

Parties involved in guideline development

Most guidelines were produced/commissioned by governmental organisations, followed by medical societies, multiple organisations, research networks and research centers. General practitioners (GPs) were involved in the development of the majority of the included guidelines (19/26); in six guidelines the lead-author of the guideline was a GP. In three guidelines, the development was led by an association of GPs and in ten guidelines at least one GP was involved in the development among many other authors. Only four guidelines were developed without any involvements of GPs and for the remaining three guidelines it was not possible to identify the profession of the authors and, therefore, GP involvement remains unclear (Japan, India, South Africa).

Guideline recommendations for primary care

The majority of the included guidelines focused on smoking cessation in the general population ($n = 22$), two focused specifically on smoking cessation during pregnancy (France and Canada), one on smoking cessation among COPD patients (Germany) and one on smoking cessation

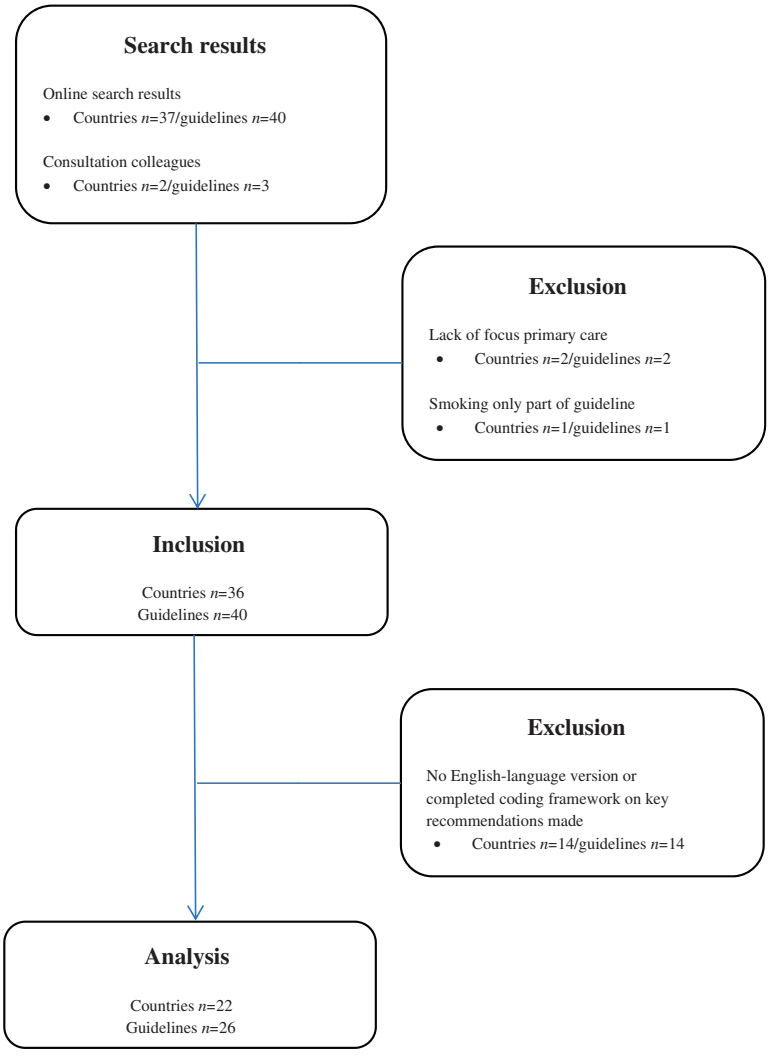

FIGURE 1. Flowchart of the study

among perioperative patients (France). Table 1 presents brief details on the funding sources and methodologies used for the development of these guidelines. A list of references for each of the guidelines can be found in Appendix A.

General population

With regard to guidelines that focus on the treatment of tobacco dependence in the general population ($n = 22$), we were able to categorise recommendations into 12 intervention types recommended for primary care:

- Each patient's smoking status should be identified and recorded (20/22);

Table 1. Details of identified national guidelines for smoking cessation in primary care

Country	Income region	Guideline focus	Most recent publication	Lead organisation	Author(s)	Funding source	Development methodology
Argentina	Upper middle	General	2011	Ministry of Health, National Quality Assurance Program in Health Care	Casetta, B. and Videla, A	None reported	Systematic literature review (guidelines and meta-analysis). Levels of evidence assigned to recommendations. Reviewed by expert panel.
Australia	High	General	2011	Royal Australian College of General Practitioners	Zwart *et al.*	Private	Not described. Levels of evidence and strength of recommendation categories assigned to recommendations
Canada	High	General	2011	The Canadian Action Network for the Advancement, Dissemination and Adoption of Practice-informed Tobacco Treatment (CAN-ADAPPT); Centre for Addiction and Mental Health	Selby *et al.*	Drugs and Tobacco Initiative, Health Canada	Review and appraisal of existing English-language clinical practice guidelines and systematic search for evidence. Levels of evidence assigned to recommendations
		Pregnancy	2010	CAN-ADAPPT; Centre for Addiction and Mental Health	Ordean, A.	Drugs and Tobacco Initiative, Health Canada	Review and appraisal of existing English-language clinical practice guidelines and systematic search for evidence. Evidence levels assigned to each recommendation
Chile	High	General	2003	Ministry of Health, Pan American Health Organisation	Marisol Acuña	None reported	Not reported
Czech Republic	High	General	2005	—	Králíková, E.	None reported	Not reported
Denmark	High	General	2011	Danish Health and Medicines Authority	Pisinger *et al.*	Ministry of Health	Based on thorough review of available guidelines from England, US, Canada, Australia and New Zealand and Cochrane reviews on smoking cessation. Tailored for Danish conditions. Written by tobacco research expert in cooperation with a general practitioner, a representative from the municipalities and a representative from smoking cessation counsellors network
France	High	General	2007	Health authority	Scemama *et al.*	Public funds	Document review, expert panel
		Pregnancy	2004	Alliance against tobacco	Delcroix *et al.*	State Insurance Fund for Free-lance Professionals, Nord-Pas-de-Calais Regional Council, Health Protection Branch, National League against Cancer,	Presentation of evidence by experts to a jury responsible for drafting the guidelines

Table 1 continued

Country	Income region	Guideline focus	Most recent publication	Lead organisation	Author(s)	Funding source	Development methodology
						National Mutual Insurance Company of Hospital Staff, Aventis; EOLYS; FIM; GlaxoSmithKline; Novartis Santé Familiale; Pfizer Pierre Fabre Santé; Roche Nicholas	
		Peri-operative	2005	French Association of Surgery	Cohendy *et al.*	Ministère de la Santé DGS; Pfizer; AltanaPharma; Sanofi-Aventis; Glaxo SmithKline; Novartis; Pierre Fabre Santé	Literature review
Germany	High	General	2004	Association of the Scientific Medical Societies in Germany (AWMF)	Batra *et al.*	Donations: DG Sucht and DGPPN, Support: Central Institute of Mental Health, department Addiction Research and Addiction Medicine in Tübingen. No third-parties or private companies	Systematic literature and critical appraisal. Level of evidence assigned to recommendations. Afterwards reviewed by an expert panel
		COPD	2008	German Society for Pneumology and Respiratory Medicine	Andreas *et al.*	None reported	Literature review and review by expert panel
India	Lower-middle	General	2011	National Tobacco Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India	Rajkumar *et al.*	None reported	Not described
Japan	High	General	2010	Japanese Circulation Society	Japanese Circulation Society Joint Working Group	None reported	Not described. Levels of evidence assigned to recommendations
Jordan	Upper-middle	General	2014	King Hussein Cancer Foundation, King Hussein Cancer Center	Hawari *et al.*	None reported	Literature review
Kyrgyzstan	Lower-middle	General	2004	Ministry of Healthcare of Kyrgyz Republic	Brikulov *et al.*	None reported	Not described
Malaysia	Upper-middle	General	2003	Ministry of Health Malaysia	Aziahbt Mahayiddin *et al.*	None reported	Adaptation of US (2000), New Zealand (2001) and American Psychiatric Association (1996) guidelines with incorporation of a systematic literature review. Levels of evidence assigned to recommendations.
Netherlands	High	General	2007	Dutch Association of General Practitioners	Chavannes *et al.*	Stop Smoking Partnership	Alignment with the multidisciplinary guideline regarding tobacco addiction developed by the Dutch Institite for

Table 1 continued

Country	Income region	Guideline focus	Most recent publication	Lead organisation	Author(s)	Funding source	Development methodology
							Healthcare Improvement and adapted for use in general practice (2004)
New Zealand	High	General	2014	Clinical Trials Research Unit (now: the National Institute for Health Innovation [NIHI]), the University of Auckland	McRobbie *et al.*	Ministry of Health	Literature review undertaken by a consortium. Guidelines developed in accordance with the AGREE tool. Levels of evidence assigned to recommendations according to the New Zealand Guidelines Group.
Norway	High	General	2004	Health and Social Affairs Agency	Huseby *et al.*	None reported	Not described
Portugal	High	General	2008	Centre for Evidence Based Medicine, University of Lisbon School of Medicine	Reis *et al.*	Pfizer (unrestricted grant)	Not described
Scotland	High	General	2004	Health Scotland, Action on Smoking and Health Scotland	West *et al.*	None reported	Not described
South Africa	Upper-middle	General	2013	South African Thoracic Society	van Zyl-Smit *et al.*	Pfizer	Review and appraisal of existing international clinical practice guidelines, applying them specific national needs. Evidence assigned to each recommendation
Sweden	High	General	2011	The National Board of Health and Welfare	Axelsen *et al.*	None reported	
UK	High	General	2000	Health Education Authority	West *et al.*	Health Education Authority; Health Development Agency	Based on meta-analytic reviews and other relevant evidence. Levels of evidence assigned to recommendations
USA	High	General	2008	U.S. Department of Health and Human Services	Fiore *et al.*	Agency for Healthcare Research and Quality; Centers for Disease Control and Prevention; National Cancer Institute; National Heart, Lung, and Blood Institute; National Institute on Drug Abuse; American Legacy Foundation; Robert Wood Johnson Foundation; University of Wisconsin School of Medicine; Public Health's Center for Tobacco Research and Intervention	Systematic literature review. Levels of evidence assigned to recommendations

- All smokers should be given brief advice to stop (20/22);
- Smokers' motivation to quit should be assessed (17/22);
- All smokers wishing to stop should be offered assistance (22/22);
- All smokers wishing to stop should be offered/encouraged to use pharmacotherapy (22/22);
- All smokers wishing to stop should be offered behavioural support (19/22);
- Self-help materials should be offered as part of tobacco dependence treatment (12/22);
- Smoking abstinence should be evaluated following treatment (5/22);
- The '5A's Framework' should be used to guide brief intervention (16/22);
- The 'ABC Framework' should be used to guide brief intervention (3/22);
- Health-care professionals should be trained in delivering tobacco dependence treatment (13/22);
- Hypnotherapy and acupuncture are not effective smoking cessation treatments (6/22).

Table 2 provides an overview of these recommendations put forth in each national guideline. Full details on the types of pharmacotherapy recommended in each national guideline are presented in Table 3.

Subpopulations

The majority of the guidelines include sections concerning the treatment of tobacco dependence among specific subpopulations (e.g., pregnant women, children and adolescents, COPD patients). Moreover, several countries developed specific guidelines for the treatment of tobacco dependence among such subpopulations. The most frequently mentioned recommendations across guidelines are described in this section (details on recommendations for specific subpopulations in each national guideline are presented in Table 4).

Pregnant women

In total, 19 guidelines targeting the general population provided recommendations for the treatment of tobacco dependence among pregnant women. In addition, France and Canada developed a specific guideline for this subpopulation. Overall, guidelines recommend that all pregnant smokers should be offered brief advice to quit and should be provided with counselling, including behavioural and pharmacological support. Of the 21 guidelines that address smoking cessation treatment among pregnant women, 16 guidelines recommended that nicotine replacement therapy (NRT) can be used to assist smoking cessation attempts made by pregnant women. In several countries, intermittent-dosage forms of NRT (e.g., gum, nasal and oral sprays) are recommended as a preferred pharmacotherapy over patches (Australia, Canada (pregnancy-specific guideline), New Zealand, Portugal and India). In contrast, guidelines from Norway, Scotland, the United States, Japan and Kyrgyzstan all recommended that NRT should not be given to pregnant women.

Table 2. Recommendations in national guidelines for smoking cessation in primary care

	Argentina	Australia	Canada	Chile	Czech Republic	Denmark	France	Germany	India	Japan	Jordan	Kyrgyzstan	Malaysia	Netherlands	New Zealand	Norway	Portugal	Scotland	South Africa	Sweden	UK	USA
Identify	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	✓
Brief advice	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assess motivation	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓			✓	✓		✓
Offer assistance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Offer pharmacotherapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Offer behavioural support	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓
Self-help	✓			✓		✓	✓	✓		✓	✓				✓	✓	✓			✓		✓
Evaluate abstinence				✓	✓		✓				✓											✓
5A's Framework	✓	✓	✓	✓	✓	✓			✓	✓	✓		✓	✓		✓	✓		✓		✓	✓
ABC Framework					✓	✓									✓							
Appropriate training	✓				✓	✓	✓	✓			✓			✓	✓			✓		✓	✓	✓
Hypnotherapy and acupuncture not effective	✓	✓						✓[a]				✓							✓	✓		

Note: 5A's = Ask, Advise, Assess, Assist, Arrange, *ABC* Ask, provide Brief advice, offer/refer to/provide evidence-based Counselling. Excluding guidelines targeting specific population

[a]The German guideline recommends hypnotherapy; acupuncture is not recommended as an effective treatment

Table 3. Types of pharmacotherapy recommended in national guidelines for smoking cessation in primary care

	Argentina	Australia	Canada[a]	Chile	Czech Republic	Denmark	France	Germany	India	Japan	Jordan	Kyrgyzstan	Malaysia	Netherlands	New Zealand	Norway	Portugal	Scotland[b]	South Africa	Sweden	UK	USA
NRT	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Bupropion	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓			✓	✓	✓
Varenicline	✓	✓			✓	✓	✓	✓	✓	✓			✓		✓		✓		✓	✓	✓	✓
Combination NRT	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Combined NRT + Bupropion	✓			✓	✓			✓			✓		✓	✓					✓			✓
Nortriptyline	✓[c]	✓[c]						✓			✓[c]			✓	✓		✓		✓			✓[c]
Clonidine	✓[c]										✓[c]						✓[c]					✓[c]

Note: *NRT* nicotine replacement therapy. Excluding guidelines targeting specific populations

[a]The Canadian guideline did not include a section of recommendations regarding pharmacotherapy. It was noted within these guideline that the development of these recommendations was in progress. At the time of writing this paper an update including recommendations for pharmacotherapy had not been released

[b]The Scottish guidelines did include recommendations for pharmacotherapy, however, these were included within recommendations for Specialist Stop Smoking Services which were not extracted for the purpose of this review. These recommended NRT, combination NRT and bupropion

[c]Second line

Black and minority ethnic groups

Guidelines from five countries made recommendations for black and minority ethnic (BME) groups: Canada, New Zealand, Norway, Portugal and Sweden. All recommend that wherever possible, culturally appropriate smoking cessation support should be offered. These guidelines also recommend that health-care workers should receive additional training in delivering smoking cessation support to BME groups.

Children and adolescents

In total, 16 guidelines made specific recommendations for children and adolescents. Overall, these include: (1) information about tobacco use among children and adolescents should be obtained on a regular basis, (2) children and adolescents should be counselled to encourage abstinence and (3) parents who smoke should be offered smoking cessation support in order to limit children's exposure to secondhand tobacco smoke. Of these guidelines, 11 guidelines recommend that NRT could be offered to adolescents who show evidence of nicotine dependence. In contrast, several other guidelines recommend that pharmacotherapy should not be offered to children and adolescents (Canada, Norway, Portugal and the USA).

Mental illness/other addiction

Eleven guidelines made specific recommendations for smokers with a mental illness or other substance addiction. Most commonly, guidelines recommend to offer counselling that incorporates all known effective components and to carefully monitor smoking cessation in which medication dosages should be adjusted if necessary. The types of pharmacotherapy recommended for the treatment of tobacco dependence among these patients differed across countries (Table 4).

Chronic illness

In total, 15 guidelines made specific recommendations for people with a chronic illness. Most guidelines recommend that NRT is safe to use in people with stable cardiovascular disease. However, NRT should be used with caution in patients with unstable cardiovascular disease (e.g., severe or unstable angina, recent myocardial infarction). Additionally, several guidelines also recommend bupropion as a safe treatment for nicotine dependence in people with cardiovascular disease (Argentina, Chile, Czech Republic, India, the Netherlands, New Zealand and Portugal).

Validity of guideline recommendations

Table 4 lists all recommendations made in the included guidelines and shows the level of evidence we assigned to them according to the Scottish Intercollegiate Guidelines Network (SIGN) system. Of all recommendations, only three ('provide brief advice', 'provide behavioural support', and 'offer/encourage pharmacotherapy') were included in the Service and Delivery Guidance and as such were assigned an evidence rating. We assigned the evidence rating 'A'

Table 4. Evidence ratings assigned to recommendations from included guidelines

	S&D Guidance (Y/N)	Evidence rating[a]	Argentina	Australia	Canada[b]	Canada pregnancy	Chile	Czech Republic	Denmark	France	France pregnancy	France peri-operative	Germany	Germany COPD	India	Japan	Jordan	Kyrgyzstan	Malaysia	Netherlands	New Zealand	Norway	Portugal	Scotland[c]	South Africa	Sweden	UK	USA
General population																												
Identify	N	–	✓	✓	✓		✓	✓	✓	✓			✓		✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	✓
Brief advice	Y	A	✓	✓	✓		✓	✓	✓				✓		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Assess motivation	N	—	✓	✓	✓		✓	✓	✓	✓					✓	✓	✓	✓	✓	✓		✓			✓	✓		✓
Offer assistance	N	—	✓	✓	✓		✓	✓	✓	✓			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Offer pharmacotherapy	Y	—	✓	✓	✓		✓	✓	✓	✓			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
NRT	Y	A	✓	✓			✓	✓	✓	✓			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Bupropion	Y	A	✓	✓			✓	✓	✓	✓			✓		✓			✓	✓	✓	✓	✓	✓			✓	✓	✓
Varenicline	Y	A	✓	✓				✓	✓	✓			✓		✓	✓					✓		✓		✓	✓		✓
Combination NRT	Y	A	✓	✓			✓	✓	✓	✓			✓			✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓
Combined NRT + bupropion	N	—	✓				✓	✓					✓				✓		✓	✓					✓			✓
Nortriptyline	N	—	✓[e]	✓									✓				✓[e]			✓	✓		✓		✓			✓
Clonidine	N	—	✓[e]										✓				✓[e]						✓					✓
Offer behavioural support	Y	A	✓	✓	✓		✓	✓	✓	✓			✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓
Self-help	N	—	✓				✓		✓	✓			✓			✓	✓			✓	✓	✓	✓			✓		✓
Evaluate abstinence	Y	A					✓	✓		✓							✓											✓
5A's framework	N	—	✓	✓	✓		✓	✓	✓						✓	✓	✓		✓	✓		✓	✓		✓		✓	✓
ABC framework	N	—						✓	✓												✓							
Appropriate training	N	—	✓					✓	✓	✓			✓				✓			✓	✓			✓		✓	✓	✓
Subpopulations																												
Pregnancy	Y	B	✓	✓		✓	✓	✓		✓	✓		✓		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Offer NRT	Y	C	✓	✓		✓	✓	✓		✓	✓		✓		✓				✓	✓	✓		✓		✓	✓	✓	
BME groups	Y	B			✓																✓	✓	✓			✓		
Children and adolescents	Y	—	✓		✓		✓	✓		✓	✓		✓			✓	✓		✓	✓	✓	✓	✓			✓		✓
Offer NRT	N	—	✓				✓	✓		✓[d]			✓			✓	✓		✓	✓	✓					✓		
Mental illness/ other addiction	Y	B/C	✓		✓			✓		✓			✓		✓				✓		✓		✓		✓	✓		
Bupropion	N	—	✓					✓		✓			✓						✓				✓					
Nortriptyline	N	—											✓										✓					
Chronic somatic illness	N	—	✓	✓				✓		✓			✓	✓	✓	✓	✓	✓		✓	✓		✓			✓	✓	
Offer NRT (CVD)	N	—	✓	✓			✓	✓		✓			✓		✓	✓	✓			✓	✓		✓				✓	
Bupropion (CVD)	N	—	✓				✓	✓							✓					✓	✓		✓					

Note: *S&D* Service and Delivery Guidance, *NRT* nicotine replacement therapy, *CVD* cardiovascular disease, *COPD* chronic obstructive pulmonary disease, *BME* black and minority ethnic groups

[a]Evidence rating based on the SIGN system: A=recommendation is supported by strong evidence, B=recommendation is supported by reasonable evidence, C=recommendation is supported by expert opinion only, I=insufficient evidence to make a recommendation

[b]The Canadian guideline did not include a section of recommendations regarding pharmacotherapy. It was noted within these guideline that the development of these recommendations was in progress. At the time of writing this review an update including recommendations for pharmacotherapy had not been released

[c]The Scottish guideline did include recommendations for pharmacotherapy, however, these were included within recommendations for Specialist Stop Smoking Services which were not extracted for the purpose of this review. These recommended NRT, combination NRT and bupropion

[d]The French guideline for the general population recommends NRT only for adolescent of 15 years and older

[e]Second line

(strong evidence) to 'provide brief advice' and 'provide behavioural support'. With some exceptions, the majority of the included guidelines recommend the use of NRT, a combination of several forms of NRT, bupropion and varenicline; all of which we assigned the evidence rating 'A'. Fewer guidelines recommended combined treatment with NRT and bupropion, or the use of nortriptyline or clonidine as second-line treatments. These recommendations were not included in the Service and Delivery guidance and as such have not been assigned an evidence rating.

Recommendations concerning pregnant women, BME groups and people with mental illness were assigned an evidence rating 'B' (supported by reasonable evidence). People with other addictions were assigned the rating 'C' (supported by expert opinion only). For the purposes of our review, mental illness and other substance addictions were placed in a single group to reflect the content of the national guidelines; these groups are treated separately in the Service and Delivery Guidance. Children and adolescents were not assigned an evidence rating as a priority group. Rather, the Service and Delivery Guidance assigned a rating of 'I' (insufficient evidence to make a recommendation) to stop smoking interventions and 'B' to prevention and tobacco control. The use of NRT for pregnant women was assigned the evidence rating 'C'. The use of pharmacotherapy for children and adolescents, people with cardiovascular disease and people with mental illness were not assigned an evidence rating as these were not included in the Service and Delivery Guidance.

DISCUSSION

This study aimed to assess: (1) the parties which were involved in the development of national guidelines for smoking cessation, (2) the recommendations that are made for primary care within these guidelines and (3) how these recommendations correlate with each other (consistency) and with the state-of-the arts evidence of what is effective (validity).

Main findings

In our study, 26 guidelines from 22 countries were included in the analyses. Four of these guidelines focused on the treatment of tobacco dependence among specific subpopulations: pregnant smokers (Canada and France), perioperative (France) and COPD patients (Germany). Most guidelines were produced/commissioned by governmental organisations, followed by medical societies, multiple organisations, research networks and research centers. Although most guidelines were developed in collaboration with GPs, only a minority of the guidelines was developed by a GP as the lead author.

Overall, recommendations that focused on the treatment of tobacco dependence in primary care among the general population corresponded well with each other across guidelines. The

majority of these guidelines recommended that smokers should be identified, be offered a brief advice to quit, be assessed for motivation to quit, and be offered assistance to quit with behavioural support and pharmacotherapy. Also, the majority recommended the use of the '5A's' framework to guide brief intervention.

We found more inconsistency across details of specific recommendations. For example, the specific content (practical counselling techniques vs. no details on content) and delivery format (e.g., only telephone or face-to-face vs. multiple formats) of behavioural support differed greatly throughout guidelines. These inconsistencies can be partly explained by the differences in the services available at the country level (e.g., the Australian guideline mentioned telephone support since they have a national quitline).

Other inconsistencies among recommendations were related to the provision of pharmacotherapy for smoking cessation among the general population. Excluding the Canadian and Scottish guidelines, who did not make recommendations relating to the use of pharmacotherapy, NRT was recommended by all guidelines. Although a combination of NRT products was recommended by a majority of the guidelines (19/22), varenicline was recommended by only 15 of 22 guidelines. Recommendations to the use of nortriptyline (9/22), a combination of NRT and bupropion (9/22), and clonidine (4/22) were less common. The discrepancies between these recommendations may be due to differences in medication licensing across countries, or to a difference in access or interpretation of the current available scientific evidence. Also, we argue that costs of medication could be a possible barrier in certain countries for uptake of certain recommendations into the guideline.

Finally, recommendations for specific subpopulations were also less consistent throughout guidelines. For example, 15 guidelines recommended that NRT could be used when needed for pregnant women, while five guidelines recommended that NRT should not be used during pregnancy. Similarly, 10 guidelines recommended that NRT could be used for children and adolescents, while four recommended that NRT should not be used in this group. Possibly these inconsistencies are related to the level of evidence available for these subpopulations, which mostly undefined and otherwise limited to level B or lower (Table 4). Cultural influences—such as the position of pharmacotherapy as well as the position of the subpopulations in society—may play a role as well.

Strengths and limitations of this study

The current study is one of the first to systematically identify and analyse the nature and extent of a large number of practice guidelines for the treatment of tobacco dependence in primary care. Moreover, it is the first to compare guideline recommendations across countries and with state-of-the-art evidence for both the general population and specific subpopulations.

However, some limitations need to be taken into account when interpreting the results. Firstly, we only included guidelines that were written or translated into English. Non-English guidelines that could not be translated were only included if the guideline authors were willing to provide the necessary information, and data was thus not derived directly from these guidelines.

Secondly, several guideline recommendations made in the Service and Delivery Guidance were not mentioned in any of the included national guidelines. These include types of pharmacotherapy treatment (nicotine-assisted reduction to stop—evidence rating B), unlicensed stop smoking treatment (e.g., electronic cigarettes—evidence rating C), and the identification of routine and manual workers as an additional priority group (evidence rating B). The lack of uptake of recommendations regarding electronic cigarettes can be explained by their recent rapid rise on the market, which mainly started only after the development of most of the included guidelines (most of them dating from 2011 and earlier). It illustrates a need of frequent updates of the national guidelines. The lack of inclusion of other recommendations in the identified guidelines may indicate a translational gap of the latest evidence. We, therefore, recommend future studies that aim to identify this translational gap, raise awareness among guideline developers and trigger them to update guidelines and include the latest evidence.

Thirdly, we were unable to rate the quality of several recommendations within the guidelines because they did not match with the recommendations within the Service and Delivery Guidance (identify smokers', 'assess motivation', 'offer assistance' and 'use the 5 A's framework'). This was likely due to vague descriptions of the recommendations within the guidelines.

Finally, although we managed to analyse the consistency and validity of the guideline recommendations, this study does not provide insight into how these guideline recommendations are currently being implemented in each country.

Implications for future research and practice

Results of our study indicate that, although some consensus on smoking cessation recommendations already exist, there is room for improvement with regard to the inconsistencies we found. Therefore, we suggest that the development of an international smoking cessation guideline for primary care, drawing upon the latest evidence and written by international clinical, policy and academic experts could provide a template to optimise future national guidelines. Based on our study findings, we developed a checklist of recommended smoking cessation intervention components as a 'tool for practice' for primary care professionals (Supplementary Material). Although this checklist presents universal key recommendations for the treatment of tobacco dependence in primary care, both health professionals and guideline developers need to take into consideration their own national health- and economic context when applying

these recommendations. Among these considerations should be cultural adaptations tailored to, for example, specific risk groups.

CONCLUSIONS

Our study shows that there is almost universal agreement between guidelines regarding the need in primary care to identify smokers, to offer some form of advice to quit and to offer behavioural and pharmacological support to quit. Discrepancies between guideline recommendations were greatest for these latter interventions, which are likely due to different interpretations of the evidence and/or differences in the contextual health environments of countries. International primary care guidance for smoking cessation that is dynamic, (co-) written by primary care experts and drawing from the latest evidence would be a very useful resource for clinicians and policy makers to develop and optimise national guidelines.

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Author Contributions

M.V., E.B. and R.v.d.K. contributed to the interpretation of the data, drafting and critical revision of the manuscript and gave final approval of the version to be published. K.S. and G.A. contributed to the conception of the study, data collection, data analysis and interpretation, and gave final approval of the manuscript version to be published. S.W. and A.Mc. contributed to the conception of the study, data collection, data analysis and interpretation, drafting and critical revision of the manuscript and gave final approval of the version to be published. N.C. contributed to the conception of the study, data analysis and interpretation, drafting and critical revision of the manuscript and gave final approval of the version to be published.

Competing interests

A.Mc. has received travel funding, honorariums and consultancy payments from manufacturers of smoking cessation products (Pfizer Ltd, Novartis UK and GSK Consumer Healthcare Ltd). Other authors declare no conflict of interests.

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PART II
TOWARDS A SOLUTION

FACILITATING IMPLEMENTATION SUCCESS OF LUNG HEALTH PROGRAMMES BY ENGAGING AND LEVERAGING THEIR LOCAL CONTEXT

CHAPTER 6

IMPLEMENTING LUNG HEALTH INTERVENTIONS IN LOW- AND MIDDLE-INCOME COUNTRIES – A FRESH AIR SYSTEMATIC REVIEW AND META-SYNTHESIS

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Take home message: This systematic review and meta-synthesis shows why implementation of lung health interventions often fails in low- and middle-income countries, and it provides critical factors to prevent failure with their level of evidence.

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Trial Registration Number: The FRESH AIR study is registered under trial registration number: NTR5759. http://www.trialregister.nl/trialreg/admin/rctsearch.asp?Term=23332

ABSTRACT

The vast majority of patients with chronic respiratory disease live in low- and middle-income countries (LMICs). Paradoxically, relevant interventions often fail to be effective particularly in these settings, as LMICs lack solid evidence on how to implement interventions successfully. Therefore, we aimed to identify factors critical to the implementation of lung health interventions in LMICs, and weigh their level of evidence.

This systematic review followed Cochrane methodology and Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) reporting standards. We searched eight databases without date or language restrictions in July 2019, and included all relevant original, peer-reviewed articles. Two researchers independently selected articles, critically appraised them (using Critical Appraisal Skills Programme (CASP)/ Meta Quality Appraisal Tool (MetaQAT)), extracted data, coded factors (following the Consolidated Framework for Implementation Research (CFIR)), and assigned levels of confidence in the factors (via Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual)). We meta-synthesised levels of evidence of the factors based on their frequency and the assigned level of confidence (PROSPERO:CRD42018088687).

We included 37 articles out of 9111 screened. Studies were performed across the globe in a broad range of settings. Factors identified with a high level of evidence were: 1) "Understanding needs of local users"; 2) ensuring "Compatibility" of interventions with local contexts (cultures, infrastructures); 3) identifying influential stakeholders and applying "Engagement" strategies; 4) ensuring adequate "Access to knowledge and information"; and 5) addressing "Resource availability". All implementation factors and their level of evidence were synthesised in an implementation tool.

To conclude, this study identified implementation factors for lung health interventions in LMICs, weighed their level of evidence, and integrated the results into an implementation tool for practice. Policymakers, nongovernmental organisations, practitioners, and researchers may use this FRESH AIR (Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups) Implementation tool to develop evidence-based implementation strategies for related interventions. This could increase interventions' implementation success, thereby optimising the use of already-scarce resources and improving health outcomes.

INTRODUCTION

Chronic respiratory diseases (CRDs) are a silent and growing epidemic in low- and middle-income countries (LMICs). Chronic obstructive pulmonary disease (COPD) is now the third leading cause of death worldwide; over 90% of these deaths and 80% of asthma-related deaths occur in LMICs [1–5]. LMICs are disproportionately burdened by CRDs because of the early and high exposure to risk factors for lung impairment [6–13]. Suboptimal access to diagnostic and treatment options in LMICs additionally exacerbates disease severity [6, 11]. Although promising interventions targeting CRD have existed for decades, many fail to translate into meaningful health outcomes. The disappointing intervention effects are often attributed to implementation failure [14–18]. In some estimates, over 60% of organisations' implementation efforts are unsuccessful [19]. Implementation success of clean cookstove programmes is often reported as strikingly low, with stove adoption rates of 4–10% [20–25].

However, implementation, the act of carrying an intervention into effect [26], is complex. Throughout the entire implementation process, from the dissemination of an intervention to its sustained use [27], numerous factors determine success or failure. These implementation factors are often interacting and influential at multiple levels. To better understand the factors so that they can be adequately addressed in implementation strategies, factors can be pragmatically structured. The Consolidated Framework for Implementation Research (CFIR) integrated 42 implementation factors from existing implementation theories [18], and categorised them in five domains: 1) innovation characteristics (e.g. the adaptability of an intervention); 2) outer setting (e.g. understanding the needs of local users); 3) inner setting (e.g. resource availability); 4) characteristics of individuals (e.g. self-efficacy); and 5) process (e.g. engagement of stakeholder). The importance of each factor depends on the context [28, 29]. Hence, implementation strategies are more successful when context-specific factors are known and addressed.

Therefore, it is essential to understand which specific factors play a role in the context of CRDs in LMICs. Paradoxically, despite the highest burden of CRD in LMICs, precisely in these countries, evidence on what factors determine implementation success is limited, fragmented and of varying methodological quality [30–33]. Extrapolating the evidence from high-income countries to LMICs is inappropriate because of differences in health, economic and cultural contexts. Several calls already highlighted the need for high-quality implementation research in LMICs [25, 34–37]. Therefore, in this study, we aimed to identify factors critical to the successful implementation of interventions targeting CRDs in LMICs, and to weigh their level of evidence.

METHODS

This systematic review and meta-synthesis is part of the Horizon2020 FRESH AIR project (Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups), addressing the implementation of prevention, diagnosis, and treatment of CRD in low-resource settings (trial registration number: NTR5759) [38]. This review is registered at PROSPERO (CRD42018088687) and follows Cochrane methodology [39, 40] and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) reporting standards [41].

All steps of the review process were performed by two researchers (E.A. Brakema and D. Vermond) independently. Results were compared, and discrepancies solved through discussion. A third researcher (R.M.J.J. van der Kleij) was consulted when consensus could not be reached. We systematically applied validated tools throughout the entire process, to enhance the reproducibility and transparency of our outcomes (figure 1).

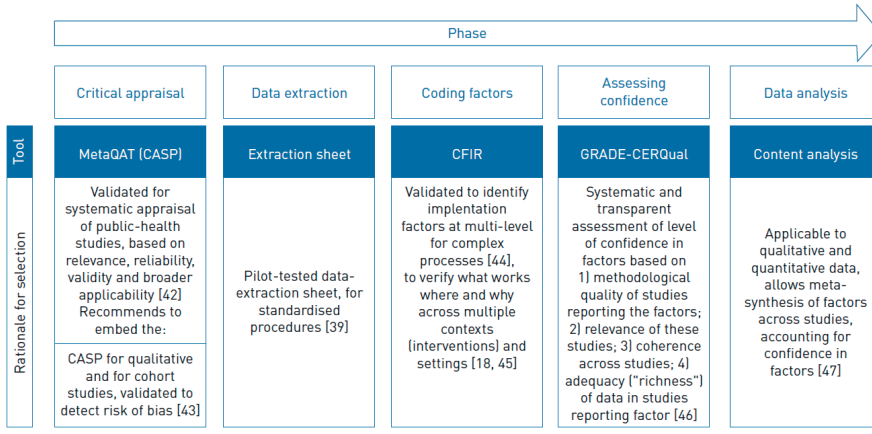

FIGURE 1 Tool used in each phase. Meta-QAT: Meta Quality Appraisal Tool; CASP: Critical Appraisal Skills Programme; CFIR: Consolidated Framework for Implementation Research; GRADE-CERQual: Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research.

Search strategy and selection criteria

We developed the search strategy together with a certified medical librarian; it contained (synonyms of) implementation, LMICs and CRD or specific relevant interventions such as "smoking cessation" (appendix 1). We focussed on asthma and COPD as the most prevalent chronic lung diseases. In PubMed, Embase, Global Health Database, Cochrane, PsycINFO, Emcare, Web of Science and CINAHL, we searched without language restriction for articles published by Oct 23, 2017, and updated our search on July 10, 2019. We included all relevant, original, peer-reviewed articles focussing on the implementation of interventions targeting CRD in LMICs (as classified by the World Bank [48]). As recommended for studying implementation, quantitative,

qualitative and mixed-method articles were considered relevant [26]. Articles were excluded if they focussed on legislation at a national governmental level (e.g. implementation of tobacco taxes) or on hypothetical interventions (e.g. theoretical willingness to adopt an intervention), if no factors were reported, or if no full text was available after contacting the authors. Our orienting search resulted in a disproportionate number of articles on the implementation of clean cooking interventions targeting household air pollution. To avoid this specific intervention dominating all review findings, we decided to split our review into two parts. This first review regards the implementation of all but clean cooking interventions, while the second (to be published later) will be exclusively dedicated to those.

Full operationalisation of the search criteria is presented in appendix 1. In addition, we manually searched Google and Google Scholar for the full articles from identified conference abstracts and study protocols, and screened all references from relevant reviews and the included articles.

Critical appraisal

To critically appraise the included articles on relevance, reliability (reporting quality), validity and applicability, we used the validated Meta Quality Appraisal Tool (MetaQAT) [42] (appendix 2) and, as recommended, we embedded the Critical Appraisal Skills Programme (CASP) into it [43]. Results served as input for the assessment of level of evidence of the identified factors (see data analysis).

Data extraction

We extracted descriptive study characteristics (author, year, study design, country, setting/population, intervention, type of outcomes measures used and funding source) and the implementation factors using a pilot-tested, standardised sheet. Speculations (such as "Factor A might have influenced implementation") or repetitions in the reporting of factors within the same article were not extracted. We extracted modifiable factors (e.g. factors to address user demographics would be extracted, but demographics on their own would not), to serve the design of future implementation initiatives. Only factors based on original data were extracted. If multiple articles were based on the same study, we compared the article's aim, methods and results in detail. If these were similar, we extracted data from the article that scored highest in our appraisal. If they differed (e.g. one was a pilot version and the other the scale-up of the same study), data from both (or more) articles were used.

Data analysis

For our meta-synthesis (weighing of the factors) we used content analysis, in which all data are categorised into themes and the frequencies of the themes are determined. Content analysis is suitable for both qualitative and quantitative evidence [47].

First, we categorised all identified implementation factors by deductive coding using the CFIR [18]. We inductively added several codes to the CFIR (such as "language" or "role model") when our extracted factors did not match existing codes (appendix 3). Second, we used the Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) tool to determine the level of confidence in the importance of the coded factors. The GRADE-CERQual tool has four components (figure 1), and the results of the critical appraisal served as input for scoring those (e.g. a high MetaQAT score for relevance translated into "no to very minor concerns" in the GRADE-CERQual component "relevance") [46]. Third, each factor was awarded a maximum of four points per component per study in which it appeared (four points for "no to very minor concerns" regarding the component in that specific study, three for "minor concerns", two for "moderate concerns", and one for "substantial concerns"). Hence, factors were awarded higher scores when they appeared in more studies (the principle of content analysis), and when the components methodology, relevance and adequacy of the study were appraised as high. The fourth GRADE-CERQual component "coherence" was not rated, because the number of studies in which the factor appeared already accounted for coherence. To conclude, the higher a factor scored, the higher the level of evidence to regard it as an important factor.

Role of the funding source

This study was funded by the European Union Research and Innovation programme Horizon2020 (Health, Medical research and the challenge of ageing) under grant agreement no. 680997. The funders had no role in study design, data collection, data analysis, data interpretation or writing of the report. All authors had full access to all the data and E.A. Brakema, D. Vermond, R.M.J.J. van der Kleij and N.H. Chavannes, the guarantor, had the final responsibility for the decision to submit the study for publication.

Reflexivity

Members of our research team came from diverse backgrounds (researchers and clinicians from psychology and medicine, with work experience in high-income countries, LMICs, or both). In these roles, we had experienced working conditions characterised by many of the factors we identified, such as lack of resources and personnel. We recognised that we were potentially more receptive to factors we had experienced ourselves, so adhered to our standardised extraction procedures.

RESULTS

Search results

Our search resulted in 9111 unique articles. After full-text screening, we included 37 articles derived from 33 different studies (figure 2 and table 1). One article was excluded from the analysis [49], as its factors were based on the exact same study data as another article which scored higher in the critical appraisal [50].

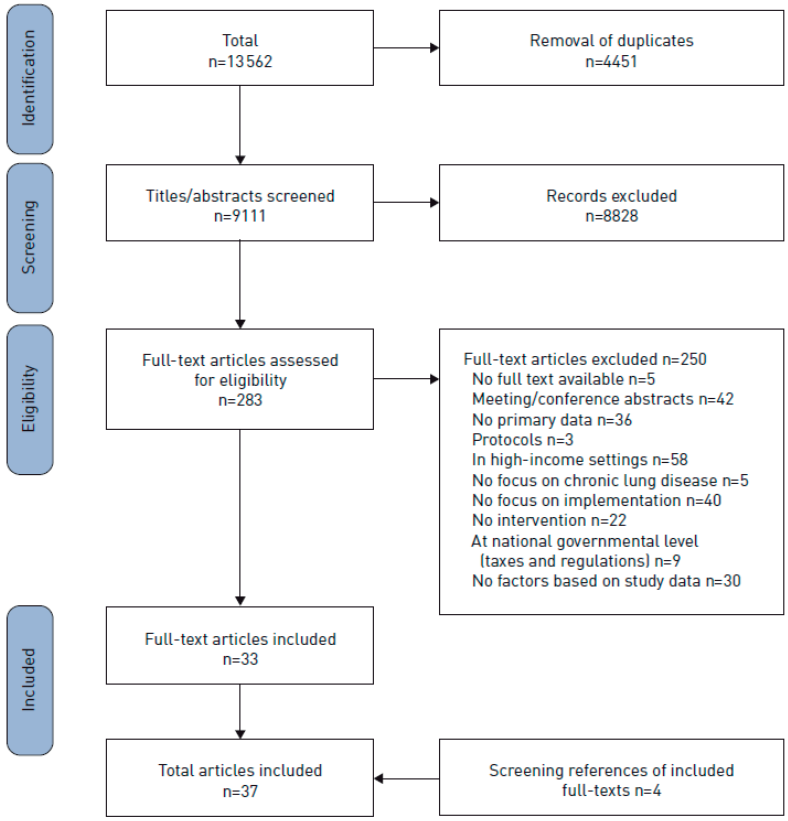

FIGURE 2 Flow diagram of screening process.

Study characteristics

The studies resulting from our search were conducted in 17 different LMICs across five geographical regions: Latin America (Brazil [51–55], the Dominican Republic [56], Mexico [57], Surinam [58]), Africa (Malawi [59], South Africa [60–62]), the Middle East (Lebanon [63], Syria [64]), Asia (China [65–69], India [49, 50, 70–75], Indonesia [73, 76], Malaysia [77], Nepal [78, 79], Pakistan [80], Russia [81], Thailand [82–83]) and Oceania (Fiji [85]) (table 1 and figure 3). Most

studies were based in healthcare settings (n=17; primary care (n=9), secondary care (n=5), primary/secondary care combined (n=3)), followed by schools (n=13), and the community (n=6). The majority of the study interventions focussed on tobacco (n=27; cessation (n=10), prevention (n=8), both (n=2) and control (i.e. smoking-free setting) (n=7)). Three studies focussed on interventions to improve the implementation of guidelines. One study focussed on quality improvement of COPD management, one on delivery of integrated asthma/COPD care, and one on the adaptation of post-partum rituals using biomass smoke to "protect" newborns. Three articles used quantitative methods for determining implementation factors, 31 used qualitative methods, and two used both.

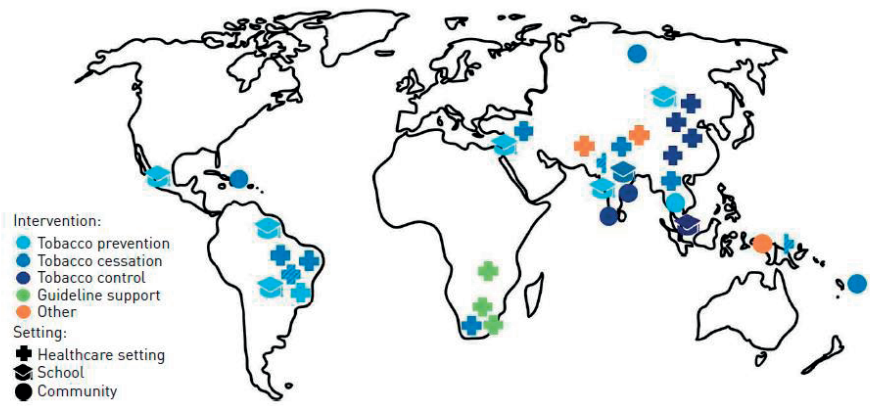

FIGURE 3 Study settings and interventions. Symbols with two colours indicate the study covered both interventions. Half a symbol means half of the study was conducted in this setting and the other half in another setting.

Critical appraisal of the studies

The quality of the articles varied: 19 articles scored high in the MetaQAT on relevance to the research question, 17 scored medium and one scored low (table 1, and for further details appendix 4). Articles scored variably on reliability (15 high, 11 medium, 11 low) and the lower scores were often due to unclear reporting of methods. Data analyses and researcher reflexivity were particularly poorly reported in many qualitative articles, which affected the reproducibility and transparency (thus validity). 12 articles scored high on validity, 10 scored medium, one scored low and for 14 articles validity was unclear.

Implementation factors

45 implementation factors were identified, with a large variation in factors' levels of evidence (appendix 5). The factors with the highest level of evidence are described in further detail below, these belonged to CFIR domains "Process", "Inner setting" and "Outer setting" (figure 4). A full overview of all weighed factors, their definitions and illustrations of how they occurred in theVincluded studies is detailed in appendix 6.

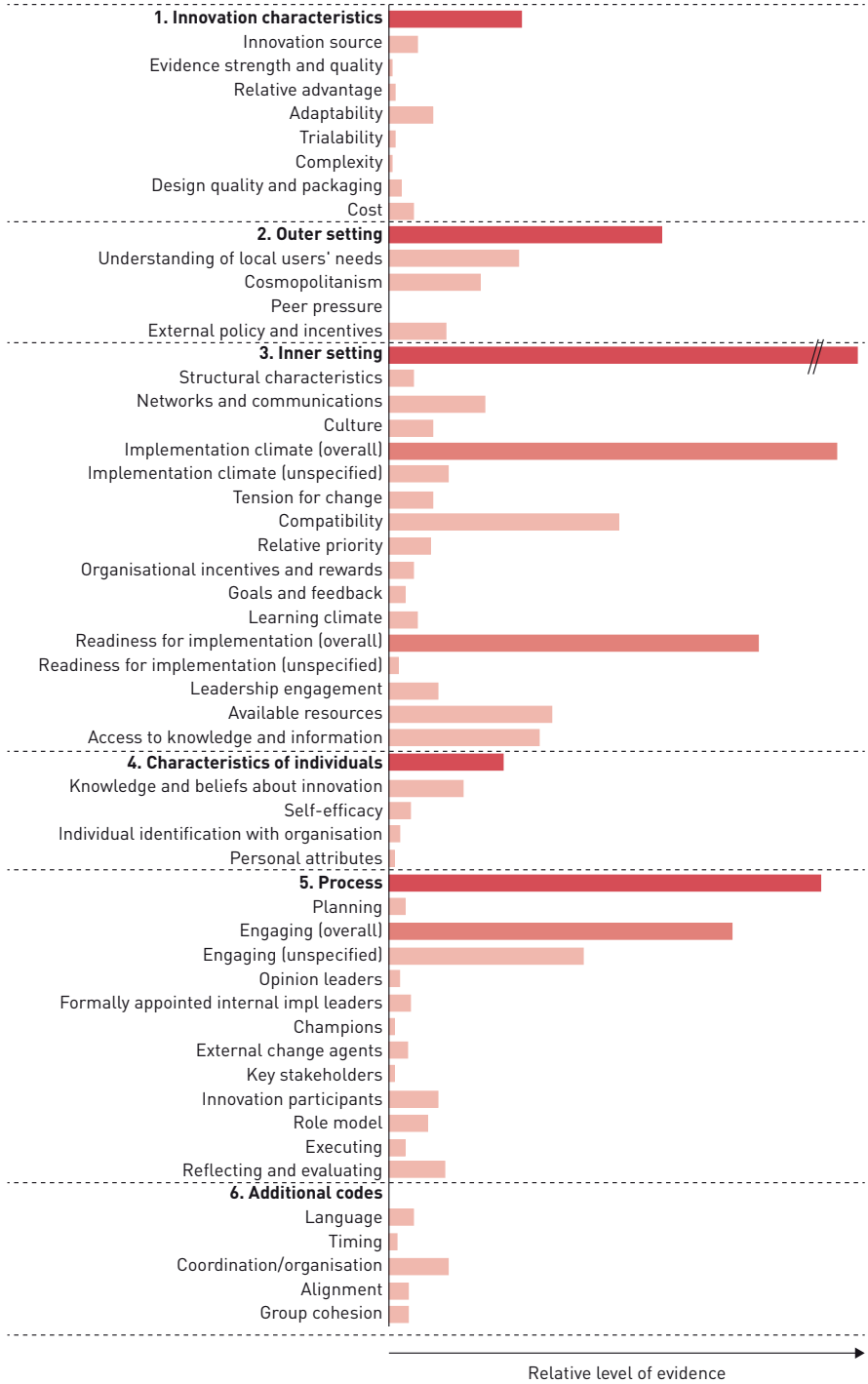

FIGURE 4 Full overview of implementation factors per domain, and the relative level of evidence for the factor.

"Engaging", "attracting and involving appropriate individuals in the implementation and use of the innovation (…)" [18], in the domain "Process" was coded 72 times across 29 articles. Identifying influential stakeholders before and during the implementation process, and developing effective engagement strategies was often reported as "crucial". Moreover, authors stated that the context determined who was considered as influential. The articles addressed relevant deliverers (e.g. teachers, staff, health workers), potential collaborators (e.g. government officials, village leaders or other authorities who could block implementation if not successfully engaged) and recipients of the intervention (e.g. "all villagers at once" versus "initially only highly respected villagers") as important stakeholders to consider. Among a broad range of reported strategies, engagement was frequently established after gaining trust and commitment from the participants, and when a sense of ownership was created (e.g. through participatory approaches). Equally, failure to engage stakeholders was attributed to the lack of engagement activities, e.g. demotivation of intervention recipients due to lack of ongoing communication.

"Compatibility" was another factor with a high level of evidence, coded 48 times across 23 articles. Categorised in the subdomain "Implementation Climate" (domain "Inner setting"), compatibility is defined as the degree of fit between meaning and values attached to the innovation and of the involved individuals, and how the innovation fits with existing workflows and systems [18]. Implementation success was often attributed to embedding interventions into local, existing infrastructures (e.g. the primary care infrastructure), carried out by people in already established networks (e.g. community health workers), and when aligned with local cultural values. This can, for example, be achieved in highly participant-centred interventions. In one study it was stated: "Perhaps the most important lesson was eventually letting go of some of our own techniques and agendas and allowing an indigenous culture to develop their own program." The local participants developed their own programme and implementation strategy in this study, aligned with their local context and, hence, implementation was highly successful [85].

The second important subdomain in the domain "Inner setting" was "Readiness for implementation" (coded 76 times across 32 articles), of which "Access to knowledge and information" (28 times, 22 articles) and "Available resources" (37 times, 21 articles) were defining factors. Studies generally reported the lack of these factors as implementation barriers. Particularly training in knowledge and skills (e.g. knowledge on risks to lung health or motivational interviewing skills) were reported as insufficient, including lack of access to educational materials. The most commonly lacking resources were time and personnel. Other notable lacking resources were limited physical space (such as crowded consultation rooms), insufficient materials (medication, equipment) or assets (electricity). Funding to overcome these barriers was often not feasible, but authors reported that the (lack of) resources should always be considered in the implementation strategy. Where possible, adaptations can then be made accordingly.

Another notable factor was understanding and accurately prioritising on the "Needs of local users" ("Outer setting"). For example, deliverers in one study realised that Chinese parents did not necessarily feel a need for smoking cessation. They also recognised the parents' need for connecting with their child (and children had a unique position in the Chinese one-child families). Deliverers then educated the children on smoking and cessation, which eventually helped to motivate their parents to quit [66]. Level of evidence was also high for "Cosmopolitanism" (networks of the organisation with external organisations; "Outer setting") and "Networks and Communications" ("Inner setting").

Notably, all factors appeared strongly interrelated; e.g. engaged stakeholders could provide adequate knowledge about the needs of those served by the organisation, which could improve compatibility, which in turn could increase the perceived advantage of the intervention. Also, when comparing the implementation factors and their level of evidence across the geographical regions, findings were highly similar. We compared Latin America, Africa, and Asia (China and India were considered both individually and as part of Asia). The Middle East (n=2) and Oceania (n=1) were not considered because of the small number of studies. Only for China there was a notable difference; factors related to the "Outer setting" (e.g. "External policies and incentives") were reported less frequently compared with the other regions.

To facilitate future implementors in the translation of the comprehensive overview of all factors to practice, we summarised the factors in a practical, simplified and manageable implementation tool (figure 5 and appendix 7). The tool contains factors prioritised by their level of evidence and illustrates those factors with examples of how to address them.

DISCUSSION

Main results

In this systematic literature review and meta-synthesis, we identified and weighed factors critical to the implementation of interventions targeting CRD in LMICs. Factors for which the level of evidence was high were: 1) understanding needs of local users; 2) compatibility of the intervention with the local context (such as the political and health infrastructure, or the culture); 3) identification of influential stakeholders and application of engagement strategies; 4) adequate access to knowledge and information (including skills); and 5) sufficient available resources. Additional factors were identified with a lower level of evidence. Most important recommendations for future implementors were compiled in the FRESH AIR Implementation Tool.

TABLE 1. Characteristics of the included studies and critical appraisal, by author

Author	Study design	Country	Setting; population	Intervention	Summary of appraisal			
					Rv	R	V	A
Aghi, 2016*[1]	Qualitative study within an RCT	India	Public urban and rural schools; health educators, lead teachers and staff	Tobacco cessation	+	-	-	/
Aldinger (IUHPE – Promotion & Education, 2008*[2]	Qualitative (institutional ethnography)	China	Primary to vocational schools; administrators, staff, teachers, students, and parents	Tobacco prevention within programme of health-promoting schools	/	/	/	+
Aldinger (Health Education Research, 2008*[2]	Qualitative (institutional ethnography)	China	Primary to vocational schools; administrators, staff (such as school doctors), teachers, students and parents	Tobacco prevention within programme of health-promoting schools	-	+	/	+
Asfar, 2016	Qualitative study within an RCT	Syria	Primary healthcare setting; physicians and medical students	Tobacco cessation	+	-	?	/
Assanang-kornchai, 2014	Qualitative (action research)	Thailand	Primary healthcare setting; healthcare workers (nurses, administrators, directors)	Tobacco, alcohol, and substance use screening and brief intervention	/	/	/	+
Bheekie, 2006	Qualitative study preparing for an RCT	South Africa	Primary healthcare setting; trained nurses, with a supervisory position as care coordinators	Train-the-trainer programme on implementation of respiratory guidelines on (obstructive) lung diseases	+	+	+	/
Bteddini, 2017	Mixed-method, with quantitative survey and participatory approach for qualitative data	Lebanon	7 public and 7 private schools throughout the country; trained external facilitators training 10 sessions for 844 students	Waterpipe smoking prevention/ delay of starting to smoke	/	+	+	+
Castaldelli-Maia, 2017	Qualitative	Brazil	Urban psychosocial care units (primary care) across the country; diverse health professionals (e.g. dentist, nurses, physicians, managers)	Tobacco cessation	+	/	?	/

Author	Study design	Country	Setting; population	Intervention	Summary of appraisal			
					Rv	R	V	A
Chatterjee, 2017	Qualitative	India	Rural villages; community members (programme managers, coordinators, health workers and stakeholders at village level)	Tobacco-free village	+	/	/	+
Cruvinel, 2013	Quantitative, survey design (correlations)	Brazil	Urban, primary healthcare; 149 diverse workers (e.g. community health workers, nurses, physicians)	Training on tobacco, alcohol and drug use screening and brief intervention	/	+	+	/
Elsey, 2016	Mixed-method, factors derived from qualitative data (action research)	Nepal	Urban and rural primary healthcare; patients, healthcare providers, managers and policy makers	Tobacco cessation - Behaviour support	+	+	+	+
Goenka, 2010*[3]	Mixed-method study within an RCT	India	32 Urban, public & private schools; professionals with a master in psychology, sociology, or nutrition who taught teachers and peer leaders	Tobacco prevention by teachers and peer-leaders	/	+	/	/
Groth-Marnat, 1996	Qualitative	Fiji	Traditional village; community members	Tobacco cessation	+	/	?	/
Ishaak, 2014	Mixed-method, factors derived from qualitative data	Suriname	Urban junior high school; management and teachers	Tobacco and other drug prevention	/	/	/	/
Khan, 2019	Mixed-method, embedded in RCT, factors derived from qualitative data	Pakistan	30 Primary and secondary level public healthcare facilities; care providers (15 received intervention, interviews in 4 of the centres)	Integrated COPD/asthma care	+	+	+	+
Malan, 2015	Qualitative	South Africa	Primary care practice; care providers (nurses and physicians)	Brief behaviour change counselling (5A's) for tobacco, diet, physical activity and alcohol abuse	/	+	+	+
Marsiglia, 2014	Qualitative for the factors reported, within a quantitative study	Mexico	Urban public middle schools; teachers	Tobacco and other substance use prevention	/	-	?	-

Author	Study design	Country	Setting; population	Intervention	Summary of appraisal			
					Rv	R	V	A
Mash, 2010	Qualitative, prospective (outcome mapping)	South Africa	Urban and rural, primary care to specialised care with a focus on the public sector; doctors, clinical nurse practitioners, pharmacists, National Council for Medical Schemes, the Department of Health, universities and training bodies patients	Asthma-guideline implementation and dissemination	+	/	?	/
McAlister, 2000	Qualitative for the factors reported, within a quantitative study	Russia	Community level; hospital staff, intervention for community smokers	Stop smoking campaign	+	/	?	/
Medeiros, 2016	Mixed-methods, factors derived from qualitative data	Brazil	Urban schools; teachers, school administrators, coaches, other stakeholders (e.g. municipality) and students	Tobacco prevention within a drug use prevention programme	/	+	+	+
Mehanni, 2019	Qualitative	Nepal	Small rural hospital (managed through a public-private partnership)	Quality improvement initiative for management of COPD	+	-	?	/
Melson, 2017	Mixed-methods within pilot RCT; factors derived from qualitative data (quantitative data n.a., regard hypothetic factors prior to implementation). Pro- and retrospective	Malaysia	Secondary school; students	Peer-led anti-smoking intervention (smoke-free class)	+	+	+	+
Nagler, 2012*[1]	Qualitative, formative pilot study preparing for an RCT	India	One public urban and one rural school, not included in the RCT; health educators and teachers	Tobacco cessation – school based	/	+	+	/
Nichter, 2010	Qualitative	India & Indonesia	Lead public & private medical schools and outreach to their communities	Training network for tobacco prevention (curricula), outreach and clinic on smoking cessation	+	-	?	/

Author	Study design	Country	Setting; population	Intervention	Summary of appraisal			
					Rv	R	V	A
Ossip, 2016	Qualitative (Rapid Assessment Process)	Dominican Republic	Urban, peri-urban & rural communities with active Community Technology Centers; a multidisciplinary team including specialists of psychology, anthropology, nursing, epidemiology, statistics and public health (from the US) and medicine (DR)	Tobacco cessation – participatory approach	+	/	?	/
Pawar, 2015*[1]	Qualitative factors reported within a quantitative study, embedded in an RCT	India	72 Public urban and rural schools; health educators, lead teachers and staff	Tobacco cessation - lay interventionist teaching teachers	/	-	?	-
Pereira, 2016	Quantitative, population-based cross-sectional survey design	Brazil	Urban public and private schools; 263 school managers (headmasters, pedagogical coordinators, coordinators of the prevention programmes)	Tobacco prevention within a drug use prevention programme	/	+	/	/
Perry, 2008*[3]	Qualitative study (translational research) within an RCT following translational research	India	32 urban schools, half were public and half were private; school administration, teachers, and peer-leaders	Tobacco prevention	/	-	?	/
Persai, 2015	Qualitative	India	At district level; senior district officials	Tobacco control	/	+	+	+
Portes, 2014	Qualitative, retrospective	Brazil	Urban primary healthcare units in a medium-sized municipality; municipal programme coordinator, and senior health professionals trained on smoking cessation or local managers	Tobacco control – training healthcare professionals on facilitating treatment & prevention activities (Furthermore, interventions on governmental level, n.a. to our study)	+	+	+	+

Author	Study design	Country	Setting; population	Intervention	Summary of appraisal			
					Rv	R	V	A
Prasodjo, 2015	Mixed-method, factors derived from qualitative data (amongst which participatory action research)	Indonesia	Rural community; local institutions (policy makers, medical staff, community leaders and other stakeholders)	Post-partum smoke ('Sei') traditions – Behavioural change communication campaign targeting household air pollution	+	-	/	/
Rosati, 2012	Mixed-methods, factors derived from qualitative data	Thailand	Urban family setting; health educators towards families	Tobacco, alcohol and other substance abuse prevention, sex education	/	/	/	/
Sodhi, 2014	Mixed-methods, factors derived from qualitative data	Malawi	30 urban and rural, government funded and non-government funded health centres; primary healthcare workers: clinical officers, medical assistants, and nurses	Train-the-trainer on guideline use for providing integrated primary lung healthcare	/	/	/	+
Vitavasiri, 2010	Quantitative questionnaire	Thailand	676 Thai hospitals; personnel	Smoke-free hospitals	+	-	?	-
Wang, 2008	Qualitative	China	County-level hospitals; health professionals, hospital president, director of preventive health, representatives of the hospitals	Smoke-free hospitals	+	+	+	+
Xiao, 2013	Mixed-method, factors concerned qualitative data	China	41 Hospital across the country, the majority from a tobacco control network; medical doctors and directors	Smoke-free hospitals	/	-	?	+
Ziedonis, 2012	Qualitative	China	Hospital-based mental health centre; personnel and patients	Smoke-free hospitals	+	-	?	/

Studies were prospective unless otherwise indicated. Rv = relevance, R = reliability, V = validity, A = applicability to a wider public health context. RCT = randomised controlled trial. + High / Medium - Low ? Unclear score in appraisal. Relevance 1 = Evaluation of implementation was a primary outcome of the article. *Articles from the same study. *[1] Findings from Aghi et al. were excluded from the analysis, as Pawar et al. based their findings on the same study data and had higher appraisal scores. Nagler et al. based findings on a different study data (pilot study) and was included. *[2&3] Findings from both studies were included as these were based on different study data.

Strengths and limitations

To the best of our knowledge, this systematic review is the first to focus on factors critical to the implementation of diverse CRD-interventions. It focussed on LMICs, precisely where the burden of disease is highest, while evidence is fragmented and often poor for these settings. This review had a rigorous design and conduct, following Cochrane methodology and PRISMA reporting standards [39–41]. Every step was standardised and performed independently by two researchers. Validated tools were applied at each stage [18, 42, 43, 46], with a transparent description of their operationalisation. Moreover, we adopted a comprehensive approach with an extensive search in eight databases with no language/date restrictions. We synthesised real-world evidence from highly diverse settings and countries in the included studies, resulting in a high generalisability of the findings to other settings [86]. In fact, the LMICs in this review were broadly representative of the population distribution across the worlds' continents, among others with many studies conducted in China and India.

However, several relevant types of interventions were underrepresented or even absent in the implementation literature, such as patient education, self-management or pulmonary rehabilitation. Due to the small number of existing studies that focus on such interventions, we were unable to assess whether their implementation factors meaningfully differed from tobacco-related interventions. However, as the desired implementation behaviour is focussed on a similar health goal in similar settings, we assume that there will be at least some overlap in implementation factors. Meanwhile, the high representation of tobacco-related studies in literature remains welcome, with 80% of the world's smokers living in LMICs [87]. As another limitation, we recognise along with other authors that implementation studies are poorly indexed, and we possibly missed relevant studies [88]. Yet, data saturation was still achieved in the identified factors and the hierarchy of their level of evidence. Notably, absence of evidence (factors not reported) should not be interpreted as evidence of absence (factors not important); [47] we could only determine the level of confidence in the importance of factors, for which we relied on the existing evidence.

Comparison to previous literature

Our findings partly overlap with implementation factors considered important for clean cooking interventions as reported in two reviews [89, 90]. First, our factors "Compatibility" and "Understanding local users' needs" correspond to "user needs" (e.g. the ability of clean cookstoves to give the food the right taste or save fuel). Second, our factors "Engaging" and "Access to knowledge and information" correspond to "community involvement" and "user training". The authors of these studies similarly observed that barriers could turn into facilitators when these are adequately addressed and vice versa. They also concluded that factors should be addressed simultaneously because they all interrelate. The overlap between their findings and ours may not be surprising, as clean cooking interventions similarly target CRD in

LMICs. Possibly, this supports the assumption mentioned earlier that implementation factors would not differ substantially for those chronic lung health interventions in LMICs that have not yet been studied.

Implementation is a relatively unexplored topic in LMICs, and we predominantly relied on qualitative articles. Qualitative studies allow for a deeper understanding of the how, what and why of implementation processes [91]. As opposed to in quantitative studies, the concept "high level of evidence" cannot be quantified or tested on significance in qualitative studies. Therefore, a combination of qualitative with quantitative (mixed-method) evidence would be highly welcome; such studies are still largely unavailable. The need for more high-quality implementation evidence for LMICs has been highlighted repeatedly [25, 34–37, 92]. Systematic reviews are particularly scarce.

Interpretation and implications for implementation initiatives

Our findings could serve future implementation initiatives, especially those initiatives targeting CRD in LMICs. To facilitate the design of effective implementation strategies for CRD-related interventions, we have developed a comprehensive overview of all implementation factors, their level of evidence and examples of how they played a role in the included studies (appendix 6). In addition, we translated factors from the comprehensive overview into a more pragmatic and hands-on tool for practice (figure 5). Throughout the implementation process, implementors should address these factors in their strategy, and should continuously monitor the effectiveness of their strategy to improve it accordingly [93].

Therefore, awareness of the implementation factors requires additional evidence on how to adequately address them [93, 94]. A suggestion for how to address the two critical factors "Compatibility" and "Understanding local users' needs", is developing, testing and disseminating "homegrown" interventions [95]. This was done in another FRESH AIR study by conducting an initial explorative mixed-method rapid assessment of the local context [96]. The results of this assessment informed implementation strategies for improved cookstove interventions in Uganda, Vietnam and Kyrgyzstan [97]. First, the context assessment revealed that communities and their health workers poorly understood the risk of household air pollution and therefore felt no need for change. Hence, the intervention was preceded by an awareness-raising programme. Second, the rapid assessment helped to identify the relevant influential stakeholders in the settings (e.g. village leaders, district health officers). These stakeholders were then involved in the design of the implementation strategy, which ensured high compatibility of the strategy with the local reality and "Engaged the stakeholders" (the third critical factor) for the subsequent delivery [98].

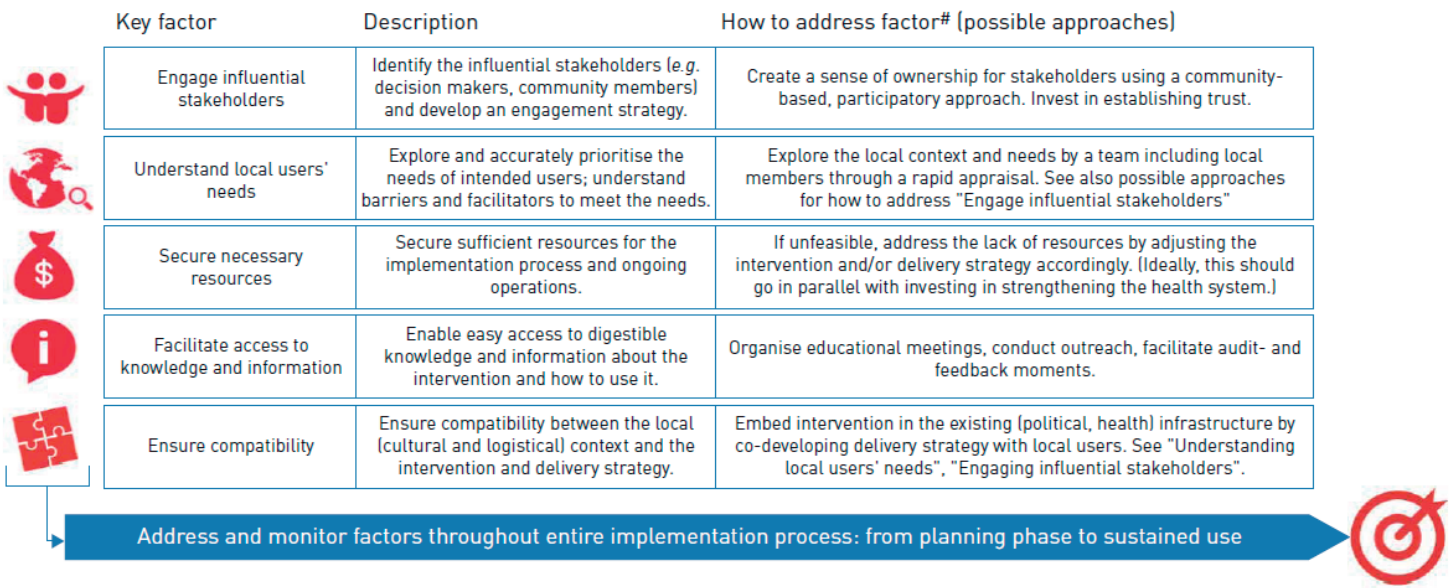

FIGURE 5 Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR) Implementation Tool. #: These suggestions are based on the literature specific for interventions targeting chronic respiratory disease in low- and middle-income countries, and on additional, general implementation literature. See Appendix 7 for recommended use of the tool and details on the references.

A creative example of addressing the fourth critical factor, "Access to knowledge and information and skilled staff", could be introducing task-sharing between physician and non-physician health workers. This proved to be effective in lowering blood pressure in LMICs [99]. The fifth critical factor, "Resource availability", can be particularly challenging to address. One included study reported that workshop facilitators overcame the barrier of transportation costs by ride sharing and delivering several sessions per visit to reduce the number of visits [63]. Reducing the impact of the lack of resources generally requires innovative system strengthening [16].

Overall, opinions on how to address implementation factors most effectively turned out to be highly heterogeneous among experts [100]; additional how-to evidence is required.

Implications for implementation research

Studies that systematically evaluate approaches of how to address implementation factors are needed to provide solid and detailed evidence for future initiatives. We are currently working on part two of this review, which focuses on the implementation of clean cooking interventions. However, we argue that future studies should also focus on topics beyond tobacco and clean cooking, such as personalised asthma action plans or pulmonary rehabilitation [87]. The studies included in this review consistently missed economic evaluations, so we recommend future studies to also include those [101]. Furthermore, results from the critical appraisal of the studies showed that research quality could generally benefit from more standardised methods and more structured reporting of, for example, context characteristics, implementation strategies and their conduct. These and additional recommendations are further outlined in an article on improving health-care provider practices for LMICs [93], and in the STandards for Reporting Implementation Studies [88].

Implications for practice

Guiding implementation processes by evidence-informed implementation strategies could enhance implementation success. Successful implementation can substantially increase interventions' effectiveness [17]. This could, in turn, optimise the use of already limited resources and decrease the high direct and indirect costs associated with CRD in LMICs [102, 103]. Above all, implementation success could improve health outcomes.

CONCLUSION

In this study, we systematically searched the literature for factors critical to the successful implementation of lung health interventions. We meta-synthesised the factors' level of evidence and developed an implementation tool for practice. Priority for future implementors should be to understand needs of local users, ensure compatibility of the intervention with the local

context, engage influential stakeholders, facilitate adequate access to knowledge and information, and secure sufficient resources. Use of the FRESH AIR Implementation Tool could facilitate policymakers, non-governmental organisations, practitioners, researchers and community members to design evidence-based, tailored implementation strategies to enhance implementation success. This could hence optimise the use of already scarce resources and, ultimately, improve health outcomes.

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CHAPTER 7

LET'S STOP DUMPING COOKSTOVES IN LOCAL COMMUNITIES. IT'S TIME TO GET IMPLEMENTATION RIGHT.

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COMMENTARY

We most welcome the comment by Thakur, van Schayck and Boudewijns1 on our article on the effects and acceptability of implementing improved cookstoves.2 Adoption rates of improved cookstoves by local communities are often strikingly low. The authors underline the urge to advance cookstove implementation strategies, and reinforce the approach used in the FRESH AIR project.2 They highlight several important factors to increase adoption success and call for further research on the topic. We want to build on this comment by reflecting on decades of substantial discrepancies between the disappointing adoption rates of improved cookstoves, and the subsequent failure to adapt implementation strategies accordingly. We argue that it is not necessarily the lack of evidence that impedes the success of implementation strategies for improved cookstoves. Moreover, it is the lack of use of the evidence by implementors. We propose several ideas for overcoming this evidence-to-practice gap.

The need for improved cookstoves

Improved cookstoves have been on the market for over seven decades. The rationale for their need is simple: three billion people worldwide rely on solid fuels (e.g., wood and coal) as their main energy source.3 Burning solid fuels in open fires or inefficient stoves has detrimental health and environmental consequences. Inhalation of polluted air is ranked the fifth risk of deaths and sixth risk for disability-adjusted life-years globally,4 as it causes among others impaired lung development, respiratory infections and cardiovascular disease.5–7 Besides, solid fuel use causes widescale deforestation and up to 25% of global black carbon emissions; black carbon emissions are the largest contributors to climate change after carbon dioxide emissions.8,9 Hence, developing a technical solution to reduce air pollution and fuel consumption and distributing it among local communities should solve the problem. Right?

The discrepancy between implementation evidence and implementation strategies

Improved stoves, with their higher combustion efficiency, would generate less smoke and consume less fuel. Therefore, improved stoves as a solution to the problems above seems as plausible to reasonable minds as it seems appealing to idealists' emotions (and idealism drives many researchers to do what they do, after all). As Aristotle knew already, this combination of logos and pathos is a powerful persuader, which could explain the numerous attempts to push cookstoves into local markets despite the accumulating evidence that their adoption is failing.7,10 Improved cookstoves— outside of the laboratory setting—have hardly demonstrated any consistent improvements in health outcomes (high-quality articles reported no health benefits, some health benefits, or inconclusiveness).10–14 In the real world, clean cookstoves have turned out to be incredibly challenging to implement. Adoption rates frequently remain unreported, but studies that report on adoption success use descriptions as 'largely discourag-

ing', 'a mere 10%', 'only 4%', 'rare', and 'very low'.15–19 If adopted, improved stoves are often used concurrently with traditional stoves (known as stove-stacking), which may lead to even higher levels of air pollution and fuel consumption.20 Although these observations and analyses of implementation factors were already described in the eighties and nineties,19,21–24 implementation strategies and adoption rates generally appear not to have changed accordingly.

How to move forward in implementation?

Facing the facts: the adoption of improved cookstoves by local communities has largely failed since the stoves appeared on the market 70 years ago, draining funds available for resource-limited settings. Meanwhile, the health and environmental problems related to solid fuel use have become more urgent than ever.25,26 Community-focused approaches, creation of public awareness on the risks of kitchen smoke, provision of stove usage information, assurance of maintenance, involvement of women and an appropriate business model were outlined as implementation facilitators by Thakur et al.1 Other consistently reported, related, factors are characteristics of the stove (e.g., costs or real-world effectiveness), compatibility between the stove and local needs and perceptions (e.g., meeting taste preferences to avoid stovestacking), and favourable policies (e.g., laws, regulations, and subsidies), as outlined in existing reviews into barriers and facilitators to the adoption of improved cookstoves.10,20,27–30 (These reviews referred to were among the most recent ones; however, we are aware of over 20 existing cookstove implementation reviews since 2010). Interestingly, these factors do not differ from the factors described in reviews >30 years ago.19,21–24 We agree with Thakur et al. that generating new evidence on implementation is useful, but only provided that implementation strategies and processes are reported in detail, adoption rates and stove-stacking are systematically and objectively assessed,31 and follow-up time is 4 years or more, as underlined by recent Nobel Prize winner Esther Duflo and her colleagues.11 Although this can be challenging (in FRESH AIR our funding was only adequate for six to twelve months of follow-up), this should be the norm for future implementation studies.

However, above all, this comment is a call to actually use the existing evidence in the design and execution of implementation strategies for improved stoves. Doing so requires efforts from all stakeholders involved. To facilitate designs of effective implementation strategies, the existing bulge of cookstove implementation evidence should be consolidated in an easy-to-use way, such as a state-of-the-art implementation tool. The tool should then be applied in future cookstove implementation projects and researchers should ensure to constantly update it according to the latest evidence and priorities.32 Researchers should also connect to brokers in large network organisations, such as the Clean Cooking Implementation Science Network, the Clean Cooking Alliance (formerly Global Alliance for Clean Cookstoves) and the World Health Organization (WHO). These organisations should promote and distribute the implementation tool to make it wellknown and easily available. Policymakers should ensure to consult it for

decision-making. Furthermore, funders, non-governmental organisations, and development institutions such as the World Bank should exclusively grant support for proposals and project plans with adequate implementation strategies that address the implementation factors in the tool. Lastly, carbon credit (offset) projects should incentivise on improved cookstove adoption instead of distribution. Collaborative efforts and constant networking for knowledge exchange between all stakeholders are vital, to ensure everyone is on the same, up-to-date, page. As a start, we have reached out to Thakur, van Schayck and Boudewijns to team up and start developing this implementation tool.

The steps above could facilitate idealism to team up with evidence-based realism and help to get implementation right. Only then we can actually assess whether improved stoves are consistently effective in the real world, acknowledging that challenges persist even with perfectly implemented improved cookstoves (like decreased levels of household air pollution that remain above the WHO recommended levels10). However, until clean fuels such as electricity are affordable and available for everyone (or until long-term research into well-implemented stoves proves us differently), we should strive for improved, evidence-based implementation of improved cookstoves, to ultimately improve environmental and health outcomes.

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Competing interests The authors declare no competing interests.

Author contributions EB wrote the first and subsequent versions of the paper. EB & DV systematically identified literature relevant to implementation of improved cookstoves. RvdK, DV, FvG, BK, and NC reviewed the paper critically and approved the final version.

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CHAPTER

FACTORS CRITICAL TO IMPLEMENTATION SUCCESS OF CLEANER COOKING INTERVENTIONS IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES: PROTOCOL FOR AN UMBRELLA REVIEW

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ABSTRACT

Introduction

Over a third of the world's population relies on solid fuels as their primary energy source. These fuels have damaging effects on health, air quality and forest resources. Interventions to promote access to cleaner solid fuel cookstoves and clean fuels have existed for decades. However, the adoption by local communities has largely failed, which led to a waste of resources and suboptimal outcomes. Therefore, the objective of this umbrella review is to identify factors that determine implementation success for cleaner cooking interventions in low-resource settings and weigh their level of confidence in the evidence.

Methods and analysis

We identified systematic and narrative reviews examining factors that influence the acquisition, initial adoption or sustained use of cleaner solid fuel cookstoves and clean fuels at any scale by a literature search in PubMed, Embase, Global Health Database, Cochrane, PsycINFO, Emcare, Web of Science and CINAHL, without date or language restrictions. The search was conducted on 23 October 2017 and updated on 10 July 2019. Reviews based on qualitative, quantitative or mixed-methods studies were included and will be appraised using the Meta Quality Appraisal Tool combined with the Assessment of Multiple Systematic Reviews. Data will be extracted and factors affecting implementation will be coded using the Consolidated Framework for Implementation Research. The Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative Research tool will be used to determine the level of confidence in the coded factors. Two researchers will independently conduct these steps.

Ethics and dissemination

This umbrella review does not require the approval of an ethical review board. Study results will be published in an international peer-reviewed journal. The outcomes will be converted into two practical tools: one for cleaner solid fuel cookstoves and one for clean fuels. These tools can guide the development of evidence-based implementation strategies for cleaner cooking interventions in low-income and middle-income countries to improve implementation success. These tools should be pilot-tested and promoted among regional and global initiatives.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This umbrella review will aggregate up-to- date evidence on factors critical to implementation success for cleaner cooking interventions in low-resource settings and weigh the level of confidence in the evidence.
- We will comprehensively search eight databases without date or language restrictions, and two researchers will independently apply validated tools throughout each step of the process.
- Narrative reviews will also be included in the study, as only a fraction of the literature has been reported in systematic reviews; the lower methodological rigour of narrative reviews (compared with systematic reviews) will be considered during appraisal of the methodological quality of the reviews.
- The identified implementation factors will be integrated into two hands-on implementation tools to facilitate the design of evidence-based implementation strategies for cleaner cooking interventions and hence stimulate the translation of evidence into practice.

INTRODUCTION

The use of solid fuels for cooking is a deep-rooted practice for approximately 2.8 billion people, especially in low-income and middle-income countries (LMICs).1 Solid fuels include biomass fuels (such as wood, dung, crop residues and charcoal) and coal. Combustion of solid fuels leads to emission of greenhouse gases and black carbon, aggravating climate change. It also leads to high levels of household air pollution affecting health.2 Furthermore, collecting fuels leads to forest degradation and deforestation and is time consuming for women and children involved in fuel gathering.3 Interventions that promote the replacement of traditional cookstoves (that use solid fuels or kerosene as fuel) by cleaner solid fuel cookstoves (later referred to as cleaner cookstoves) or clean fuels seem to be promising solutions due to higher combustion efficiency and lower emissions. Clean fuels include liquefied petroleum gas (LPG), natural gas, alcohol fuels, biogas, solar cookers and electricity.4 Kerosene stoves are relatively efficient but are discouraged due to significant health risks.4 Cleaner cookstoves came on the market in the 1950s and were later supported by promising laboratory-based experiments with different models, trying to improve combustion efficiency.5 6 Subsequently, many non-governmental organisations and governments promoted the large-scale rollout of these stoves. The push for a transition to clean fuels has come into force since World Health Organisation (WHO) published guidelines for indoor air quality and household fuel combustion. 7 However, real-world outcomes of interventions that promoted the switch to cleaner cookstoves or clean fuels have often not been fruitful.5 6 Many of the programmes ran into hurdles and failed8; adoption rates are often not reported in the literature, and if they are, rates may vary between 4% and 10%.9–13 Moreover, even if cleaner stoves and clean fuels are used in local communities, they are often combined with traditional ones.14 Amidst scarce resources, implementation efforts have thus largely been a waste of time, money, energy and human resource. Progress in large-scale implementation has been inexplicably slow.3 15

Implementation, the act of carrying an intervention into widespread use, is a complex process.16 Although the failure to implement cleaner cooking interventions has been reported already in the 1980s and 1990s,8 13 17–19 implementation strategies and adoption rates have generally not changed accordingly. Numerous additional studies have since then examined barriers and facilitators for the implementation of cleaner cooking interventions, including more than a dozen systematic and narrative reviews. Although evidence has been consolidated in a study by Puzzolo *et al*,20 an up-to- date overview of the evidence, including more recently published reviews, is missing. Furthermore, evidence of factors that influence the implementation of clean fuels was limited in this study. Therefore, we will conduct an umbrella review or in other words a review of systematic and narrative reviews. We aim to systematically identify critical factors for implementation success of cleaner cooking interventions in LMICs and to weigh their level of evidence. We define implementation success as sustained predominant use of cleaner cook-

stoves and clean fuels.21 As we expect limited evidence on sustained use (defined as use for 1–2 years after acquisition or use for more than 2 years20), we will also include factors that relate to acquisition (defined as purchase or installation) and initial adoption (defined as use for less than 1 year from acquisition20) of cleaner cooking interventions. Findings will be consolidated in two easy-to- use implementation tools: one for cleaner cookstoves and one for clean fuels. These tools can practically guide the development of evidence-based implementation strategies. Use of these tools could ensure more effective use of scarce resources and, ultimately, alleviate climate change and improve health outcomes.

METHODS AND ANALYSIS

This study is part of a larger study conducted by Brakema *et al*.22 This latter study focused on critical implementation factors for interventions targeting chronic lung disease in LMICs, as part of the Horizon 2020 Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR) project.23 Because the search resulted in a high number of articles that focus on the implementation of cleaner cooking interventions, it was decided to split the review into two parts. The review of Brakema *et al* includes articles on implementation of all interventions other than cleaner cooking interventions (such as tobacco cessation or the implementation of guidelines), while the current study is an umbrella review that includes reviews focusing on cleaner cooking interventions. The study is registered at PROSPERO (CRD42018088687). Because the methodology for this umbrella review differs from the methodology used in the review by Brakema *et al*,22 and because an umbrella review of systematic and narrative reviews is not common,24 25 it was decided to record the protocol for this study to increase transparency.

Search strategy and inclusion criteria

The initial search was part of the study conducted by Brakema *et al*.22 The search strategy was developed together with a certified medical librarian. Search terms included (synonyms of) implementation, LMICs and interventions targeting chronic lung health, including cleaner cooking interventions. No names of fuels or specific cooking interventions, such as LPG or biogas, were included in the search strategy. This is a limitation of the study. Cleaner cooking interventions were included regardless whether they were defined in terms of health benefits. The search terms are displayed in online supplemental material S1. Searches were conducted using the databases PubMed, Embase, Global Health Database, Cochrane, PsycINFO, Emcare, Web of Science and CINAHL, with no date or language restrictions. The search was conducted on 23 October 2017 and updated on 10 July 2019. The full search strategy and the operationalisation is described elsewhere.22 Furthermore, experts in the field of cleaner cooking interventions will be consulted to identify relevant publications from July 2019. All reviews regarding the

implementation of cleaner cookstoves and clean fuels in LMICs were extracted from the results and will be used in the current study. Given the expected large number of cookstove studies covered in reviews other than systematic reviews (narrative reviews), it was decided to be inclusive and not limit the search to systematic reviews only. Reviews based on quantitative, qualitative or mixed-methods studies will be considered relevant.16 Articles will be excluded if they focus on legislation at a national governmental level or on hypothetical interventions. Besides, articles will be excluded if no factors that influence implementation are reported or if the full text is not available after contacting the authors.

The steps that will be conducted, and the tools used to conduct these steps, are displayed in figure 1. Methodological quality assessment, data extraction and data analysis will be conducted in the same manner for systematic and narrative reviews. The risk of biased recommendations in narrative reviews will be accounted for during appraisal of the methodological quality of the reviews.

Methodological quality assessment

The Meta Quality Appraisal Tool (MetaQAT)26 combined with the Assessment of Multiple Systematic Reviews (AMSTAR)27 will be used to assess the methodological quality of included studies. The MetaQAT assesses the relevancy, reliability, validity and applicability of the included studies.26 The AMSTAR will be embedded into the MetaQAT, as recommended by the MetaQAT authors.26 The results will be used as input for the assessment of confidence in the evidence.

Data extraction

Data will be extracted using standardised pilot-tested extraction forms.28 We will extract data on descriptive characteristics (author; year; narrative/systematic review; whether the review included quantitative, qualitative or mixed-method studies; country; setting/population; fuel used before intervention; intervention targeting cleaner cookstoves vs clean fuels (type); outcome; data sources; funding source of the review; role of funding organisation) and implementation factors. Factors will not be extracted if they are speculations.

Data analysis

Content analysis will be used for data analysis.29 Content analysis is a research technique for making replicable and valid inferences from data to their context.30 It can be used to synthesise qualitative and quantitative data.29 First, to prepare the data for content analysis, the implementation factors will be coded using the Consolidated Framework for Implementation Research (CFIR).31 The CFIR is validated for identifying implementation factors at multilevel for complex processes32 and helps to understand what works where and why across multiple contexts (interventions) and settings.31 33 Implementation factors are categorised in five domains: (1) intervention characteristics, (2) outer setting, (3) inner setting, (4) characteristics

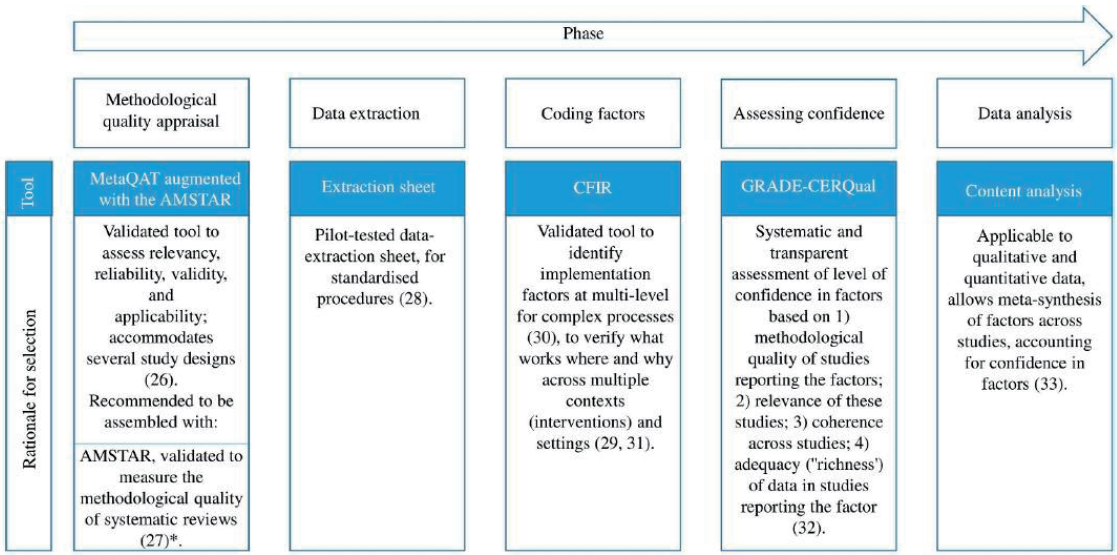

Figure 1 Tools that will be used in each phase. Adapted from Brakema *et al*.[22] *Tools to assess the quality of narrative reviews are not in the list of recommended design-specific companion tools to augment the MetaQAT tool.[26] Therefore, it was decided to use the AMSTAR-tool for systematic and narrative reviews. AMSTAR, Assessment of Multiple Systematic Reviews; CFIR, Consolidated Framework for Implementation Research; GRADE-CERQual, Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research; MetaQat, Meta Quality Appraisal Tool.

of individuals involved and (5) the implementation process.31 Each CFIR domain includes several constructs. Several constructs were added to the CFIR by Brakema *et al*,22 such as the extent to which language affects the implementation process. If relevant, more constructs will be added inductively to the framework. Second, the Grading of Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) will be used to assess the confidence in the included factors.34 The GRADE-CERQual consists of four domains: methodological limitations, relevance, coherence and adequacy. However, coherence will not be included as this will be taken into account in the end by counting the number of studies that mention the factor. For each of the other three domains, a score will be assigned per study in which the factor appeared. The score for adequacy will be determined based on the richness of the data. Relevance and methodological limitations will be scored on the aforementioned MetaQAT-AMSTAR tool (relevance and reliability+validity, respectively). This score ranges from one point (substantial concerns) to four points (no to very minor concerns). Third, an overall level of confidence in the factor will be determined by totalling the scores of the three domains. This total score will thus be higher if the studies' adequacy, relevance or quality of the methodology was appraised as high or if the factor appeared in more studies (the principle of content analysis). Guidance to preclude the double-counting that overstates the evidence due to overlap among reviews is limited and inconsistent.35 To gain insight into the frequency of double-counting, a matrix of the primary studies included in each review will be presented.36

At least two authors will independently conduct the screening and selection process, the data extraction and the quality appraisal of the included studies. A third researcher will solve any discrepancies. Endnote will be used to manage records and data throughout the review. In case of deviations from the protocol, these amendments will be described in the final paper.

Patient and public involvement

Patients and the public will not be involved in this research.

Ethics and dissemination

This umbrella review does not require the approval of an ethical review board. Study results will be published in an international peer-reviewed journal. The outcomes will be converted in two practical tools, one for cleaner cookstoves and one for clean fuels, that can guide the development of evidence-based implementation strategies for cleaner cooking interventions in LMICs. These tools should be pilot-tested in future cookstove implementation projects and adapted accordingly. Furthermore, the tools should be presented to brokers in large networks, including the Clean Cooking Implementation Science Network, the Clean Cooking Alliance, and WHO. We have already reached out to several of these organisations. Ideally, these organisations should then promote the use of the tool to make it well known and easily available.

DISCUSSION

With this umbrella review, we aim to consolidate all available evidence on critical factors for successful implementation of cleaner cookstoves and clean fuels in LMICs and weigh the level of confidence in the evidence. Implementation methodologies are considered as main priorities in implementation science, especially in low-resource settings.37–39 This umbrella review uses a comprehensive implementation science framework, includes up-to- date data from both systematic and narrative reviews and will result in two practical tools that may aid in the development of evidence-based implementation strategies. An example of such a tool can be found in the study of Brakema *et al*.22 These tools should help to develop evidence-based implementation strategies for cleaner cooking interventions in the field.

With the increasing number of scientific reviews comes a need for third-level analyses, combining evidence of multiple reviews.40 Various terms are given to these overviews of reviews, including meta-reviews, review of systematic reviews, reviews of reviews or umbrella reviews.41 A precise definition of the different terms is unclear. However, the common denominator is that they often only assess systematic reviews. Umbrella reviews are usually more inclusive of different types of systematic reviews compared with the other overview of reviews.41 We decided to also include narrative reviews in this umbrella review given the nature of the sector. However, narrative reviews may increase the risk of biased recommendations as they have less stringent criteria for information selection and appraisal than systematic reviews.42 We will account for this risk of bias as the level of confidence in the evidence is based on the quality of the methodology of the review in which the factor is reported. Excluding narrative reviews would exclude a considerable amount of available evidence. We decided not to distinguish between factors influencing adoption and factors influencing sustained use, as we expect limited evidence on sustained use only. Furthermore, in cleaner cooking literature, adoption and sustained use are often not clearly distinguished. 43 Ideally, studies would investigate the outcomes of cleaner cooking interventions over the course of several years, as the outcomes are known to differ over time.44 Notably, we will weigh confidence in the factors that influence the implementation of cleaner cookstoves and clean fuels, based on the frequency of occurrence in the studies, and the quality of the study in which the factors are reported. This should not be interpreted as weighing or prioritising the importance of the factors.45 46 We also decided not to separately report on barriers and facilitators, as reversed barriers will most likely serve as facilitators and vice versa.22 46 We decided to include both cleaner cookstoves and clean fuels in this review, although the first are often not classified as 'clean' according to the guidelines of WHO due to high exposure levels.4 7 However, cleaner cookstoves can play an important role in the transition to clean fuels and are therefore included in this review. Furthermore, newer cleaner cookstoves, such as advanced biomass cookstoves, will be included in this umbrella review, but it

is likely that these will not be covered by the identified reviews. However, findings of the other cleaner cookstoves are probably largely applicable to the newer cleaner cookstoves.20

This study will result in two tools with an overview of implementation factors, confidence in the evidence of the factors and practical examples for implementers to promote large-scale uptake of cleaner cookstoves and clean fuels, respectively. These tools can therefore complement WHO Clean Household Energy Solutions Toolkit.47 Successful implementation, including sustained use, of cleaner cooking interventions could ultimately alleviate climate change and improve health outcomes.48

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Competing interests None declared.

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CHAPTER

FACILITATORS AND BARRIERS TO THE IMPLEMENTATION OF IMPROVED SOLID FUEL COOKSTOVES AND CLEAN FUELS IN LOW-INCOME AND MIDDLE-INCOME COUNTRIES: AN UMBRELLA REVIEW

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SUMMARY

2.6 billion people rely on solid fuels for cooking or heating. Accelerating access to cleaner solutions is critical to reduce the negative effects of solid fuel use. Despite abundant evidence on how to implement these solutions, previous attempts have been disappointing. An overview of the evidence is lacking and translation of the evidence to practice is limited. We conducted an umbrella review using eight databases to consolidate evidence on factors that influence the implementation of improved solid fuel cookstoves and clean fuels in low-income and middle-income countries, weigh the level of confidence in existing evidence, and develop two practical implementation strategy tools. We identified 31 relevant reviews consisting of 13 systematic and 18 narrative reviews, covering over 479 primary studies. We found 15 implementation factors supported by the highest level of evidence. Regarding improved solid fuel cookstoves these included 'cost', 'knowledge & beliefs about the innovation', and 'compatibility'. For clean fuels these included 'cost', 'knowledge & beliefs about the innovation', and 'external policy & incentives'. The factors were synthesised into the Cleaner Cookstove Implementation Tool (CleanCIT) and the Clean Fuel Implementation Tool (CleanFIT). These tools can be used to optimise implementation, thereby improving health, environmental, climate, and gender equity outcomes.

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INTRODUCTION

Every day, 2.6 billion people use traditional solid and polluting fuels and rudimentary stoves to cook or to heat their homes, mainly in low-income and middle-income countries (LMICs).[1] These traditional technologies negatively impact health (leading to both chronic and acute ailments and to premature mortality), the environment (forest degradation and deforestation), and the climate crisis (emissions of greenhouse gases and black carbon).[2-4] Because many women have primary responsibility for cooking tasks, they bear a disproportionate share of the negative health risks from household air pollution. Additionally, women and children often spend several hours a day on cooking-related tasks including fuel collection, food-processing activities, cooking, and cleaning, resulting in time poverty (less time for education, rest and leisure, and income-generating activities).[2] Cleaner cooking interventions could offer a solution. In view of the negative effects on health, climate, and gender, opportunity costs of not transitioning to cleaner cooking solutions (including deaths, disability-adjusted life years, carbon prices, and women's time) are estimated at US$2.4 trillion per year.[2] Cleaner cooking solutions include improved solid fuel cookstoves (subsequently referred to as cleaner cookstoves) and clean fuels. Cleaner cookstoves are defined as any improvement from an open fire, traditional inefficient

stove, or a kerosene stove. They include improved wood stoves, pellet stoves, and briquette stoves. Clean fuels include electricity, liquefied petroleum gas (LPG), natural gas, biogas, solar cookers, and alcohol fuels, and their corresponding technologies.[5] Clean fuels are expected to have the largest impact on health, environment, climate, and gender equity and are therefore critical to achieving substantial gains.[6] Cleaner cookstoves, on the other hand, generally have limited effects on household air pollution, as emission levels often remain above the WHO-Air Quality Guideline levels.[5] Nevertheless, as clean fuels are unlikely to be widely available in the near future, cleaner cookstoves are needed in the interim.[2,7]

Successful implementation, defined as the sustained (more than one year of use after acquisition) and predominant use of cleaner cooking solutions, is crucial to achieving health, environmental, climate, and gender equity improvements.[3,7] Decades of experience has shown that the implementation of cleaner cooking interventions is both challenging and complex.[7] Even where transition is achieved, uptake is often only partial (also referred to as stacking).[8] A successful implementation process requires the involvement of multiple sectors including, amongst others, the social, environmental, political, health, and financial sectors. Furthermore, the involvement of multiple stakeholders is needed, such as intended users and local groups, local and national governments, financial institutions, commercial enterprises, and non-governmental organisations. Besides, a successful implementation process requires careful attention to contextual factors on a micro-level (e.g. household factors), meso-level (e.g. wider context-specific conditions), and macro-level (e.g. policies). Implementation science provides a multi-sectoral and systematic approach to this challenge.[7,9] Identifying and pragmatically structuring factors that enable or limit implementation can improve understanding of the implementation process, which in turn may lead to improved evidence-based implementation strategies that accelerate the widespread access to cleaner cooking interventions.[7]

To date, hundreds of studies have assessed the implementation process of cleaner cooking interventions and dozens of literature reviews have been conducted. However, the implementation success of cleaner cooking interventions is generally considered poor.[10,11] Although a plethora of evidence exists, an up-to-date overview is lacking and there is little translation of academic evidence to help guide implementation in practice. Therefore, in this umbrella review we consolidated all available evidence from existing literature reviews covering factors that influence the acquisition, initial adoption, and sustained use of cleaner cookstoves and clean fuels in LMICs. Furthermore, we weighed the level of confidence in the evidence for these factors and translated our findings into two practical tools for developing evidence-based implementation strategies for future cleaner cooking interventions. In conducting our umbrella review, we address the following question: which factors enable or hamper acquisition, initial adoption, and sustained use of cleaner cookstoves and clean fuels with corresponding technologies in LMICs and what is the level of confidence in the evidence supporting these factors?

METHODS

This umbrella review (review of systematic and narrative reviews) was part of a broader review conducted by Brakema et al.[12] as part of the Horizon 2020 Free Respiratory Evaluation and Smoke exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR) project.[13] The study was registered with PROSPERO (CRD42018088687) and a peer-reviewed study protocol is available.[14] Due to a lack of reporting standards for umbrella reviews (currently under development[15]), we followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) reporting standard.[16]

Panel 1: Search strategy and selection criteria

Sources: PubMed, Embase, Global Health Database, Cochrane, PsycINFO, Emcare, Web of Science, and CINAHL

Date or language restrictions: None

Search terms: (Synonyms of) implementation, LMICs, and interventions targeting chronic lung health, including cleaner cooking interventions (for full details, see appendix pp 2-3)

Inclusion criteria: Reviews were included if they

- Reported on facilitators and/or barriers to the implementation (acquisition, initial use, or sustained use) of cleaner cookstoves or clean fuels
- Were systematic and narrative reviews that covered quantitative, qualitative, or mixed-methods studies[17]
- Were peer-reviewed
- Regarded rural or urban settings in LMICs (as defined by the World Bank classification[18])
- Addressed a switch from either traditional cookstoves or kerosene stoves (hence, changes from one clean fuel to another clean fuel, from a cleaner cookstove to a clean fuel, or from a cleaner cookstove to another cleaner cookstove were excluded)

Exclusion criteria: Factors were excluded if they were solely based on hypothetical interventions or speculations

Search strategy

Reviews were originally identified during a search conducted in a broader review by Brakema et al.[12] The search was developed together with a certified librarian (panel 1). The search was performed on the 23rd of October 2017 and updated on the 10th of July 2019. Two experts in the field of cleaner cooking (researchers and members of the clean cooking implementation science network; see acknowledgements) were consulted to identify relevant reviews up to the 13th of January 2022. Full details, including the search strategy, are available in the protocol and appendix pp 2-3.[14]

Selection criteria

Selection criteria are provided in panel 1. Because we anticipated limited evidence in the literature concerning implementation factors that influence sustained use, we also included acquisition (purchase or installation) and initial adoption (use for less than one year from acquisition) in this review.[19] A distinction was made between cleaner cookstoves and clean fuels, as we expected that the factors determining implementation success of each would differ. The protocol stated that articles would be excluded if they focused on legislation at a national governmental level.[14] Nevertheless, we decided to include these articles as we felt we could not neglect the central role that governments play in implementing national policies and strategies that prioritise cleaner cooking, in developing and enforcing regulations and standards, and in enlarging and investing in infrastructure.[2] Review selection, including title and abstract screening and full-text screening, was conducted using independent verification by two or more authors.

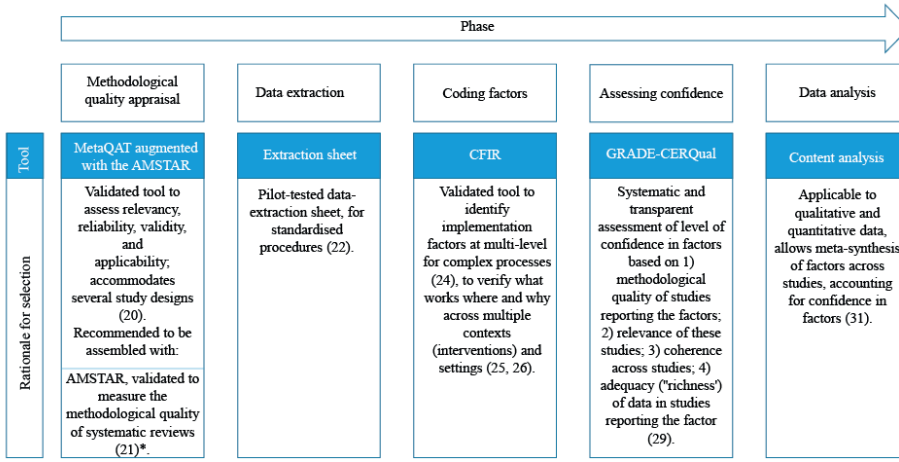

FIGURE 1: Tools applied in each phase, adapted from Brakema et al.[12] and reproduced from Boudewijns et al. with permission from BMJ Publishing Group Ltd[14].

Quality appraisal and data extraction

Reviews were appraised and data were extracted and analysed in five steps using validated tools (Figure 1). Two researchers conducted all steps independently and a third researcher was consulted to resolve any disagreements. First, the methodological quality of the reviews was appraised using the Meta Quality Appraisal Tool (MetaQAT).[20] This tool is validated to assess the relevancy, reliability, validity, and applicability of studies, and accommodates several study designs. The tool was augmented with the Assessment of Multiple Systematic Reviews (AMSTAR) tool

(see appendix pp 4-10 for further details).[21] The MetaQAT/AMSTAR tool contains descriptive rather than numeric appraisals and is designed to document relevant information to enhance transparency. The results of the quality appraisal provided the basis for assessing confidence in the evidence during step four. This approach accounted for risk of biased recommendations from narrative reviews during the meta-synthesis. Second, data on descriptive review characteristics and factors influencing the implementation of cleaner cooking interventions were extracted using standardised data extraction forms and were summarised in tables (appendix pp 11-21).[22] We did not distinguish between facilitators and barriers, as reversed facilitators can often be interpreted as barriers and vice versa.[12,23] Both modifiable (e.g. fuel accessibility) and non-modifiable factors (e.g. age) were extracted.

Evidence synthesis

The third step involved the coding of factors that influence the implementation of cleaner cooking interventions using the Consolidated Framework for Implementation Research (CFIR).[24] This is a validated tool to identify implementation factors for complex processes from a multilevel perspective, in order to verify what works where and why across multiple contexts and settings (appendix pp 22-70).[24-26] The CFIR is recommended for use in environmental health areas.[27,28] The framework includes five domains, each including several constructs: 1) intervention characteristics, 2) outer setting, 3) inner setting, 4) characteristics of individuals involved, and 5) the implementation process.[24] During the fourth step, confidence in the evidence of the extracted factors was calculated using the Grading of Recommendations Assessment, Development, and Evaluation-Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) tool.[29] The GRADE-CERQual can be applied to several fields, including environment and international development.[30] This tool consists of four domains: methodological limitations, relevance, coherence, and adequacy. For each of these domains, we assigned a score per included review, ranging from one point (substantial concerns) to four points (no to very minor concerns).[29] A score for coherence was not assigned, as the fit between the data was taken into account during the content analysis (step five). The score for the methodological limitations was based on the reliability and validity category of the Meta-QAT/AMSTAR tool; the score for relevance was based on the relevance category of the Meta-QAT/AMSTAR tool; and the score for adequacy was based on the data sources (appendix p 71). The content analysis allowed for meta-synthesis of factors across reviews while accounting for confidence in factors.[31,32] This step was conducted separately for factors influencing the implementation of cleaner cookstoves and clean fuels. Reviews that did not distinguish between factors for cleaner cookstoves and clean fuels were included in both analyses. For each factor (categorised by the CFIR), we determined a score by multiplying the score for the quality of the review in which the factor was mentioned (step four) by the number of reviews in which the factor was mentioned (appendix pp 72-81). To account for varying levels of reporting detail across reviews, each CFIR construct was taken into account only once for each review, even though various implementa-

tion factors were coded to the same CFIR construct (e.g. age and household composition are different implementation factors, but we used the same CFIR construct 'other personal attributes' for both). Finally, we calculated the overall level of confidence in the factors by totalling the scores of the three domains. Hence, higher score indicates higher adequacy, relevance, and/or quality of the review, and/or a higher frequency of the factor. The implementation factors supported by evidence with the highest level of confidence, including the level of evidence and practical examples, were consolidated in a comprehensive overview.

Different systematic reviews may include the same primary studies, resulting in double counting of certain evidence. Therefore, a matrix of primary studies included in systematic reviews was prepared to gain insight into double counting of primary studies.[33] Because narrative reviews often do not present the studies included, narrative reviews were not included in the matrix (appendix pp 82-112).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the article.

RESULTS

From a screening of 9111 unique articles, 31 reviews were included, of which 13 were systematic[6,23,34-44] and 18 were narrative[3,8,45-60] reviews (Figure 2). The systematic reviews included 479 unique primary papers. The included reviews were published between 1992 and 2022 and were conducted in a variety of geographical settings. Twelve reviews reported factors affecting the implementation of clean fuels, including electricity, LPG/bottled gas, biogas, solar cookers, and alcohol fuels (ethanol and methanol). It should be noted that two reviews included kerosene as a clean fuel.[36,53] Eighteen reviews described implementation factors concerning (a wide variety of) cleaner cookstoves, seven reviews reported separate factors for cleaner cookstoves and clean fuels, and eight reviews did not differentiate between cleaner cookstoves or clean fuels. Details of the included reviews are provided in Table 1 and appendix pp 7-20.

Quality appraisal

Twenty-two articles achieved a high score for relevance in the MetaQAT, nine articles achieved a medium relevance score, and none had a low score (appendix pp 7-10). The reliability of the included articles varied, with eleven articles achieving a high score, ten a medium score, and ten a low score. The main reasons underlying low or medium reliability were unclear reporting of methods and lack of information on data sources. In terms of validity, seven, fifteen, and nine articles achieved a high, medium, or low score, respectively. Lower scores were often due to risk

of bias, methodological flaws (e.g. no duplicate data extraction and no assessment of the quality of included studies), or unclear reporting of analytical methods. The applicability score was high for seventeen articles and medium for fourteen articles. The kappa with linear weighting was 0.56, indicating moderate reviewer agreement. The systematic reviews had limited overlap in the primary studies they had included (see appendix pp 82-112).

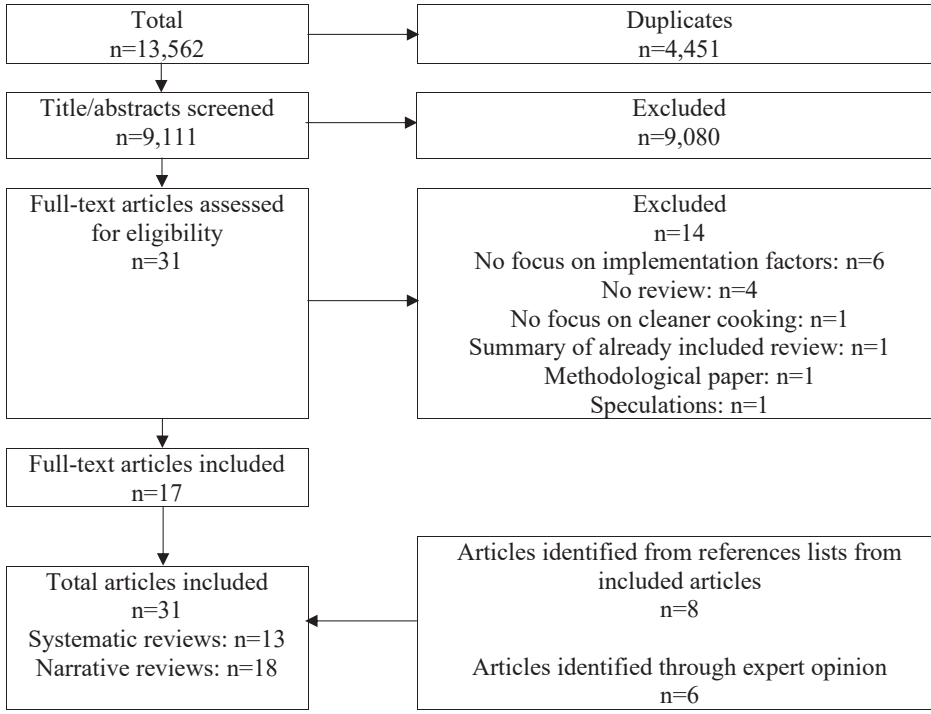

FIGURE 2: Diagram outlining study selection

Implementation factors and the Cleaner Cookstove Implementation Tool (CleanCIT)

We found that the influence of factors on successful implementation varied markedly depending on the technology being introduced and the specific context. The 15 factors (CFIR constructs) for which the level of confidence in supporting evidence was highest, based on our content analysis, were summarised in a practical tool (CleanCIT) (Figure 3). Examples of each factor are included in appendix pp 113-114, and a full list of factors for each CFIR construct is included in appendix pp 29-49. The three factors with the best supporting evidence for an influence on implementation accounted for 19% of the sum scores of the content analysis and are described below.

TABLE 1: Characteristics of the included reviews

First author, year [reference]	Study design	Intervention[1]
Barnes, 1993 [45]	Narrative review	**Stove:** Improved cooking stoves (different types)
Bonan, 2017 [46]	Narrative review	**Stove:** Improved cookstoves (all kinds of innovation) **Fuel:** Electricity connection (on-grid, off-grid and decentralized power provision both micro photovoltaic and home solar system, and improvements in the quality of the electricity supply)
Clemens, 2018 [47]	Narrative review	**Fuel:** Biodigester implementation through market development (Africa Biogas Partnership Program)
Energy Sector Management Assistance Program (ESMAP), 2020 [34]	Systematic review	**Stove and fuel (no distinction):** Modern Energy Cooking Services (transition is treated as any upward movement from a baseline cooking system to an improved one, as defined by the studies and programs evaluated)
Furszyfer Del Rio, 2020 [43]	Systematic review	**Stove:** Improved cookstoves
Gall, 2013 [48]	Narrative review	**Stove:** Improved cookstoves
Gill-Wiehl, 2021 [49]	Narrative review	**Stove and fuel (no distinction):** Improved biomass stoves, biogas, LPG, electricity, ethanol, natural gas, solar oven/cooker
Goodwin, 2015 [35]	Systematic review	**Stove and fuel (no distinction):** Cleaner cooking interventions
Guta, 2022 [44]	Systematic review	**Stove:** Improved biomass stove **Fuel:** Electric stove, LPG, biogas, solar cooker/heater, and ethanol
Karanja, 2019 [50]	Narrative review	**Stove and fuel (no distinction):** Clean bioenergy cookstoves (improved biomass stoves, biomass gasifier stoves, biogas stoves, and ethanol stoves)
Khandelwal, 2017 [51]	Narrative review	**Stove:** Improved cookstoves
Kowsari, 2011 [52]	Narrative review	**Stove and fuel (no distinction):** Modern energy systems
Leach, 1992 [53]	Narrative review	**Fuel:** Modern energy sources (among others LPG/bottled gas, kerosene, electricity)
Lewis, 2012 [36]	Systematic review	**Stove:** Improved cookstoves **Fuel:** Clean fuels (kerosene, LPG, electricity, or solar)
Lindgren, 2021 [61]	Narrative review	**Stove:** Biomass improved cookstoves (e.g. rocket, forced air, gasifier or top lift updraft stoves, addition of a chimney) **Fuel:** Solar cookers
Martinot, 2002 [55]	Narrative review	**Stove:** More efficient biomass stoves **Fuel:** Renewable energy (biogas stoves and solar cookers)
Mittal, 2018 [37]	Systematic review	**Fuel:** Small-scale biogas plants

First author, year [reference]	Study design	Intervention[1]
Puzzolo, 2016 [6]	Systematic review	**Fuel:** Clean fuels (LPG, biogas, solar cooking, and alcohol fuels)
Puzzolo, 2019 [56]	Narrative review	**Stove and fuel (no distinction):** Clean fuels: electricity (grid and photovoltaic), LPG, alcohol fuels (ethanol/methanol), biogas, compressed biomass pellets
Quinn, 2018 [57]	Narrative review	**Stove and fuel (no distinction):** LPG, biogas digesters and stoves, ethanol, compressed biomass fuels (pellets and briquettes); all meeting the ISO Tier-4 standard for emissions
Rehfuess, 2014 [23]	Systematic review	**Stove:** Improved solid fuel stoves
Ruiz-Mercado, 2011 [3]	Narrative review	**Stove and fuel (no distinction):** Clean fuels and cookstoves
Shankar, 2014 [58]	Narrative review	**Stove:** Improved cookstoves
Shankar, 2020 [8]	Narrative review	**Stove:** Biomass pellets **Fuel:** LPG, electric/induction cooking, ethanol, biogas
Sharma, 2017 [59]	Narrative review	**Stove:** Improved cookstoves (forces draft gasification and natural draft combustion/gasification)
Shen, 2015 [38]	Systematic review	**Stove:** Clean cookstoves **Fuel:** Clean fuels
Stanistreet, 2014 [39]	Systematic review	**Stove:** Improved solid fuel stoves
Thomas, 2015 [40]	Systematic review	**Stove:** Improved stove interventions
Thurber, 2013 [41]	Systematic review	**Stove:** Improved biomass cookstoves
Van der Kroon, 2013 [60]	Narrative review	**Fuel:** Modern forms of energy (e.g. electricity and LPG)
Vigolo, 2018 [42]	Systematic review	**Stove:** Improved cooking stoves

1 Bold text = paper included in analysis of cleaner cookstoves, clean fuels, or both.

The factor associated with the highest level of evidence regarding implementation was cost. High initial costs, lack of access to credit, and ongoing costs for maintenance were reported as key barriers to the acquisition and sustained use of cleaner cookstoves in several reviews. As the price of a cleaner cookstove is comparatively high relative to the purchasing power of a lower income household (and compared to traditional stoves that are produced at no cost), reviews recommended considering ways to facilitate the purchase. Addressing affordability constraints, e.g. by community lending schemes, price incentives, or free repairs, could to some extent address the high upfront costs. Evidence supporting a role for subsidies was inconsistent, with some reviews reporting that subsidies facilitated adoption, while others reported that adoption rates for cleaner cookstoves did not increase.

The second best supported factor was knowledge & beliefs concerning the innovation. Reviews showed that a higher level of education is generally positively associated with the adoption of cleaner cookstoves. A lack of prior knowledge about available cookstoves or the consequences of cooking with traditional and inefficient stoves inhibited the transition. Programs that used behaviour change techniques, including shaping knowledge and social support, reported higher adoption rates than those without. Public cooking demonstrations, training sessions, and campaigns are useful tools for communicating the advantages of cleaner cookstoves to a community. It is recommended that all implementation efforts anticipate the value that end users place on cleaner cookstoves, including safety, cleanliness, home improvement, and short-term health benefits.

The third best supported factor influencing implementation was compatibility. Many programs failed to accommodate the fact that the specifics of cooking vary by culture, geography, season, fuel type, local practices, and cooking needs. Several reviews reported that cleaner cookstoves suitable for the preparation of local dishes were preferred. Examples of facilitators of implementation included the suitability of the stove to meet the household's cooking demands, the ability to accommodate multiple fuels, fuel sizes and pot types, the fit of the stove in the typical kitchen space, technologies that did not affect the taste of food, and compatibility with current cooking schedules. A few reviews indicated that the additional energy services obtained from traditional stoves, such as heating and lighting, was a factor hindering adoption of cleaner cookstoves. Furthermore, a cleaner cookstove needs to be compatible with cultural practices, traditions, and beliefs.

Other factors associated with high confidence in the level of evidence included design quality & packaging, relative advantage, physical ability to change, delivery infrastructure, external policy & incentives, other personal attributes, access to knowledge & information, available resources, peer pressure, needs & resources of users, engage innovation participants, and reflecting & evaluating. In total, 44 factors (constructs) are included in the CFIR, of which 37 were reported to influence the implementation of cleaner cookstoves in various reviews (Figure 4).

Implementation factors and the Clean Fuel Implementation Tool (CleanFIT)

The 15 constructs supported by evidence with the highest level of confidence are summarised in the CleanFIT in Figure 5. Practical examples of each factor are included in appendix pp 115-116, and a full list of factors for each CFIR construct is included in appendix pp 50-70. The three factors with the best evidence for influencing implementation of clean fuels and corresponding technologies, covering 21% of the total sum scores of the content analysis, are described below.

Factors best supported by evidence in descending order	Description
	Consider initial and regular costs of the cleaner cookstove, including limited access to credit
	Take into account individuals' attitudes toward and value placed on the cleaner cookstoves as well as familiarity with facts and principles related to the cleaner cookstove
	Ensure compatibility between the local context (e.g. cultural and environmental conditions) and the cleaner cookstove
	Secure that the quality, including the presentation and assemblage, of the cleaner cookstove is good
	Ensure that there is a perceived advantage of the cleaner cookstove as compared to the traditional stove
	Understand the economic and non-economic factors within a household that determine the individual's ability to change
	Ensure that the infrastructure for delivery and maintenance of the cleaner cookstoves is available, of high quality, and reliable
	Understand and support external strategies to spread cleaner cookstoves, including policies, subsidies, regulations, legislation, and standards
	Take into account other personal traits, including the age and gender of the individual
	Facilitate access to knowledge and information about the cleaner cookstove and how to use it
	Secure sufficient resources for the implementation process and ongoing operations
	Be aware of the role that peers and social networks play in the decision to adopt the cleaner cookstove, in positive or negative ways
	Explore and accurately prioritise the needs of intended users
	Engage the end-users in the development, implementation, and use of the cleaner cookstoves
	Ensure feedback about the progress of the implementation and the quality of the cleaner cookstoves

FIGURE 3: The CleanCIT, evidence-based implementation strategy tool for cleaner cookstoves; the order reflects the level of evidence for the factor (not its importance). Practical examples are provided in appendix pp 113-114 (photo used with permission of copyright owner and the individual pictured)

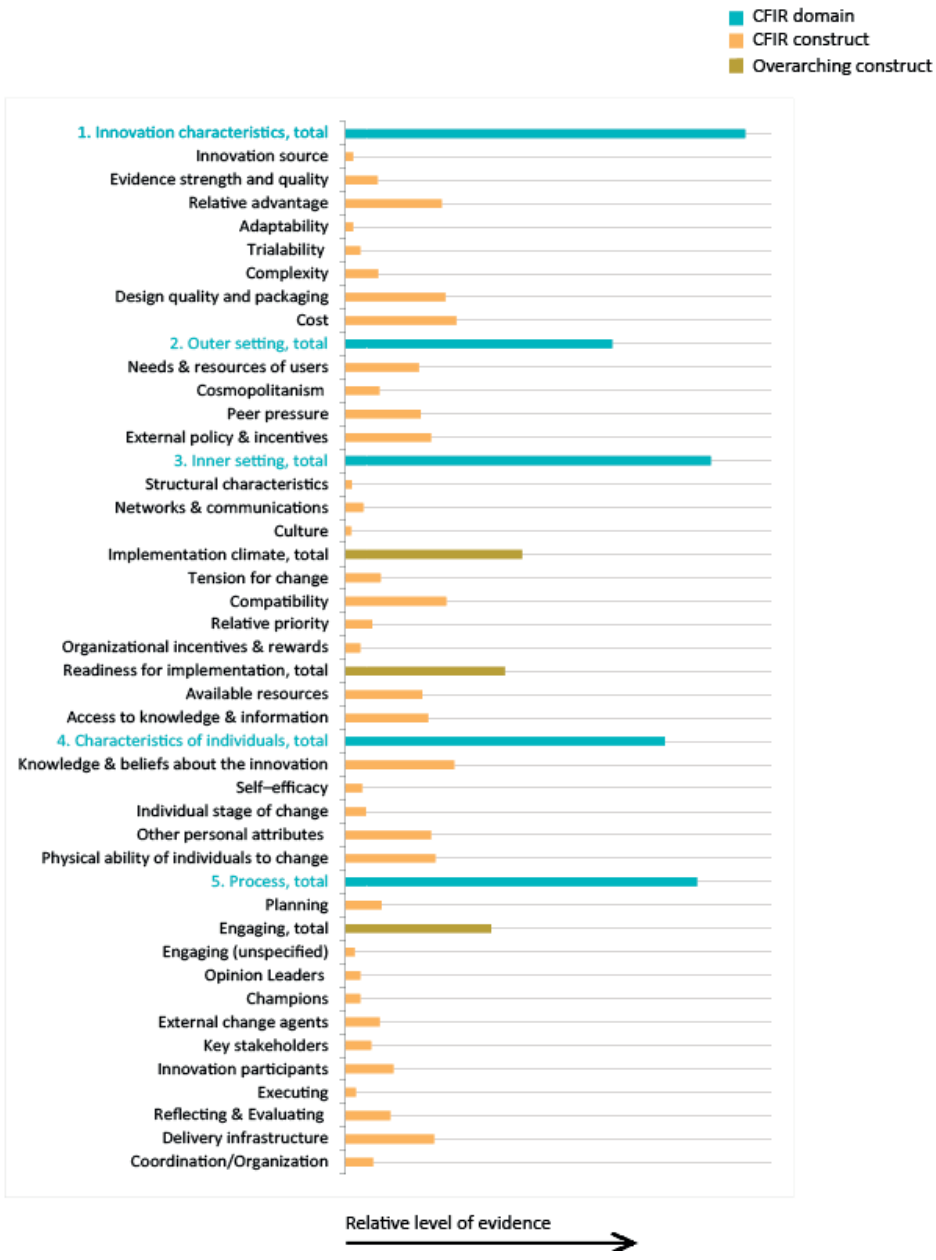

FIGURE 4: Overview of implementation factors per domain and relative levels of evidence for the factors for cleaner cookstoves. Bar sizes indicate the relative certainty as to whether the factor influences implementation, CFIR (overarching) constructs are described in appendix pp 22-27 and at https://cfirguide.org/.

Factors best supported by evidence in descending order	Description
	Consider initial and regular costs of the clean fuel and corresponding technology, including limited access to credit
	Take into account individuals' attitudes toward and value placed on the clean fuel and corresponding technology as well as familiarity with related facts and principles
	Understand and support external strategies to spread the clean fuel and corresponding technology, including policies, subsidies, regulations, legislation, and standards
	Understand the economic and non-economic factors within a household that determine the individual's ability to change
	Ensure that the infrastructure for delivery and maintenance of the clean fuel and corresponding technology is available, of high quality, and reliable
	Take into account other personal traits, including the age and gender of the individual
	Ensure compatibility between the local context (e.g. cultural and environmental conditions) and the clean fuel and corresponding technology
	Secure that the quality, including the presentation and assemblage, of the clean fuel and corresponding technology is good
	Secure sufficient resources for the implementation process and ongoing operations
	Ensure that there is a perceived advantage of the clean fuel and corresponding technology as compared to the traditional fuel/stove
	Be aware of the role that peers and social networks play in the decision to adopt the clean fuel and corresponding technology, in positive or negative ways
	Facilitate access to knowledge and information about the clean fuel and corresponding technology and how to use it
	Minimise the perceived difficulty of the intervention, such as the radicalness and intricacy required to implement
	Understand the degree to which stakeholders perceive the current situation as intolerable or needing change
	Explore and accurately prioritise the needs of intended users

FIGURE 5: The CleanFIT, evidence-based implementation strategy tool for clean fuels; the order reflects the level of evidence for the factor (not its importance). Examples are provided in appendix pp 115-116 (photo used with permission from owner and person on the picture)

Similarly to the analysis of cleaner cookstoves, the factor associated with the highest level of evidence regarding implementation was cost. Affordability constraints concerning the upfront capital costs of the clean fuel technology, ongoing fuel costs, and maintenance were all reported as barriers to successful implementation. Monetary incentives, including subsidies, were often reported to increase adoption, although they may also limit adoption upon withdrawal. Several reviews recommended ensuring access to credit and avoiding lumpsum payments. The main role of fuel prices was to cause a shift between fuels among those households that use several fuels, with fuel price differentials being more likely to result in a 'backward' substitution than an 'upward' transition.

The second best supported factor was knowledge & beliefs regarding the innovation. As seen with the adoption of cleaner cookstoves, several reviews identified a positive relationship between education level and a switch to clean fuels and corresponding technologies. Knowledge and awareness of the benefits of using clean fuels enabled adoption. Perceptions of cleanliness (e.g. no soot/ash), home improvement, and safety were often mentioned as highly valued by end users.

External policy & incentives was the third best supported factor influencing implementation. This includes external strategies to promote the adoption and use of clean fuels and corresponding technologies, including policies, subsidies, regulations, legislation, and standards. Examples were policy changes that lead to higher income levels or financial support targeted to the poor, a government's commitment to the provision of infrastructure, as well as market and trade policies, including supportive and effective instruments for regulation, certification, and standardisation. Furthermore, the need for collaborative action to promote behavioural change and/or to create a conducive policy environment was highlighted.

Other factors well-supported by evidence included physical ability to change, delivery infrastructure, other personal attributes, compatibility, design quality & packaging, available resources, relative advantage, peer pressure, access to knowledge & information, complexity, tension for change, and needs & resources of users. In total, we identified 36 factors (constructs) in the reviews that influence the implementation of clean fuels and corresponding technologies (Figure 6).

Similarities and differences between the implementation of cleaner cookstoves and clean fuels

Most factors supported by a high level of evidence were found to influence the implementation of both cleaner cookstoves and clean fuels, although we found some differences in the level of supporting evidence. For example, external policy & incentives was supported by a higher level of evidence for clean fuels compared to cleaner cookstoves. This could be due to the influence

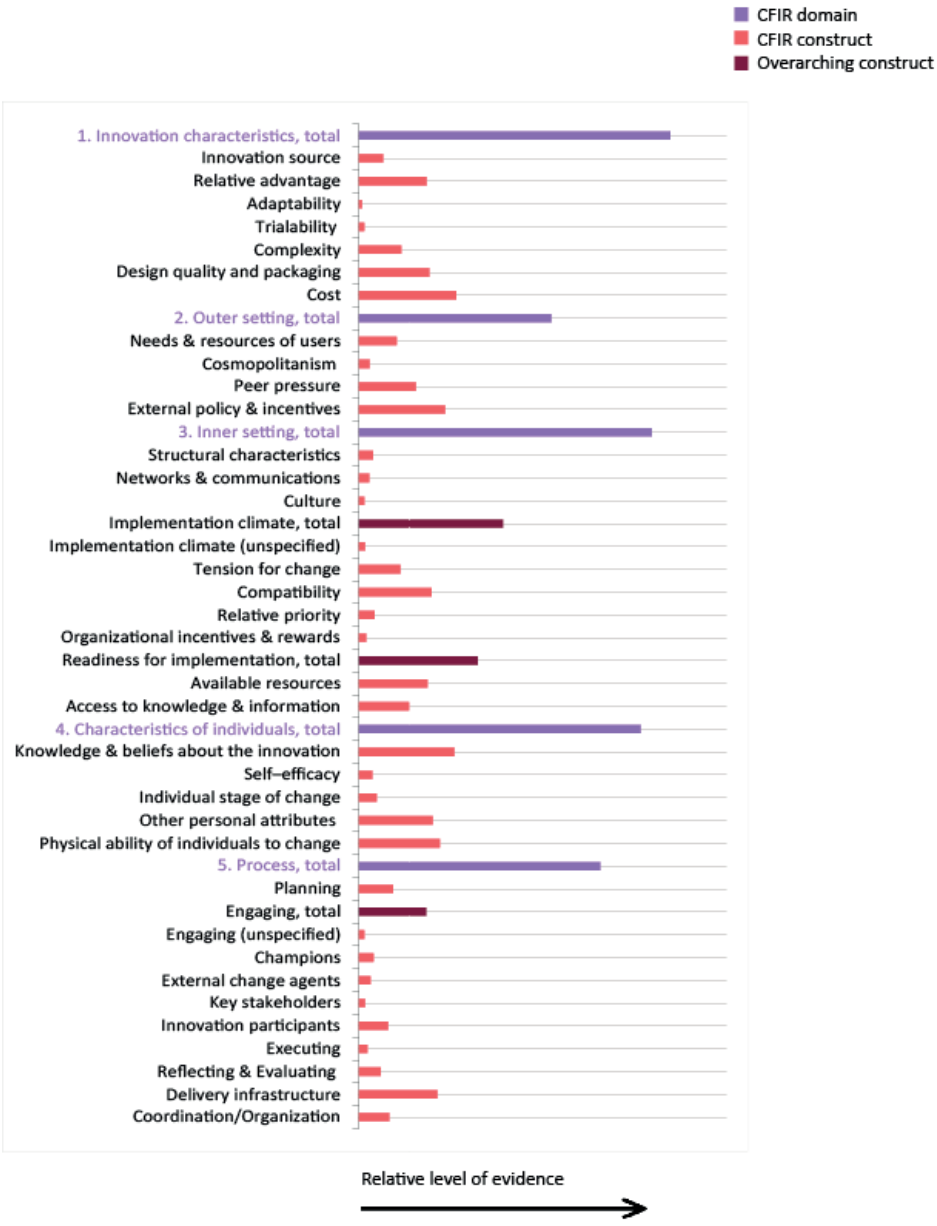

FIGURE 6: Overview of implementation factors per domain and relative levels of evidence for the factor for clean fuels. Bar sizes indicate the relative certainty as to whether the factor influences implementation. CFIR (overarching) constructs are described in appendix pp 22-27 and at https://cfirguide.org/.

of policy tools on upfront costs and recurrent fuel costs, which are often relatively high, and due to the regulations and standards needed to promote a safe and sustainable supply of clean fuels.

Conversely, compatibility was supported by a higher level of evidence in the case of cleaner cookstoves. An explanation for this difference could be that we have learned from mistakes made during implementation efforts of cleaner cookstoves (which have a longer history) and consequently compatibility is more carefully considered during the implementation of clean fuels and corresponding technologies (this does not imply that it is unimportant, but rather that it has already been taken into account).

DISCUSSION

Summary of findings

In this umbrella review, we aggregated and weighed the level of confidence in evidence found in 31 systematic and narrative reviews covering 479 primary studies on factors critical to the implementation success of cleaner cooking interventions in LMICs. Our results demonstrate that a range of factors synergistically influence acquisition, initial adoption, and sustained use, indicating that a comprehensive approach to cleaner cookstove and clean fuel implementation is needed. The 15 factors supported by the highest level of evidence were consolidated in the CleanCIT and the CleanFIT, including examples of their influence in practice.

Interpretation of results

The level of confidence in evidence supporting a particular factor should not be interpreted as a prioritisation of the relative importance of a factor and neither should it be seen as an indication of order in the steps of implementation. Rather, it simply represents the relative certainty as to whether a factor influences implementation. We would argue that all factors included in the tools should be properly addressed or at least considered. Conversely, the absence of a factor does not necessarily imply that the factor is not important, but may simply indicate a lack of available evidence. We therefore advocate that missing evidence will be obtained in future studies. It should also be noted that the presentation of evidence in reviews is dependent on the methodologies used and on the perspective of the researcher, implementer, and end user.

Considerations

The factors identified here should be clearly addressed or at least considered during the development of evidence-based implementation strategies for cleaner cooking interventions. The tools developed in the course of this study will help programmes avoid neglecting important factors, such as local needs, financing options, or after-sales support, when designing implementation strategies, all of which were shortcomings encountered in earlier programmes.[34] These tools will help accelerate the large-scale implementation of cleaner cooking interventions but should not be interpreted as a guarantee of successful implementation. Facilitators and barriers for implementation are highly dependent on contextual factors, but due to the nature of

the study we were not able to distinguish between different regions or countries. Tools and reports to assess the current state of household energy in specific regions or countries are readily available, for example the Clean Household Energy Solutions Toolkit (CHEST).[62] Some of the factors mentioned can be tackled by small, local organisations, while others require the involvement of (inter)national institutions or governments. For example, shaping knowledge through marketing messages, word of mouth, or practical demonstrations can be carried out by a local implementer.[43] Meanwhile, energy policy and regulations regarding the production and distribution of energy carriers and energy appliances are the responsibility of local or national institutions or governments.[52] We decided to include all factors in the tools, regardless of the organisation that can tackle those, to urge implementers to at least consider how these factors could influence their implementation strategy. This underlines the importance of a multilevel stakeholder approach and a system-wide perspective regarding cleaner cooking interventions. Factors influencing acquisition, initial adoption, and sustained use were not distinguished in this study, but it should be noted that the extent to which the factors influence the one or the other may differ. The same applies to large and small-scale implementation. Finally, in line with the pledge "to leave no one behind" in the Agenda for Sustainable Development 2030, we recommend at least considering equity in relation to gender, socioeconomic status, and the urban-rural divide. These issues are further elaborated on in a study by Puzzolo.[6]

Strengths and limitations

Commitment to implementation research is a prerequisite to enhance health in the face of increasingly harmful environmental trends.[9,63] To the best of our knowledge, this is the first review of reviews to have consolidated and weighed evidence on factors critical to the successful implementation of cleaner cooking interventions. However, bridging the gap between research and practice requires more than evidence alone.[63] Therefore, we developed two new evidence-based implementation strategy tools. These tools provide a practical overview of factors influencing the implementation of cleaner cookstoves and clean fuels, as well as presenting the level of supporting evidence, together with examples of how these factors impact implementation. By adhering to the PRISMA reporting standard, the study was rigorous in design and execution,[16] and reproducibility and transparency were ensured throughout the entire process by use of validated tools applied by two independent researchers. The study included an extensive literature search, with no date or language restrictions, and although the search was originally conducted in July 2019, consultation of experts allowed us to identify relevant publications up to January 2022. We decided to include both systematic and narrative reviews in this umbrella review, as only a fraction of all literature is captured by systematic reviews. Double inclusion was addressed in systematic reviews, but was not possible in the case of narrative reviews. Unfortunately, grey literature sources (such as policy reports) were not included, although we acknowledge that these contain important data. Previous literature has highlighted the challenge of identifying data in non-academic literature.[34] In addition, while specific names of fuels (e.g.

biogas or ethanol) were not included as search terms, we do not expect that this has led to a review being missed. Finally, kerosene, a relatively efficient fuel but with significant health risks, was considered a clean fuel by two reviews.

Recommendations for implementation initiatives

To those contemplating the challenge of implementation, we would stress that hundreds of papers have been dedicated to this complex subject. Therefore, we strongly advocate the design of a comprehensive strategy regarding implementation of cleaner cookstoves and clean fuels. This strategy should consist of a multilevel stakeholder approach and a system-wide perspective. The CleanCIT and CleanFIT (Figures 3 and 5) developed in this study suit this purpose. In collaboration with stakeholders, we now plan to further develop these tools as an inclusive online interactive platform, and recommend pilot-testing of the tools and, if successful, their subsequent promotion to regional and global initiatives. Lastly, we advise continuous monitoring of the effectiveness of any implementation strategy, together with the adoption of necessary improvements. The Reach, Effectiveness, Adaption, Implementation, and Maintenance (RE-AIM) framework is a suitable tool for assessing the effectiveness of a certain strategy.[7]

Recommendations for implementation research

Collating data from numerous fragmented studies, we have distilled clear recommendations that can be used to improve current practice, and we are therefore confident that this umbrella review will boost the implementation of cleaner cooking. For future research, we recommend the use of standardised methods and structured reporting, e.g. the Standards for Reporting Implementation Studies (StaRI) statement[64]. Echoing a common recommendation, we urge clarification of the definitions 'adoption' and 'sustained use', as these are used interchangeably in many reports.[61] For example, The Adoption Index developed by the Clean Cooking Alliance can be used to quantify rates of adoption.[65] Furthermore, several reviews have indicated that exclusive use of cleaner cooking solutions is unusual and that fuel stacking (the use of multiple stoves and/or fuels) is common practice.[8,57] As stacking reduces the potential benefits of cleaner cooking interventions, we advise to offer (a range of) cleaner cooking solutions to meet the household's diverse cooking demands.[66] Furthermore, in addition to paying attention to the uptake and sustained use of clean cooking solutions, we also recommend focussing on the suspension of solid fuels and traditional stoves. A recent systematic review highlighted the differences in factors that influence household uptake and sustained use of less polluting fuels and stoves versus those that influence use and suspension of solid fuels.[44] We recommend future studies to assess the role of stacking in their research. Objective measurements regarding the use of fuels and technologies, for example by stove use monitors, may help to better understand the adoption process and the impact of the use of one or multiple cleaner cooking solutions.[3] In this review, we merged data on a variety of clean fuels (electricity, LPG, natural gas, biogas, solar cookers, and alcohol fuels). However, we would recommend to separately review the role

of implementation factors with regard to these specific fuels when more evidence becomes available. Further studies are needed to better understand implementation factors influencing sustained use, as existing reviews often have short follow-up and therefore only cover the acquisition and initial adoption of cleaner cookstoves or clean fuels. Finally, the reliability of the strategy tools deserves further research, with special attention for the prioritisation of the importance of known factors.

CONCLUSION

With 2.6 billion people using traditional fuels and stoves daily, and climate crisis as the greatest threat to public health in the 21st century,[67] there is an urgent need to accelerate the implementation of cleaner cooking interventions. The evidence presented in this umbrella review supports a comprehensive approach to the development of evidence-based implementation strategies, including at least the 15 factors identified here, and argues for a multilevel stakeholder approach and a system-wide perspective. This umbrella review, and especially the CleanCIT and CleanFIT, will serve as a useful basis for the planning and delivery of cleaner cooking interventions. This, in turn, may facilitate significant health gains, less forest degradation and deforestation, mitigating effects on our climate, and gender equity.

Key messages

- Expediting access to cleaner cooking is crucial to mitigate the effects of solid fuel use on health, environment, climate, and gender equity.
- Of the dozens of literature reviews conducted on how to implement cleaner cooking interventions, comprising hundreds of studies, few have been translated into practice and the implementation success of cleaner cooking interventions is generally considered poor.
- Our study identified and consolidated the facilitators and barriers that need to be addressed to improve the successful implementation of cleaner cooking solutions, weighed the level of confidence in the existing evidence, and developed two practical implementation strategy tools to bridge the gap between academic evidence and practice.

The Cleaner Cookstove Implementation Tool (CleanCIT) and the Clean Fuel Implementation Tool (CleanFIT) serve to improve the inclusion of important factors during implementation strategy development and hence avoid waste of scarce resources; this, in turn, may accelerate large-scale implementation of cleaner cooking interventions.

Contributors

EvAB conceptualized the study and together with EsAB, elaborated the concept and design. Title and abstract screening were conducted by EvAB and DV. EsAB and MT or CH conducted the full-text screening. Methodological quality appraisal, data extraction, coding of factors, assessing of confidence, and data analysis were conducted by EsAB and MT or CH, supervised by EvAB. DV made the matrix for double counting. EsAB wrote the first version of the manuscript and developed the figures. EvAB supervised the various stages of the writing of the manuscript. DV, RMJJvdK, NHC, BK, and OCPvS critically reviewed the paper. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. JP Bayley has edited the manuscript. He was funded by Maastricht University and Leiden University Medical Center.

Declaration of interests

EsAB is part-time employed at the Dutch Spark for Clean Cooking Solutions. Other authors declare no competing interests.

Data sharing

The results of the quality appraisal, data extraction, and CFIR coding are documented on more than 310 pages. These are available from the corresponding author on reasonable request.

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CHAPTER 10

A SYSTEMATIC APPROACH TO CONTEXT-MAPPING TO PREPARE FOR HEALTH INTERVENTIONS – DEVELOPMENT AND VALIDATION OF THE SETTING-TOOL IN FOUR COUNTRIES

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ABSTRACT

Effectiveness of health interventions can be substantially impaired by implementation failure. Context-driven implementation strategies are critical for successful implementation. However, there is no practical, evidence-based guidance on how to map the context in order to design context-driven strategies. Therefore, this practice paper describes the development and validation of a systematic context-mapping tool. The tool was cocreated with local end-users through a multistage approach. As proof of concept, the tool was used to map beliefs and behaviour related to chronic respiratory disease within the FRESH AIR project in Uganda, Kyrgyzstan, Vietnam and Greece. Feasibility and acceptability were evaluated using the modified Conceptual Framework for Implementation Fidelity. Effectiveness was assessed by the degree to which context-driven adjustments were made to implementation strategies of FRESH AIR health interventions. The resulting Setting-Exploration-Treasure-Trail-to-Inform-implementatioN-strateGies (SETTING-tool) consisted of six steps: (1) Coset study priorities with local stakeholders, (2) Combine a qualitative rapid assessment with a quantitative survey (a mixed-method design), (3) Use context-sensitive materials, (4) Collect data involving community researchers, (5) Analyse pragmatically and/or in-depth to ensure timely communication of findings and (6) Continuously disseminate findings to relevant stakeholders. Use of the tool proved highly feasible, acceptable and effective in each setting. To conclude, the SETTING-tool is validated to systematically map local contexts for (lung) health interventions in diverse low-resource settings. It can support policy-makers, non-governmental organisations and health workers in the design of context-driven implementation strategies. This can reduce the risk of implementation failure and the waste of resource potential. Ultimately, this could improve health outcomes.

Summary Box

- Implementation failure can seriously impair the effectiveness of health interventions, thereby draining resource potential and undermining health outcomes.
- Context-driven implementation strategies can help to avoid failure. To design such strategies, practical guidance is needed on how to map local contexts.
- We developed and validated the Setting-Exploration-Treasure-Trail-to-Inform-ImplementatioN-strateGies (SETTING-tool) for mapping local health beliefs and behaviours.
- The SETTING-tool proved highly feasible, acceptable and effective in four diverse countries across the globe, demonstrating its wide applicability.

INTRODUCTION

Evidence-based interventions consistently fail to be implemented into routine practice, resulting in a substantial waste of resource potential and undermining health outcomes.1 2 Implementation—the act of carrying an intervention into effect3—is a typically effortful, complex process.4 Context-driven implementation strategies help to avoid implementation failure.2 3 5–10 However, there is no evidence-based, practical guide on how to first understand and map contexts in order to design such strategies.

Context can be defined as a set of unique characteristics and circumstances surrounding the implementation effort.11 A critical dimension of context pertains to local attitudes and knowledge regarding an intervention. 8 Health beliefs and risk perceptions shape behaviour, ranging from perceived causes of a disease to perceived barriers to change disease-related behaviour.12–14 For example, it would be unfeasible to motivate a community to instal kitchen chimneys to reduce indoor smoke, when local beliefs entail that ghosts enter homes via the chimneys. However, implementers are often unaware of such beliefs.15

Beliefs and behaviours are mostly not adequately mapped as it is resource-consuming and time-consuming. 15 Moreover, there are no standardised practical methodologies available to guide context-mapping efforts.6 16 17 The identification, development and testing of practical implementation methodologies are now considered top priorities in implementation science.16 Especially clinical researchers without implementation science expertise would benefit from systematic guidance to enable them to reproduce evidence-based methodologies in practice.18

Paradoxically, implementation evidence is particularly limited for low-resource settings, where the global burden of disease is highest and resources are scarcest.9 19 Therefore, we aimed to develop and validate a practical, systematic context-mapping tool for assessing local beliefs and behaviours in low-resource settings. To validate the tool, it was tested during a research project on chronic respiratory diseases (CRDs). CRDs are a major burden to low-resource settings; 90% of chronic obstructive pulmonary disease (COPD)-related deaths and 80% of asthma-related deaths occur in low-income and middle-income countries (LMICs).20In this paper, we describe the development and validation of the Setting-Exploration-Treasure-Trail-to-Inform-implementatioN-strateGies (SETTING-tool) in practice, and report on its feasibility, acceptability and effectiveness.

DEVELOPMENT AND VALIDATION OF THE CONTEXT-MAPPING TOOL

With a multidisciplinary expert panel including professionals from four diverse low-resource countries, we employed a multistage and multimethod approach to develop a context-mapping tool (see online supplemental appendix 1). The approach was similar to the approach for the development of the ImpRes tool.18 We first generated components for the tool based on a pragmatic literature search and methodological principles considered state-of- the art in our fields (see online supplemental appendix 1). A principle would be, for example, that mixed-method designs generally provide better insights than qualitative or quantitative research alone). Together with the expert panel, we then detailed the components (eg, use a 'Rapid Assessment Process (RAP) for qualitative data collection') based on expected feasibility, acceptability and effectiveness. We discussed these components until consensus was reached, and consolidated these into a comprehensive step-by- step tool. The resulting context-mapping tool had a stepwise approach, and was named the SETTING-tool (figure 1). Next, a research team sequentially validated the SETTING-tool prospectively in six diverse low-resource settings across four countries (see online supplemental appendix 2) within the Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR) project (Box 1). Feasibility and acceptability of the tool were evaluated using the modified Conceptual Framework for Implementation Fidelity.21 Effectiveness of the tool was assessed by determining the degree to which its application resulted in context-driven adjustments in the implementation strategies of subsequent FRESH AIR lung health interventions. Results guided iterative fine-tuning of the tool for the next setting. Online supplemental appendix 1 provides a detailed description of the full methodology for the development and evaluation of the tool.

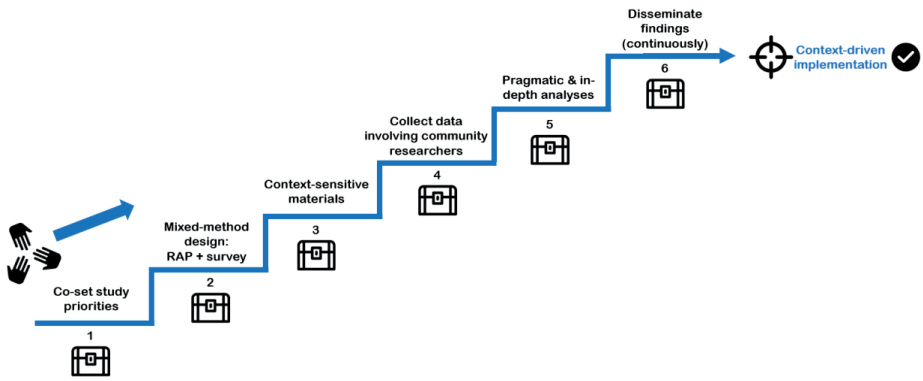

FIGURE 1. The Setting Exploration Treasure Trail to Inform implementatioN strateGies-tool; a step-by-step guide. This trail is a continuous, joint walk for researchers (those studying the context), foreseen end-users of the resulting information and other stakeholders. Certain factors, the treasures along the way, are considered to be key in successful completion of the step. RAP, rapid assessment process.

Box 1. The Horizon 2020 FRESH AIR study

The FRESH AIR project (2015-2018) studied the implementation of evidence-based chronic respiratory disease-related interventions in low-resource settings across the globe: in Uganda, Kyrgyzstan, Vietnam, and Greece. The project included preventive interventions (reducing exposure to tobacco smoke and biomass smoke), diagnostic (eg, diagnosing asthma in young children, online spirometry training), and treatment interventions (smoking cessation, pulmonary rehabilitation). The design of the implementation strategies of these interventions was context-driven, and informed by the application of the Setting-Exploration-Treasure-Trail-to-Inform-implementatioN-strateGies SETTING-tool.

https://www.ipcrg.org/projects/reearch/fresh-air (Trial ID NTR5759; trialregister.nl/trial/5644)

STEP 1: Co-set study priorities *(Figure 2)*

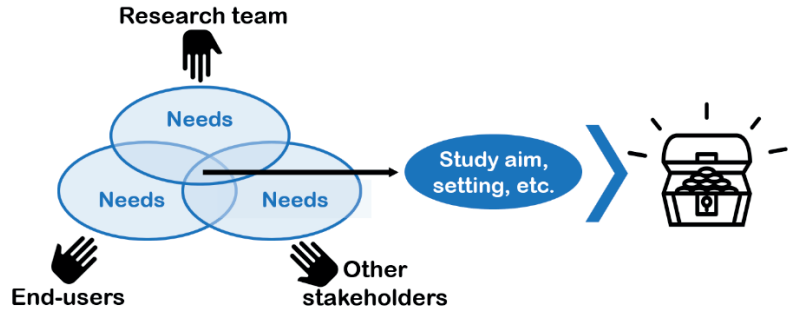

FIGURE 2. **Step 1: collaboratively set the study priorities.** Key to the treasure case (to successful completion of the step) is to define end-users of the study data, identify other stakeholders and actively engage all. Then explore the needs and coformulate the exact aim and scope of the context assessment, the setting and other priorities.

APPLICATION OF THE SETTING-TOOL IN THE FRESH AIR PROJECT

The tool is discussed step by step, including the rationale for each step and its application in the FRESH AIR project (see also table 1).

As a first step, we (the context-mapping researchers) collaboratively set the study priorities with our end-users and other influential stakeholders. We defined end-users of our study findings as (1) our FRESH AIR consortium colleagues, who would use the data to design context-driven implementation strategies for their planned interventions and (2) future implementers in similar settings, such as policy-makers, non-governmental organisations (NGOs) and health workers. The other influential stakeholders we identified, ranged from the Minister of Health

to local community members (CMs). There were diverse in terms of age, sex and educational background. They were engaged in Stakeholder Engagement Groups (see online supplemental appendix 3 table E1). Stakeholders received no financial compensation for participation. We engaged stakeholders from the beginning to ensure the study would closely meet their needs; this can be crucial in fostering uptake of the findings into practice later.3 7 22–25

Together with the FRESH AIR consortium colleagues and the Stakeholder Engagement Groups, we collaboratively set the context-mapping study's priorities. We formulated the exact study aim: 'To explore CRD-related beliefs and behaviours in diverse low-resource settings.' We used a theoretical framework (a combination of three well-stablished health-behaviour frameworks,12–14 online supplemental appendix 4) to further guide the specification of the aim and our methodological orientation.26–29 This framework consisted of factors leading to (intention to conduct) behaviour, such as the locally perceived identity of CRDs, perceived causes, and perceived barriers to change CRD-related behaviour. CRD-related behaviour included risk behaviour (tobacco smoking, cooking/ heating in a way that generates household air pollution), help-seeking behaviour by CMs, and helping behaviour by healthcare professionals.

We also determined the study settings. Implementation research generally aims to produce knowledge applicable across various settings,24 and rural settings have a high prevalence of CRD and risk factors to CRD.30 31 Therefore, six rural settings across four countries were selected purposively to represent diversity, and conveniently based on established relationships with the settings (online supplemental appendix 2 further details the settings and the definition of rural). These settings were in Uganda, Kyrgyzstan (a highland and lowland setting), Vietnam and Greece (a Roma camp and a rural Greek setting).

Second, we codesigned the context-mapping study with the end-users (the FRESH AIR consortium colleagues) and other stakeholders. Our researchers'-perspective enabled us to underpin the study with evidence-based methods, whereas the stakeholders ensured high compatibility of the selected methods with the local context. Codesigning the methods furthermore benefited the stakeholders' engagement.3 7 We cocreated a population-based, cross-sectional, observational design. Mixed-method designs generally provide a better understanding of situations than qualitative or quantitative research alone.3 32 Therefore, we adopted a mixed-method approach enabling to (1) explore and describe qualitatively how people perceive CRD, and what their related behaviour is like, and then 2) *quantify* the findings. We selected an RAP for the qualitative data collection,33 as it allowed us to timely inform our FRESH AIR colleagues on the implementation strategies of their interventions. We chose to collect the quantitative data using a survey. This enabled us to triangulate our data (to compare data collected through multiple methods, sources, theories and/or researchers) to optimise the validity of our findings (figure 3).34

Table 1 Overview of the SETTING-tool, explanation of the content and rationale for each step

STEP	Content	Rationale
1: Coset study priorities	Define end-users of the study data, identify other stakeholders, and actively engage all. Then explore the needs and coformulate the exact aim and scope of the context assessment—guided by a theoretical framework, the setting and other priorities.	Identifying and engaging stakeholders from the beginning enables that the study meets the stakeholders' needs, which can be crucial in fostering uptake of the findings into practice later.[3 7 22–25] A theoretical framework helps to guide the specification of the aim and methodological orientation.[26–29] Implementation research generally aims to produce knowledge applicable across various settings.[24]
2: Cocreate a mixed-method study design: combine a rapid assessment with a survey	Cocreate the mixed-method study design. Include (1) a qualitative rapid assessment process (RAP) in which data are collected by multiple methods, sources and researchers, and 2) a quantitative survey. Triangulate all findings. A RAP: The key principles of a RAP are (1) a system (community) perspective, (2) rapid, in-depth and iterative data collection and analysis, and (3) triangulation of data. The RAP research team immerses into a community for a short period and collects data simultaneously in subgroups using multiple methods.	Whereas the researchers can provide input on the use of evidence-based methods and a theoretical framework,[26 27] the end-users and other stakeholders can provide input on the compatibility of these methods with the local context. This collaboration furthermore stimulates the stakeholders' engagement.[3 7] Mixed-method designs generally provide a better understanding of situations than qualitative or quantitative research alone.[3 32] Triangulation of findings optimises validity of research results.[34] With a RAP, data collection is highly flexible and driven by local needs.[33 35]
3: Create context-sensitive study materials with high validity	Use evidence-based components where available throughout every substep, in our case: use (1) a theoretical framework, (2) a syndromic approach, (3) a vignette, (4) validated questionnaires, (5) a careful translation process (including translation, back-translation and according adjustments) and (6) pilot-testing of the materials.	The framework helps to theoretically underpin material development.[26–29] A syndromic (symptom-based) approach helps the participants to identify with the phenomenon studied, when a low awareness about it is expected. Use of a vignette can help to discuss topics more openly, while avoiding stigmatisation or while addressing sensitive topics.[39]
4: Collect data with a trained, diverse team including community researchers	Set up a diverse team, with local (community) researchers with an insiders' perspective combined with researchers with an external perspective. Train the team members by an experienced researcher.	Diversity in the team helps to enlighten the research topic from multiple perspectives and enrich the data.[35] The right community researchers are trusted by their community and have a thorough understanding of local networks and local health beliefs and behaviours. The combination with the 'outsiders' perspectives' helps to point out remarkable, typical local themes taken for granted by the community team members. Training secures ethical standards during data collection and enhances uniformity and high-quality data collection.[26]
5: Analyse data pragmatically and/or in-depth	Decide to analyse the data pragmatically and/or in-depth, depending on the objective.	Ensure to timely inform the implementation design for related health interventions, which may have to be supplemented by more in-depth analyses for scientific purposes. For feasibility, findings from pragmatic analyses via a 'targeted approach' can also be effective.[27]
6: Disseminate findings and promote data use (continuous step)	Continuously communicate relevant findings to the end-users and other stakeholders using a tailored message and delivery strategy.	Frequent communication with end-users and other stakeholders promotes sustained engagement and alignment, and uptake of the findings.[7 23 47 48] A systematic, practical tool designed to effectively communicate research findings can guide in facilitating knowledge uptake by policy-makers.[23] A tailored message and delivery strategy benefit information use.[23 49]

SETTING-tool, Setting-Exploration-Treasure-Trail-to-Inform-implementatioN-strateGies-tool.

STEP 2: A mixed-method study design: Combine a rapid assessment with a survey *(Figure 3)*

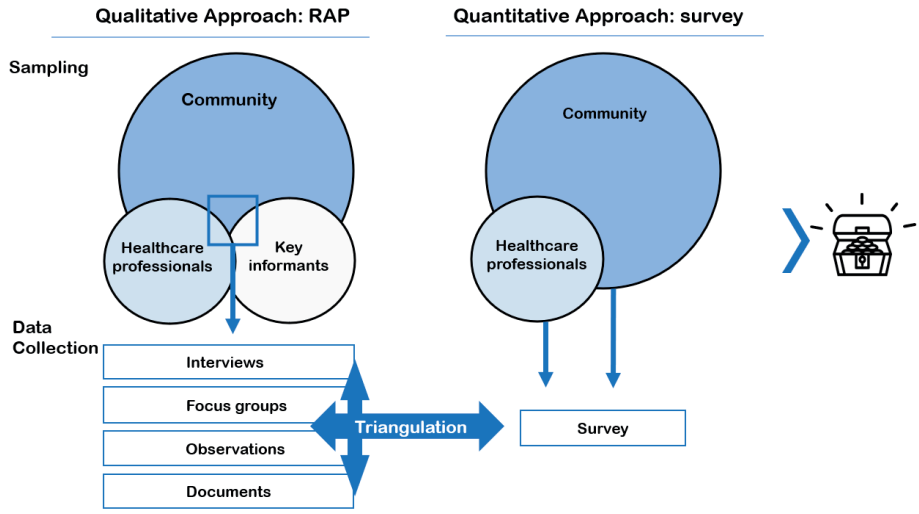

FIGURE 3. Step 2: a mixed-method study design. Key is to include (1) a qualitative rapid assessment process (RAP) in which data are collected by multiple methods, sources and researchers, and (2) a quantitative survey

The qualitative RAP

The key principles of an RAP are (1) a system (community) perspective, (2) rapid, in-depth and iterative data collection and analysis and (3) triangulation of data. We immersed into the rural communities for a short period and collected data simultaneously in subgroups using multiple methods.35 We included semistructured interviews, focus groups, documents and observations of healthcare professionals (respiratory consultations) and CMs (smoking, cooking and heating behaviour). Online supplemental appendix 2 details our planning and field methods.

Informants were selected based on opportunity and diversity (in sex, age, background, etc), to obtain rich data.26 We distinguished three participant groups: healthcare workers (HPs), CMs and key informants (stakeholders with either in-depth knowledge or an overall overview, such as religious leaders) (see online supplemental appendix 3 for inclusion and exclusion criteria). The sample size relied on when data saturation was achieved (when additional research activities would no longer result in additional insights). Preliminary findings were collated in daily debriefings with the entire team, guided by the theoretical framework. New informants were identified, and emerging themes and data saturation discussed. Iterative adaptations to the data collection materials, strategy and planning were also made. Accordingly, data collection was highly flexible and driven by local needs.33

The quantitative survey

We conducted one survey for CMs (200 per setting) and one for HPs (40 per setting). The CMs were randomly selected using a three-stage sampling approach based on the WHO 'Expanded programme for Immunisation', because it was especially suitable for rural settings.36 We then invited all eligible HPs from the nearest healthcare facilities.

Step 3 concerns the development of context-sensitive research materials with high validity. For the field methods selected in step 2, we needed corresponding materials: topic lists for the interviews and focus groups, semistructured forms for the observations, and structured questionnaires for the survey. Our theoretical framework guided the development of the research materials (eg, the construct 'perceived cause of CRD') (step 3A, figure 4).

We anticipated a low awareness of COPD, asthma and the implications.30 37 38 Hence, to enable informants to relate to the topic we adopted a syndromic (symptom-based) approach (step 3B). As informants could fear stigmatisation for tuberculosis, they could be hesitant to speak freely about respiratory symptoms. Therefore, we introduced the topic using a vignette (3C) which detailed a story about someone with slowly progressive chronic respiratory symptoms typical for COPD.39 We then probed using questions such as: 'Are there people with a similar situation living in your community?' and 'What, according to you, is the cause of the situation?'

The questionnaires for CMs and HPs were composed of validated questionnaires (3D). They included demographical questions, the revised version of the brief-Illness Perception Questionnaire,40 CM risk behaviour (solid fuel use for cooking/heating and tobacco use)41–43 and HP treatment behaviour respectively.44 Context-specific adjustments were made (eg, rainy/dry season instead of winter/summer).

STEP 3: Create context-sensitive study materials with high validity *(Figure 4)*

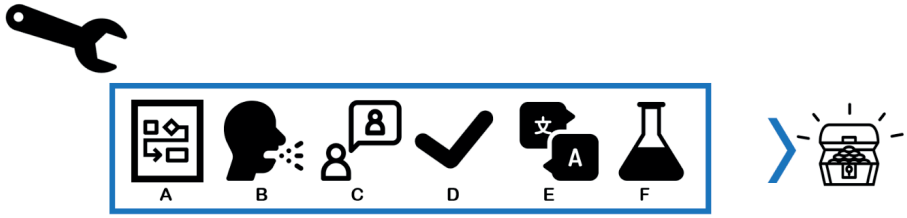

FIGURE 4. Step 3: a toolbox for creating context-sensitive materials with high validity. Key to success is to use evidence-based components where available throughout every sub-step, in our case: use (A) a theoretical framework to guide development of the materials, (B) a syndromic approach for expected low awareness of the phenomenon studied, (C) a vignette to avoid stigmatisation or address sensitive topics, (D) validated questionnaires, (E) a careful translation process and (F) pilot-testing of the materials.

The research materials were translated into each local language, back-translated and adjusted accordingly (3E). The qualitative materials were tested internally during our training sessions and iteratively improved throughout the study.27 The quantitative materials were pilot tested on feasibility and content validity among 10% or our targeted sample in each setting (3F). Resulting adaptations were, for example, replacing the Likert-scales (0–10) by multiple choice options, as scales turned out to be too abstract for local participants to comprehend. See online supplemental appendix 5 and online supplemental file 2 for the resulting research materials.

In step 4, we set up a well-trained and diverse team to collect the data. It included researchers from the communities, such as local nurses. Their insiders' perspectives offered deep understanding of local networks and prevailing themes,35 and they facilitated access to and openness of the participants. The combination with the 'outsiders' perspectives' (team members from the country's universities and Dutch researchers) helped to point out remarkable, typical local themes that were taken for granted by the community team members. Additional diversity in terms of background, age and gender helped to further enlighten the research topic from multiple perspectives and enrich the data.35 Notably, debriefing sessions generated additional data, for example, when community researchers and international researchers discussed explanations for certain findings from their own perspective. All team members received a thorough 1-day training from an experienced researcher, securing ethical standards during data collection and enhancing uniformity and high-quality data collection (online supplemental appendix 3).26 Further information on the data collection and training can be found in online supplemental appendix 3.

STEP 4: Collect data with a trained, diverse team including community researchers *(Figure 5)*

FIGURE 5 Step 4: collect data involving community researchers, who are trusted by their community and have a thorough understanding of local networks and local health beliefs and behaviours. Key to the treasure case is the combination of local researchers with an insiders' perspective, with researchers with an external perspective.

Step 5 emphasises the important difference between more pragmatic and in-depth analyses. The overall FRESH AIR project was bound to timelines that did not allow for time-consuming in-depth qualitative analyses of the context-assessment before the subsequent lung health interventions had to be implemented. Therefore, we pragmatically used our preliminary qualitative analyses of our debriefing sessions, which we communicated immediately after the RAP. We continued to update partners on the findings during the subsequent in-depth analyses.

STEP 5: Pragmatic and/or in-depth analyses *(Figure 6)*

FIGURE 6. Step 5: decide to analyse the data pragmatically and/or in-depth, depending on the objective; key to success is timely informing the implementation design for related health interventions, which may have to be supplemented by more in-depth analyses for scientific purposes.

For the in-depth analyses of qualitative data, we first transcribed the audio recordings verbatim.26 45 We coded the data both deductively and inductively, using thematic analyses to identify themes.46 Two researchers independently applied The Framework Method for data structuring and reduction (online supplemental appendix 6), compared results and discussed these until consensus was reached.45 We used appropriate qualitative software to facilitate data storing, analyses and sharing (online supplemental appendix 6). Next, data from the observations were charted into a table. These data together with field notes were used to complement and triangulate the data from the interviews and focus groups. Our quantitative data were analysed using associative analyses and descriptive statistics, in which we calculated frequencies of prevalence.

As a continuous process, we disseminated the findings using a tailored message and delivery strategy, to optimise information use among the FRESH AIR colleagues and other stakeholders.7 23 23 47–49 We communicated our preliminary findings immediately after the RAP. Further dissemination of our in-depth findings occurred during international scientific conferences. Policy-makers, NGOs and health workers were reached via international and local health conferences in each country.

STEP 6: Disseminate findings + promote data use (continuous step) *(Figure 7)*

FIGURE 7 Step 6: continuous communication between the research team, end-users, and other stakeholders by a tailored message and delivery method ensures that findings will be received and used.

VALIDATION OUTCOMES

Testing of the SETTING-tool in the six settings demonstrated that feasibility of the tool was high. Generally, all steps were implemented as intended with reasonable effort, and within our budget and time planning (online supplemental appendix 7,8). However, in the Roma setting, we needed to invest a substantial amount of time for building trust with the community. Therefore, we could only test our methodology, but did not achieve data saturation. Acceptability of the tool was consistently high; both the users of the tool and to whom it was applied considered it appropriate, based on their collaborative attitude (online supplemental appendix 7). Lastly, effectiveness of the tool was considered high; the application resulted in findings that led to multiple major context-driven changes to the planning and implementation strategies of the subsequent FRESH AIR interventions (table 2).

Table 2 Examples of major context-driven changes to the FRESH AIR intervention planning and implementation strategies

Theoretical factors*	Contextual input	Context-driven adaptations
Perceived identity of CRD	Awareness on CRDs and their implications was considerably lower than anticipated among rural communities and their healthcare professionals in Uganda, Kyrgyzstan and Vietnam.	For the Online Spirometry Trainings to improve knowledge and skills successfully, either the video content had to be adapted fundamentally to be compatible with a more basic level of understanding of CRD, or the trainings needed to be implemented in areas where the level of understanding was higher. In agreement with the stakeholders, we chose the latter strategy.
Perceived causes/ susceptibility/ cue to action	Awareness on the risk of household air pollution was low in Uganda, Kyrgyzstan and Vietnam; communities did not perceive their traditional cooking habits to be a risk for CRD, and therefore perceived no need for cleaner cooking measures.	The Awareness Programme on CRDs was expanded: the delivery strategy turned into a cascading train-the-trainer programme with a larger reach.[56] Household air pollution as a risk factor to lung health was covered extensively, creating a locally perceived need for cleaner cooking interventions. This contributed substantially to a high acceptability of the interventions (Cleaner Cooking and a Midwife-led Smoke-reduction Programme).[57 58]
Perceived causes/ benefits/ norms	A (rural) Kyrgyz norm is that 'a real man smokes', while smoking women are despised. The risk of smoke exposure during pregnancy is fairly unknown, and the man's position in the family does not allow to question his smoking behaviour. Meanwhile, the youngest son in the family is responsible for taking care of his parents later in life (the families' pension).	In the Kyrgyz Awareness Programme, we emphasised even more on the risk of smoke exposure to (unborn) children, and provided solutions to secondhand smoke exposure (smoking cessation, smoking outdoors).[56] This promoted openness to the Awareness Programme and uptake of the Smoking Cessation Counselling intervention (very brief advice).[59]
Perceived causes/ susceptibility	The Vietnamese word for 'overwork' (Lao Lu'c) resembled the word for 'tuberculosis' (Lao), and so communities and their healthcare professionals often associated exercise, including pulmonary rehabilitation, with lung impairment.	To overcome the hesitance of patients to participate in the Pulmonary Rehabilitation Programme,[60] we had to introduce a component in the programme that emphasised the benefits of exercise for respiratory symptoms.
Norms/ barriers	We had planned to also address the Roma population in Greece with our interventions, yet our RAP provided us the insight that this population was extremely hard-to-reach; working with the Roma would require years of trust, which was beyond the scope of our 3 year research and funding period.	To use our resources more effectively in Greece, we decided to prioritise solely on the rural, traditional Greek population (low-resource, rural populations) instead.
Norms/ cue to action	In rural Greece, brotherhood (filotimo) was a prevailing norm: connecting with and helping those around you was highly valued.	We embraced this norm as a motivator in the Pulmonary Rehabilitation Programme.[60] We capitalised on the positive social pressure to exercise together as a group and help each other to complete the programme by not missing a single training. The programme in Greece had almost no drop-outs.

*In many examples, multiple factors of our composed theoretical framework would apply to the contextual input. The factors with highest applicability are reported.
CRD, chronic respiratory disease; RAP, rapid assessment process.;

CONCLUSION

We have developed and validated a systematic tool for context-mapping, enabling to design context-driven implementation strategies for (lung) health interventions in low-resource settings. Its application to the FRESH AIR project demonstrated that the SETTING-tool is highly feasible, acceptable, and effective in facilitating context-driven adaptations to implementation strategies in six diverse settings across the globe.

The SETTING-tool was cocreated by an international expert panel and local end-users. Development was both theory driven and practice driven. Concepts from a rich diversity of relevant fields were consolidated, ranging from implementation science to global health. Additionally, the methodology was prospectively validated in six diverse settings in four countries on three continents: from deprived Ugandan slums, to rapidly developing Vietnamese villages, to austerity-impacted rural Greece and highly risk-burdened Kyrgyzstan. Feasibility, acceptability and effectiveness of the tool were consistently high. This demonstrates its global applicability.

However, it is difficult to assess whether better alternatives would have been available to the components included in our tool. In our pragmatic literature searches, there were no studies comparing the effectiveness of different components and certainly not across contexts. In this practice paper, we also did not compare our context-mapping outcomes against those of a control group. Lastly, although application of the SETTING-tool was feasible, the overall feasibility of working with certain populations should remain of consideration. For example, the tool's feasibility was also high in the Roma camp, yet working with the Roma population generally required more time than working in other settings.

Existing studies, frameworks and toolkits emphasised the need for context-driven implementation strategies and repetitive calls highlighted the need for evidence on how to design those.[5 6 9 16 17 19] The SETTING-tool addresses these calls by guiding the researcher step-by- step through the context-mapping process. Other than existing approaches such as Community-Based Participatory Research,[50] this tool is developed as a practical guide in the field. It covers the entire context-mapping process, including for example developing the research materials and promoting uptake of the findings. Each step is easily reproducible. Key elements for successful completion of the steps are highlighted. This structured guidance can particularly serve clinical researchers without implementation expertise.[18]

The SETTING-tool is particularly relevant as it was developed for low-resource settings, where the burden of disease is highest, while the means to combat disease and evidence on how to do so are scarcest.[5 9 19 22 51 52] Furthermore, the tool addresses two important issues that contribute to the avoidable loss of 85% of investments in health and biomedical research

(US$200 billion lost in 2010 alone): (1) failure to establish priorities based on stakeholders' needs and (2) poorly designed research methods.53 54

The SETTING-tool can be used flexibly; it can be adapted according to local needs, as long as the core elements (the six steps) remain intact and the tool remains simple to use.7 55 Researchers should also ensure to continuously collaborate closely with the stakeholders (box 2). Flexible aspects are, for example, that not every health topic requires the use of a vignette to avoid stigmatisation. Use of the tool across diverse contexts, for other health topics and by researchers that were not involved in its development, could provide further insight on the generalisability of the tool. This would also allow for assessing the importance of individuals components depending on the setting or targeted disease. Although validated in LMICs, the tool might also be transferable to high-income settings.

Box 2. Main lesson learnt

Continuous collaboration between the researchers and the stakeholders was vital for successful completion of every step of the SETTING-tool. The close collaboration helped to align the study aim with the actual needs, to promote compatibility of methods and materials with the local reality, to identify the right community researchers to join the team and to promote uptake of the findings. Additional lessons learnt are detailed in online supplemental appendix 9.

Notably, the tool focuses on local beliefs and behaviours, and it is important to remain aware of other elements that shape context.8 Systematically assessing a context on multiple elements (beliefs and behaviour, physical environment, organisational structures, etc) would require a substantial amount of resources. We would then recommend to conduct the tool's steps more pragmatically; particularly the in-depth analyses in step 5 as they are most time-consuming.

To conclude, the SETTING-tool can support researchers, policy-makers, health workers, NGOs and other implementers to apply evidence-based methods in context-mapping. This can facilitate them to design context-driven implementation strategies to increase implementation success of their health interventions, potentially avoiding the widescale waste of scarcely available resources. Ultimately, this could improve health outcomes.

Author's contributions: EB led the design, conduct and analyses of the research. Together with CP and RvdK she performed the literature searches for the theoretical underpinning of the methodology. Together with all co-authors, the identified methodological components were discussed and selected for the tool. The country experts – IT, SW, PLA, and TS – specifically focused on local acceptability and feasibility. RR trained the team and supervised application of

the methodology on the ground in the first setting. Analyses were performed by all researchers. EB wrote the manuscript and RvdK provided feedback on each version. All authors read and approved the final manuscript.

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Competing interests: None declared.

Patient and public involvement: This methodology was co-created with local stakeholders, among others with district health officers, health workers and community members. We closely collaborated through face-to-face and digital meetings.

Patient consent for publication: not applicable.

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

Ethics approval and consent to participate: research participants in the validation process provided written informed consent, and illiterate participants provided verbal consent instead. All other stakeholders (members of the research team or stakeholder engagement groups) provided verbal consent. The study was approved by the coordinating centre and by each local research ethical review board: the Medical Ethical Committee of the Leiden University Medical Centre (P16.063;04/15/2016), the Mulago Research and Ethics Committee (933;03/31/2016), the Ho Chi Minh City University of Medicine and Pharmacy (188/DHYD-HD;06/27/2016), the National Centre of Cardiology and Internal Medicine in Bishkek Ethics Committee (5;03/03/2016), and the 7th Health Region of Crete (protocol 6951;05/27/2016).

Supplementary information: Provided with the online version of this publication (Reporting guidelines, Context of settings known before the study, Theoretical framework, Additional information on study design and conduct, Qualitative analysis: Application of Framework Method, Research materials, Budget.)

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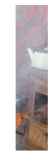
CHAPTER



MAPPING LOW-RESOURCE CONTEXTS TO PREPARE FOR LUNG HEALTH INTERVENTIONS IN FOUR COUNTRIES – A MIXED-METHOD FRESH AIR STUDY

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SUMMARY

Background Effectiveness of health programmes can be undermined when the implementation misaligns with local beliefs and behaviours. To design context-driven implementation strategies, we explored beliefs and behaviours regarding chronic respiratory disease (CRD) in diverse low-resource settings.

Methods This observational mixed-method study was conducted in Africa (Uganda), Asia (Kyrgyzstan and Vietnam) and Europe (rural Greece and a Roma camp). We systematically mapped beliefs and behaviours using the SETTING-tool. Multiple qualitative methods among purposively selected community members, health-care professionals, and key informants were triangulated with a quantitative survey among a representative group of community members and health-care professionals. We used thematic analysis and descriptive statistics.

Findings We included qualitative data from 340 informants (77 interviews, 45 focus group discussions, 83 observations of community members' households and health-care professionals' consultations) and quantitative data from 1037 community members and 204 health-care professionals. We identified three key themes across the settings; namely, (1) perceived CRD identity (community members in all settings except the rural Greek strongly attributed long-lasting respiratory symptoms to infection, predominantly tuberculosis); (2) beliefs about causes (682 [65·8%] of 1037 community members strongly agreed that tobacco smoking causes symptoms, this number was 198 [19·1%] for household air pollution; typical perceived causes ranged from witchcraft [Uganda] to a hot–cold disbalance [Vietnam]); and (3) norms and social structures (eg, real men smoke [Kyrgyzstan and Vietnam]).

Interpretation When designing context-driven implementation strategies for CRD-related interventions across these global settings, three consistent themes should be addressed, each with common and context-specific beliefs and behaviours. Context-driven strategies can reduce the risk of implementation failure, thereby optimising resource use to benefit health outcomes.

Funding European Commission Horizon 2020.

RESEARCH IN CONTEXT

Evidence before this study

To reduce the risk of implementation failure, implementation strategies need to align with locally prevailing health beliefs and behaviours. Therefore, local beliefs and behaviours should be thoroughly understood. We searched PubMed and Google Scholar for original articles and systematic reviews published up to May 6, 2021, that focused on beliefs and behaviours regarding chronic respiratory diseases in low-resource settings, with no language restrictions. We used synonyms of "beliefs" or "behaviours", and "chronic respiratory disease" (including "COPD" or "asthma"). Evidence was highly fragmented, and studies were mostly confined to one low-resource setting, in a high-income country. Studies were generally limited to either patients' knowledge about their disease (often in relation to adherence to inhalers or disease control), or to health-care professionals' knowledge and adherence to guidelines, or to specific interventions (smoking cessation). Only one qualitative study and three international, quantitative studies focused on COPD-related or asthma-related beliefs in general. Overall, the available evidence demonstrated that knowledge about COPD and asthma among patients and health-care professionals was poor. The studies did not provide insights about themes that consistently played a role in low-resource communities' beliefs and behaviours. Therefore, it is hard to determine what aspects to explore and address in implementation strategies of future lung health interventions.

Added value of this study

To address this knowledge gap, international, national academic, and community researchers teamed up to explore local beliefs and behaviours regarding chronic respiratory disease. We collected qualitative data from 340 informants in more than 200 interviews, focus groups and observations, and triangulated findings with a survey. We consistently applied the same mixed-method approach across three continents in six highly diverse settings, thereby enhancing comparability of the findings. Across slums in Uganda, highland and lowland Kyrgyzstan, rapidly developing Vietnam, austerity-impacted Greece, and an off-the-grid Roma camp we identified three common themes: (1) perceived disease identity (eg, the strong attribution of chronic symptoms to infection); (2) beliefs about causes (ranging from witchcraft in Uganda to a hot–cold disbalance in Vietnam); and (3) norms and social structures (eg, that real men smoke in Kyrgyzstan and Vietnam). We illustrated how findings were used to design context-driven implementation strategies for subsequent lung health interventions to improve their uptake. Furthermore, we provided an overview of the main characteristics per setting with their prevailing beliefs and behaviours about respiratory health to serve implementers globally; in settings with similar characteristics, implementers could be vigilant for similar beliefs and behaviours.

Implications of all the available evidence

Awareness of chronic respiratory disease is poor among low-resource communities and their health-care professionals, and leads to avoidable morbidity and mortality. This poor knowledge should be targeted by context-driven interventions that address the common and context-specific traits within the three identified themes. Future research should assess further generalisability of these themes to other settings. Furthermore, as we have learnt from the COVID-19 pandemic, there is a role for international collaboration to improve respiratory health literacy and address myths. This should be done by using a clear narrative about the identity of chronic as well as infectious disease and about their causes. Primary care is embedded in local communities and understands the local norms and social structures. Therefore, primary care has a large potential to deliver messages that align with these norms and structures, or challenge these, as required.

INTRODUCTION

WHO, global health funders, and other institutions have urged for more and better implementation research.1–4 Implementation failure can drain scarce resources and seriously undermine the effect of health programmes.5 Research is most needed for low-income and middle-income countries (LMICs), where the burden of disease is highest, health systems are weakest, and implementation evidence is scarcest.6

Implementation success depends on numerous factors. Critical is the compatibility between the programme, implementation strategy, and the local context, of which local health beliefs and behaviours are key dimensions.2,7,8 Leading theoretical models are built on the concept that health behaviour is shaped by health beliefs.9–11 To illustrate, three billion people still burn solid fuels (eg, wood or animal dung) daily. The resulting household air pollution (HAP) causes 3 million deaths and 86 million disability-adjusted life-years per year.12 Improved cookstoves that generate less smoke would be a promising solution, yet for decades their adoption by local communities has been poor. Failure to understand the households' beliefs and needs, and hence failure of the stoves to meet those beliefs and needs has been a major barrier to successful implementation of the stove programmes. Discrepancy between the perceived and actual harm of HAP is another common barrier.13 Implementation research must explore such local beliefs and related behaviours to optimise uptake of promising interventions and enable those to enter routine practice.

Of particular interest are health beliefs and behaviours related to chronic respiratory disease (CRD) in low-resource settings; chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, with 90% of deaths occurring in LMICs. Also, most

asthma-related deaths occur in LMICs.14,15 Evidence-based interventions exist, such as cleaner cooking solutions, smoking cessation, and pulmonary rehabilitation. To increase implementation success of such interventions, strategies are needed that are aligned with the health beliefs and behaviours. Therefore, in this study we aimed to map local beliefs and behaviours regarding CRD (COPD and asthma) in diverse low-resource settings.

METHODS

This study was part of the FRESH AIR implementation research project (Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups, NTR5759), targeting the prevention, diagnosis, and treatment of CRDs in low-resource settings.16 Reporting adheres to the STROBE statement for observational studies17 and COREQ guidelines for qualitative research.18 A scientific advisory committee supervised the quality of the design and conduct of the study (appendix 4 p 15). The methods are provided here in brief. For additional details, see our methods article,19 study protocol (available online), and appendix 4.

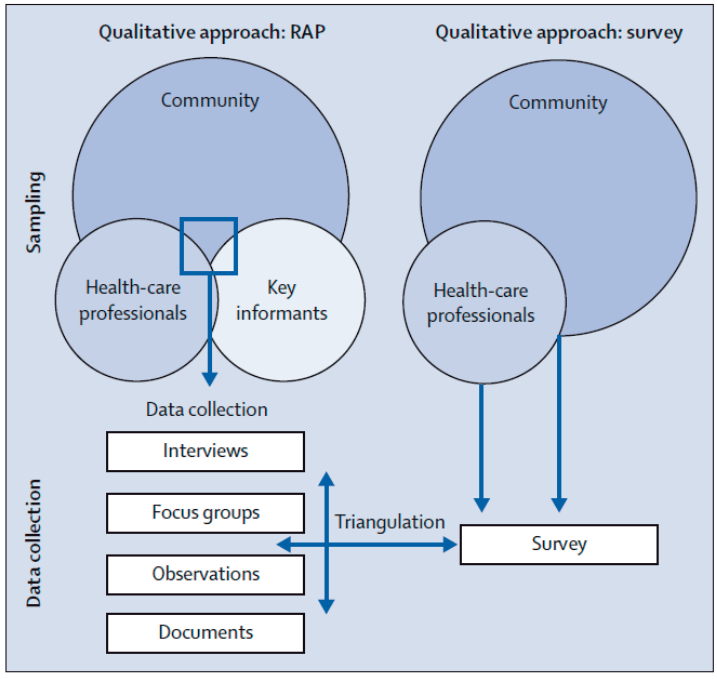


FIGURE 1: The mixed-method study design
RAP=rapid assessment process. Reproduced from Brakema and colleagues.19

Study design

We conducted a cross-sectional, mixed-method study between April 5, 2016, and Jan 27, 2017 (figure 1). Following the context-mapping method of the SETTING tool, we engaged local stakeholders and co-set study priorities; used a mixed-method design (a qualitative rapid assessment process [RAP] including in-depth interviews, focus groups, and observations of households and health-care consultations, combined with a quantitative survey); used context-sensitive materials with high validity; collected data with a trained, diverse team including community researchers; analysed the data pragmatically and in-depth; and continuously disseminated findings to relevant stakeholders to promote data use.19

A theoretical framework guided our study design and analyses. This Beliefs and Behaviours Framework was based on three well-established health behavioural models, the Theory of Explanatory Models of Illness, the Theory of Planned Behaviour, and the Health Belief Model (appendix 4 pp 2–3).9–11 It consisted of factors leading to (intention to conduct) CRD-related behaviour, such as the locally perceived identity of CRDs, perceived susceptibility to CRD, or barriers to change CRD-related behaviour. CRD-related behaviour included risk behaviour (eg, tobacco smoking), help-seeking behaviour by community members, and helping behaviour by health-care professionals.19

Development of our research materials19 (topic lists, observation forms, questionnaires) was also guided by the theoretical framework. Because we expected a low awareness of CRDs and their implications,20 we used a syndromic approach focusing on symptoms rather than disease. To avoid potential stigmatisation for tuberculosis we used a vignette21 describing a relatively young woman with symptoms typical for solid fuel use-related COPD (appendix 4 pp 2–3).22 We then asked questions such as, "Are there people with a similar situation in your community?" and "What, according to you, is the cause of the situation?". We adapted the materials to each local setting. The quantitative questionnaires included demographic questions and were a compilation of existing validated questionnaires (the revised brief-Illness Perception Questionnaire, community member risk behaviour regarding cooking or heating and tobacco use, and health-care professional treatment behaviour).23–27 The questionnaires for community members and health-care professionals were tailored according to our preliminary qualitative findings and pilot-tested in each setting.19

Participants provided written, informed consent. Participants who were unable to read or write provided audio-recorded, verbal consent instead. The study was approved by the coordinating centre and each local research ethical review board; namely, the Leiden University Medical Center Medical Ethical Committee (P16.063;04/15/2016), Mulago Research and Ethics Committee (933;03/31/2016), National Center of Cardiology and Internal Medicine in Bishkek Ethics

Committee (5;03/03/2016), Ho Chi Minh City University of Medicine and Pharmacy (188/DHYD-HD;06/27/2016), and 7th Health Region of Crete (6951;05/27/2016).

Setting

We purposively selected six rural low-resource settings in Uganda, Kyrgyzstan (two settings), Vietnam, and Greece (two settings) to represent diversity in geography, culture, risk factor exposure, and health-care and political system.19 We conveniently preferred sites where the research team or our engaged stakeholders had already well-established relationships with the communities. These were the Jinja district in Uganda, and the Ben Luc and Can Giuoc districts in Vietnam. In Kyrgyzstan, we selected a mountainous (Naryn) and a lowland (Chui) setting, because these differed substantially in lifestyle and risk exposure.28 In Greece, we selected a Roma camp and rural areas affected by the recent economic crisis in the Heraklion region (Crete; appendix 4 pp 4–10).

Study population and sampling

Our study population comprised three groups; namely, health-care professionals, defined as any worker medically addressing CRD within the community boundaries (eg, medical doctors, nurses, and clinical officers); community members aged at least 18 years; and key informants (people with either in-depth knowledge or an overall overview of community beliefs and behaviours; eg, religious leaders, pharmacists, and traditional healers). Any person physically or mentally unable to participate was excluded. For the RAP, participants were selected purposively to represent diversity in sex, age, background, and profession, and based on snowball sampling and opportunity. The engaged stakeholders helped to identify participants. Sample size was determined by the principle of a priori and inductive thematic saturation (appendix 4 pp 4–10), which we expected to be achieved with ten to 15 health-care professional interviews, ten to 15 consultation observations, ten to 15 key informant interviews, two to three community member focus groups, and ten to 15 household observations per setting. For the quantitative survey, we randomly selected health-care professionals and community members using a three-stage sampling approach suitable for rural areas. Following the WHO Expanded Program of Immunization,29,30 we targeted a sample size of 210 community members per setting, from which we pragmatically derived a targeted sample of 40 health-care professionals. The rationale and randomisation process are detailed in appendix 4 (pp 11–14) and our previously published methods article.19

Procedures

First, we conducted the RAP. This is a team-based applied technique to develop an insider's perspective of a situation within a short period of time.31 The research team situated in local community settings collected data using multiple methods. We explored CRD-related beliefs and perceptions during focus group discussions and semi-structured interviews. We studied

community members' risk behaviours (tobacco smoking, and cooking and heating on solid fuels) during structured household observations, and health-care professional's helping behaviour during observations of respiratory consultations. Additionally, we used qualitative questionnaires and conveniently collected relevant documents, such as CRD-related elements of medical curricula.32 All team members conducted the diverse qualitative methods. To ensure data collection was driven by local needs and developments, and to work towards thematic saturation, the team conducted preliminary analyses daily.31 Accordingly, we iteratively adapted the data collection strategy, and identified new informants or adapted our topic lists. We audio-recorded qualitative field activities and took fieldnotes.19 Second, we conducted a survey to triangulate the qualitative findings (figure 1). The survey questionnaires were researcher administered in the local language.

Data handling and analysis

Audio recordings were transcribed verbatim, anonymised, and translated into English. Qualitative data were thematically analysed using the Framework Method.33 Data were coded inductively and deductively, guided by the theoretical framework (Atlas.ti, version 7.5.15; appendix 4 pp 2–3). Quantitative data were analysed by descriptive statistics on the frequencies of reported beliefs and behaviours (SPSS version 25; IBM, Amonk, NY, USA). These data were used to quantify the qualitative findings (eg, to find out how many people indicated that they believed in stress as a cause for CRD). Additional information (including reflexivity) has been previously reported.19

Role of the funding source

The funders had no role in study design, data collection, analysis, interpretation, or writing of the report.

RESULTS

We included 340 qualitative informants (Uganda n=68, Kyrgyz highlands n=42, Kyrgyz lowlands n=61, Vietnam n=74, rural Greece n=73, Roma n=22). We conducted 77 interviews and 45 focus groups comprising three to eight participants, which we triangulated with observations of 61 community member households and consultations of 22 health-care professionals (appendix 4 pp 4–10). Informants had diverse ages, sex, and backgrounds. Health-care professionals ranged from physicians to medical students, and key informants from traditional healers to chairs of communal committees.

Next, we enrolled 1037 community members in the survey (Uganda n=207, Kyrgyz highlands n=210, Kyrgyz lowlands n=210, Vietnam n=210, Greece n=200; table 1; appendix 4 pp 11–14 details inclusion). Of note, no survey was conducted in the Roma camp as the qualitative data

collection pointed out that this would be unfeasible within our budget and timeframe. The overall mean age was 48·8 years (SD 16·0), with the youngest population in Uganda (41·8 years [15·3]) and the oldest in Greece (56·9 years [19·0]). More females (623 [60·1%]) than males (414 [39·9%]) participated. Of all respondents, 472 (45·5%) did not have paid work, of whom 260 (25·1% of the total) looked after the home and family (appendix 4 pp 11–14). Over one-fifth (22·2%) of the respondents reported to have similar symptoms to those described in the vignette, and one tenth (10·3%) reported to have a CRD diagnosis.

Additionally, we administered 204 questionnaires among health-care professionals (Uganda n=41, Kyrgyz highlands n=42, Kyrgyz lowlands n=40, Vietnam n=40, Greece n=41; table 2). The type of health-care professional who treated respiratory patients in Uganda varied, whereas in Kyrgyzstan most were nurses (highlands 85·7%, lowlands 80·0%), and in Vietnam and Greece most were general practitioners (Vietnam 82·5% and Greece 97·6%). Median years of practice was highest in the Kyrgyz highlands (27·5 years [IQR 16·3–36·8]) and lowest in Uganda (10·0 years [4·3–20·0]). Three key themes across the settings were identified from our qualitative data, which were then triangulated and complemented with quantitative data. Results are displayed in table 3, including the country characteristics in which they were embedded (appendix 4 pp 16–32). Additional quotes are provided in appendix 4 (pp 33–35).

Theme 1 was the locally perceived identity of chronic respiratory disease. Community members typically associated chronic respiratory symptoms with acute, communicable diseases. Although the vignette detailed a story of a person suffering from symptoms for more than 3 years, during the focus groups, the community members mostly held infections accountable. Also in the survey, community member frequently reported infections (eg, tuberculosis, flu, or a cold) to cause the symptoms (61·0% of all classifiable answers; figure 2). Meanwhile, 697 (67·2%) community members felt they understood the condition in the vignette fairly well or very well.

Community members predominantly related the symptoms to tuberculosis in both the qualitative and quantitative data (296 [28·5%] of all 1037 community members named tuberculosis as a diagnosis in the survey, totalling 70·1% of their 422 responses classifiable as infectious diagnoses).

"Coughing these days is like of three different types; some people cough as a result of HIV; others cough and even turn dark because of tuberculosis."

Uganda, focus group with women (aged ≥30 years; focus group [FG] 5)

Non-communicable diagnoses for long-lasting symptoms were mentioned less frequently (272 [39·3%] of 692 classifiable answers in the survey). The term COPD was typically completely unknown.

	Uganda (n=207)	Kyrgyz highlands (n=210)	Kyrgyz lowlands (n=210)	Vietnam (n=210)	Greece (n=200)	Total (n=1037)
Sex						
Female	143 (69·1%)	116 (55·2%)	119 (56·7%)	138 (65·7%)	107 (53·5%)	623 (60·1%)
Male	64 (30·9%)	94 (44·8%)	91 (43·3%)	72 (34·3%)	93 (46·5%)	414 (39·9%)
Age, years	42·0 (28·0–53·0)	45·0 (36·0–56·0)	48·5 (36·0–58·0)	52·0 (40·0–62·0)	60·0 (41·0–72·0)	49·0 (36·0–60·0)
Education, years	8·4 (4·0)	11·6 (2·1)	12·1 (2·1)	6·4 (3·8)	9·7 (4·3)	9·7 (4·0)
Occupational sector						
None	54 (26·1%)	114 (54·3%)	112 (58·1%)	68 (32·4%)	114 (57·0%)	472 (45·5%)
Primary	84 (40·6%)	77 (36·7%)	35 (16·7%)	66 (31·4%)	28 (14·0%)	290 (28·0%)
Secondary	17 (8·2%)	0	15 (7·1%)	14 (6·7%)	18 (9·0%)	64 (6·2%)
Tertiary	39 (18·8%)	18 (8·6%)	38 (34·3%)	44 (21·0%)	35 (17·5%)	174 (16·8%)
Other*	10 (4·8%)	0	0	2 (1·0%)	5 (2·5%)	18 (1·7%)
Has vignette-like symptoms	38 (18·4%)	59 (28·1%)	9 (4·3%)	52 (24·8%)	72 (36·0%)	230 (22·2%)
CRD diagnosis	8 (3·9%)	31 (14·8%)	9 (4·3%)	5 (2·4%)	54 (27·0%)	107 (10·3%)

Data are n (%), median (IQR), or mean (SD). CRD=chronic respiratory disease. *Mostly students. Values were missing for age (n=7 Uganda), education (n=4 Uganda, n=1 Greece), occupation (n=3 Uganda, n=16 Vietnam), symptoms (n=1 Vietnam), and CRD diagnosis (n=2 Uganda).

Table 1: **Demographics of survey participants for community members**

	Uganda (n=41)	Kyrgyz highlands (n=42)	Kyrgyz lowlands (n=40)	Vietnam (n=40)	Greece (n=41)	Total (n=204)
Sex						
Female	23 (56·1%)	40 (95·2%)	40 (100%)	27 (67·5%)	19 (46·3%)	149 (73·0%)
Male	18 (43·9%)	2 (4·8%)	0	13 (32·5%)	22 (53·7%)	55 (27·0%)
Age, years	39·5 (31·0–46·8)	46·0 (40·8–50·3)	55·0 (48·5–59·9)	42·0 (38·0–51·0)	47·0 (43·0–51·0)	47·0 (40·0–53·0)
Type						
Nurse	14 (34·1%)*	36 (85·7%)*	32 (80·0%)*	3 (7·5%)	0	85 (41·7%)*
Midwife	7 (17·1%)	2 (4·8%)	0	0	0	9 (4·4%)
General practitioner	6 (14·6%)	4 (9·5%)	8 (20·0%)	33 (82·5%)	40 (97·6%)	91 (44·6%)
Other	6 (14·6%)†	0	0	2 (5·0%)	1 (2·4%)	9 (4·4%)
Years of practice	10·0 (4·3–20·0)	22·0 (14·0–29·0)	27·5 (16·3–36·8)	16·0 (7·8–25·5)	15·0 (11·0–20·0)	17·0 (10·5–27·0)

Data are n (%), median (IQR). *27 of whom were physician assistants: n=1 Uganda (senior clinical officer), n=10 Kyrgyz highlands (feldshers), n=16 Kyrgyz lowlands (feldshers). †Five of whom were nurse assistants. Values were missing for age (n=5 Uganda, n=1 Vietnam), type of health-care professional (n=2 Uganda, n=2 Vietnam), years of practice (n=1 Uganda, n=2 Vietnam).

Table 2: **Demographics of survey participants for health-care professionals**

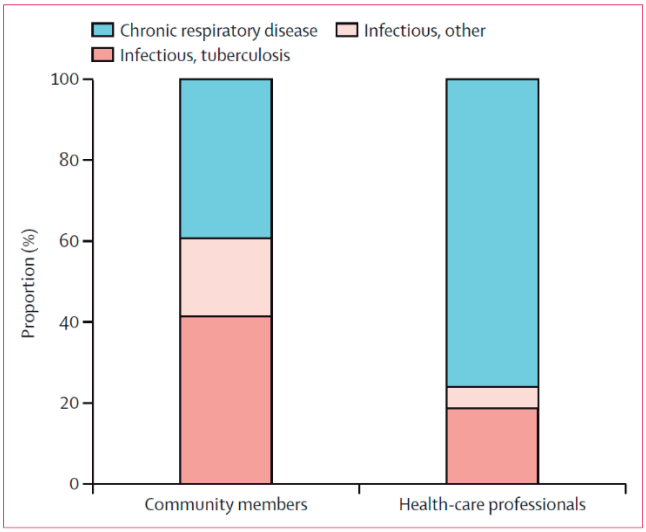


FIGURE 2: Disease to which chronic respiratory symptoms were attributed
Perceived diagnosis related to the vignette (progressive respiratory symptoms lasting for >3 years). Data include all classifiable survey responses, totalling 692 answers of community members and 242 of health-care professionals (eg, respiratory disease is not regarded classifiable). Open question; multiple answers could be given.

Interviewer: "Have you heard of COPD?"
Woman: "This is the first time I have heard of it [laughs]."
Kyrgyz lowlands, focus group with women (aged 18–30 years; FG 5)

Most Vietnamese participants, including patients with COPD and their health-care professionals, used the local word for asthma for both asthma and COPD. Even if the word COPD was recognised when probed for, its implications, symptoms, causes, and consequences were unknown.

"I have heard of COPD from the media, but I do not know the cause of the disease. I do not know if COPD is caused by smoking or not."
Vietnam, focus group with men (aged ≥60 years; FG 7)

Community members usually recognised the terms asthma and chronic bronchitis when probed for, and sometimes mentioned them spontaneously; however, the meanings attached to the terms differed from medical connotations. For example, the non-communicable and chronic nature of the diseases were not mentioned, also not when probed for. Greek community members were an exception. They almost never mentioned tuberculosis during the qualitative field activities, and only twice in the survey (appendix 4 pp 36–38). Their awareness of CRD was higher; the term COPD was known by most community members and all health-care professionals. However, community members would not spontaneously use the word COPD,

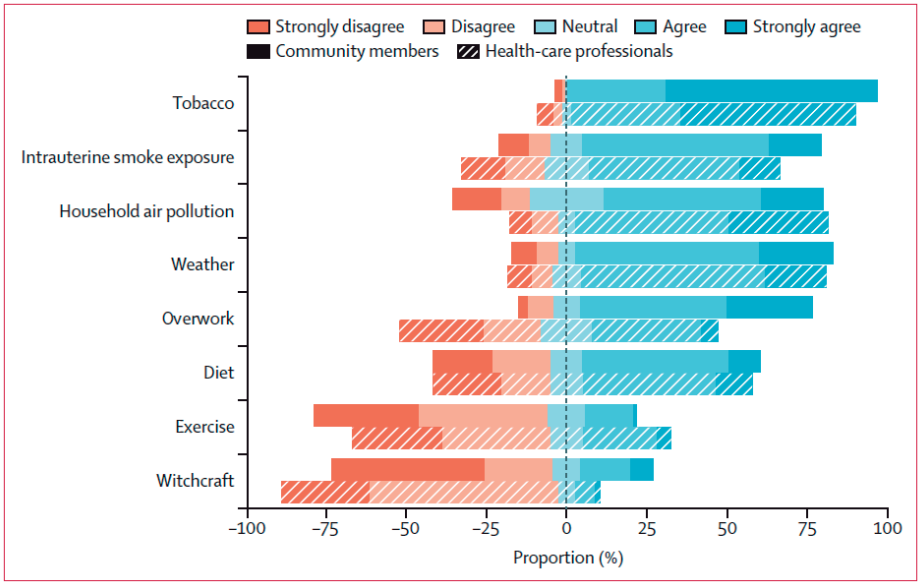


FIGURE 3: Perceived causes for chronic respiratory symptoms

The extent to which survey participants (n=1037 community members and n=204 health-care professionals) agreed with each factor as a cause. Missing values intrauterine smoke exposure n=2 community members; household air pollution n=2 community members, n=1 health-care professional; the weather n=1 health-care professional; overwork n=1 health-care professional; diet n=2 health-care professionals; exercise n=4 community members, n=1 health-care professional; witchcraft n=1 community member.

but speak of a respiratory condition instead. Understanding of COPD, such as its cause and consequences, was also poor among Greek community members.

Most surveyed health-care professionals across the settings indicated that they had seen a case similar to the vignette in the past 12 months (159 [77·9%] of 204). They attributed the chronic respiratory symptoms in the vignette much more to non-communicable diagnoses than the community members (192 [79·3%] of all 242 classifiable answers in the survey; figure 2, appendix 4 pp 36–38). However, tuberculosis was still a commonly perceived diagnosis. 39 (19·1%) of 204 health-care professionals named tuberculosis as a diagnosis, totaling 78·0% of all their 50 responses classifiable as infectious diagnoses. Similarly, all eight interviewed Ugandan health-care professionals considered tuberculosis the most likely diagnosis for the vignette. When the interviewer added that a tuberculosis test was negative, the health-care professionals considered a false-negative result more likely than an alternative diagnosis. The occurence of post-tuberculosis lung damage was never mentioned. Two health-care professionals mentioned that untreated tuberculosis lasting for 3 years would be unusual.

	Uganda	Kyrgyzstan (highlands)	Kyrgyzstan (lowlands)	Vietnam	Greece (rural)	Greece (Roma)
Contextual information (secondary sources)						
Country's income level*	Low	Lower middle	Lower middle	Lower middle	High	High
CRD prevalence†	COPD 6·1–16·2%; asthma 4·4%	COPD 36·7%; asthma 3·7%	COPD 10·4%; asthma 3·7%	COPD 3·3–9·4%; asthma 3·8%	COPD 3·5–10·6%; asthma 5·10%	Higher than for non-Roma‡
Tuberculosis incidence (per 100 000)†	200 (117–303)	110 (84–127)	110 (84–127)	176 (112–255)	4·3 (3·7–5·0)	4·3 (3·7–5·0)
Tobacco use and household air pollution (this study, quantitative data)						
Survey participants	207	210	210	210	200	No survey
Tobacco use (daily)	3 (1·4%)	38 (18·1%)	46 (21·9%)	53 (25·2%)	52 (26·0%)	NA
Female	0	0	2 (4·3%)	5 (9·4%)	33 (36·5%)	NA
Male	3 (100%)	38 (100%)	44 (95·7%)	48 (90·6%)	19 (63·5%)	NA
Age of onset, years	27·0 (13·7)	18·1 (3·5)	20·4 (7·4)	23·7 (12·1)	18·8 (4·5)	NA
Daily number of cigarettes	5 (0)	14·5 (9·5)	16·5 (9·5)	13·6 (9·2)	18·0 (12·8)	NA
Exposing others to smoke	2 (66·7%)	25 (65·8%)	27 (58·7%)	43 (81·1%)	36 (69·2%)	NA
Desire to stop	3 (100%)	36 (94·7%)	41 (89·1%)	38 (71·7%)	39 (75·0%)	NA
Stop attempt past 12 months	1 (33·3%)	28 (73·7%)	26 (56·5%)	30 (56·6%)	16 (30·8%)	NA
Household air pollution						
Cooking practices						
Open or surrounded fire	110 (53·1%)	25 (11·9%)	7 (3·3%)	79 (37·6%)	9 (4·5%)	NA
Daily solid fuel use (winter)	198 (95·7%)	201 (95·7%)	127 (60·5%)	89 (42·4%)	29 (14·5%)	NA
Daily clean fuel use (winter)	7 (3·4%)	18 (8·6%)	153 (72·9%)	193 (91·9%)	196 (98·0%)	NA
Location (most common)	Separate room or building	Room used for living or sleeping	Separate room or building	Separate room	Separate room	NA
Ventilation (most common)	Open window or door	Open window or door or chimney	Open window or door or chimney	Open window or door	Open window or door or hood	NA

Heating practices						
Use of heating	22 (10·6%)	210 (100·0%)	210 (100·0%)	0	200 (100·0%)	NA
Same stove as cookstove	13 (6·3%)	201 (95·7%)	130 (61·9%)	NA	3 (1·5%)	NA
Central heating	0	1 (0·5%)	0	NA	100 (50·0%)	NA
Solid fuel use	21 (95·5%)	210 (100·0%)	203 (96·7%)	NA	122 (61·0%)	NA
Clean fuel use	0	0	10 (4·8%)	NA	66 (33·0%)	NA
CRD-related themes (this study, qualitative data)						
Community members attributed chronic respiratory symptoms	To a low extent to CRD, to a high extent to infection, to a very high extent to tuberculosis	To a low extent to CRD, to a high extent to infection, to a high extent to tuberculosis	To a low extent to CRD, to a high extent to infection, to a high extent to tuberculosis	To a low extent to CRD, to a high extent to infection, to some extent to tuberculosis	To a high extent to CRD, to a high extent to infection	To a low extent to CRD, to a high extent to infection, to some extent to tuberculosis
Health-care professionals attributed chronic respiratory symptoms	To a low extent to CRD, to a high extent to infection, to a very high extent to tuberculosis	To a low extent to CRD, to a high extent to infection, to a high extent to tuberculosis	To a low extent to CRD, to a high extent to infection, to a high extent to tuberculosis	To a low extent to CRD, to a high extent to infection, to some extent to tuberculosis	To a high extent to CRD, to a low extent to infection	To a high extent to CRD, to a low extent to infection
Perceived causes	Cold weather, dust, stress, smoking, witchcraft or spiritual, underlying HIV/AIDS	Cold weather, stress, smoking, Evil eye (witchcraft or spiritual)	Cold weather, stress, smoking, Evil eye (witchcraft or spiritual)	Hot–cold disbalance, overwork, smoking, tidal wave	Cold weather, humidity, stress, smoking	Cold weather, smoking, household air pollution
Social factors related to health-keeping and health-seeking	One should not believe in spiritual powers (although others do)	Real men smoke, women should not. This proud nomad nation is self-reliant and does not seek medical help	Real men smoke, women should not	Real men smoke, women should not. Men cannot refuse an offered cigarette. Mother and newborn should undergo coal-burning ritual	*Filotimo*; one should support those around you (including patients in need)	A common distrust to seek help for symptoms outside the community

Data are n, n (%), or mean (SD), unless otherwise specified. CRD=chronic respiratory disease. COPD=chronic obstructive pulmonary disease. NA=not applicable. *As classified by the World Bank (accessed May, 2020). †Data are as specific to the setting as possible. See appendix 4 (pp 16–32) for data sources. ‡No data were identified for Roma in Greece specifically; two large European reports indicated that CRD prevalence was higher for Roma than for non-Roma. Values were missing for tobacco use (n=1 Uganda), age of onset (n=1 Greece), daily cigarettes (n=2 Uganda, n=2 Vietnam, n=1 Greece), location cooking area (n=2 Greece). For the themes in the table not elaborated in the text, see appendix 4 (pp 33–35) for supporting quotations.

Table 3: **Simplified overview of relevant setting characteristics for implementing CRD-related interventions**

"As far as I know, if it was tuberculosis it would have intensified more than that, to that extent, it wouldn't have stayed there for 3 years."

Uganda, interview with nurse (health-care professional 11)

In eight out of 41 observed respiratory consultations among 11 Ugandan health-care professionals, sputum was checked for tuberculosis, whereas none of the consultations included (diagnostic) questions directed towards asthma or COPD. Health-care professionals in Uganda, Kyrgyzstan, and Vietnam were also almost exclusively visited for acute symptoms, rather than for follow-up of chronic symptoms. None but the Greek health centres were equipped with a spirometer (after inquiring, a nurse in the Kyrgyz highland confirmed to have one and demonstrated a peak flow meter). In Greece, health-care professionals were also visited for chronic symptoms, to monitor disease control or discuss inhalation medication.

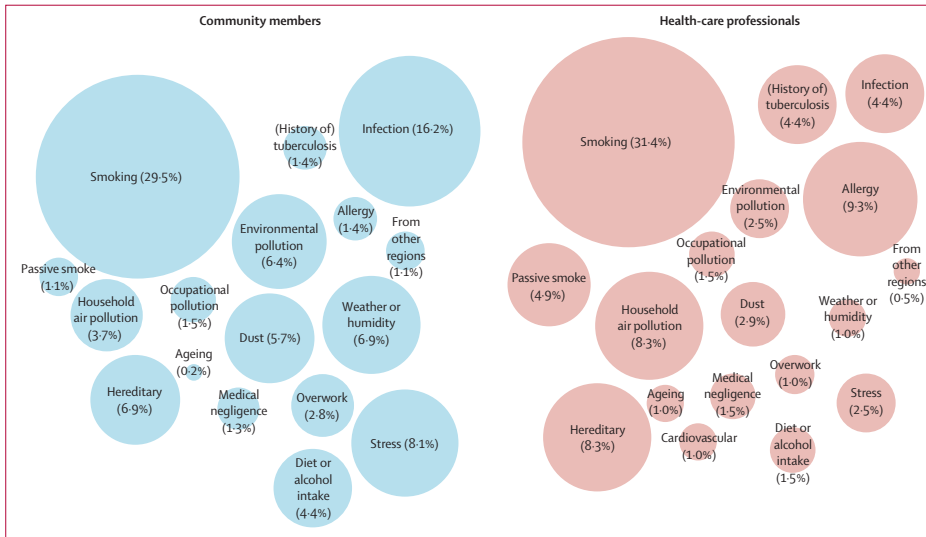
Health-care professionals were generally familiar with the terms asthma, COPD, and chronic bronchitis (appendix 4 pp 36–38), but associated these diseases mainly with their acute manifestations (such as a status asthmaticus). Many considered asthma too severe to treat in their primary care practice; asthma required treatment in referral hospitals. In multiple Kyrgyz interviews, asthma was regarded as the end stage of respiratory problems. Of the 163 Ugandan, Kyrgyz, and Vietnamese surveyed health-care professionals, 68 (41·7%) answered to (be able to) prescribe asthma inhalers. Qualitative data indicated that inhaler availability and affordability was low. Again, Greek health-care professionals were an exception. In the interviews they described asthma and its implications closely aligned with biomedical conceptions. The observations and survey confirmed that the health-care professionals generally followed well established Greek guidelines. Appendix 4 (pp 39–42) details health-care professionals perceptions and clinical behaviour.

Theme 2 was the perceived causes for chronic respiratory symptoms. Community members and health-care professionals in each setting strongly related respiratory symptoms to the quality of the air they inhaled, influenced by dust, factory smoke, and other forms of polluted air. The harm of tobacco smoke was especially well understood (figures 3, 4).

"I was smoking so much that I felt it was harmful for me. I had sputum, dyspnoea, fatigue..."

Greece: focus group with men (aged 30–60 years; FG 9)

Qualitative field activities demonstrated that smokers were generally male. During several interviews and focus groups the men mentioned to be mindful of smoke exposure towards pregnant women and babies; however, the observations revealed that second-hand-smoke exposure was common. Notably, three out of six men in a Vietnamese focus group indicated to smoke every time, everywhere, regardless of other household members.



	Uganda	Kyrgyz highlands	Kyrgyz lowlands	Vietnam	Greece	Uganda	Kyrgyz highlands	Kyrgyz lowlands	Vietnam	Greece
Smoking	93 (45·6)	26 (12·4)	33 (15·7)	43 (20·6)	109 (54·5)	6 (14·6)	10 (23·8)	12 (30·0)	11 (27·5)	25 (61·0)
Passive smoke	1 (0·5)	0 (0·0)	0 (0·0)	7 (3·3)	3 (1·5)	0 (0·0)	3 (7·1)	0 (0·0)	7 (17·5)	0 (0·0)
Household air pollution	18 (8·8)	0 (0·0)	9 (4·3)	7 (3·3)	4 (2·0)	6 (14·7)	4 (9·5)	2 (5·0)	3 (7·5)	2 (4·9)
Occupational pollution	7 (3·4)	1 (0·5)	3 (1·4)	2 (1·0)	2 (1·0)	0 (0·0)	0 (0·0)	1 (2·5)	1 (2·5)	1 (2·4)
Environmental pollution	7 (3·4)	0 (0·0)	9 (4·3)	37 (17·7)	13 (6·5)	1 (2·4)	0 (0·0)	3 (7·5)	1 (2·5)	0 (0·0)
Dust	9 (4·4)	23 (11·0)	8 (3·8)	14 (6·7)	5 (2·5)	1 (2·4)	1 (2·4)	2 (5·0)	2 (5·0)	0 (0·0)
Allergy	2 (1·0)	7 (3·3)	2 (1·0)	0 (0·0)	3 (1·5)	3 (7·3)	2 (4·8)	3 (7·5)	1 (2·5)	10 (24·4)
Weather or humidity	7 (3·4)	22 (10·5)	8 (3·8)	16 (7·7)	18 (9·0)	1 (2·4)	6 (14·3)	7 (17·5)	1 (2·5)	0 (0·0)
Infection	7 (3·4)	62 (29·7)	72 (34·3)	7 (3·3)	18 (9·0)	3 (7·3)	3 (7·1)	1 (2·5)	2 (5·0)	0 (0·0)
(History of) tuberculosis	3 (1·4)	3 (1·4)	3 (1·4)	5 (2·4)	0 (0·0)	3 (7·3)	3 (7·1)	2 (5·0)	1 (2·5)	0 (0·0)
From other regions	2 (1·0)	3 (1·4)	6 (2·9)	0 (0·0)	0 (0·0)	0 (0·0)	1 (2·4)	0 (0·0)	0 (0·0)	0 (0·0)
Overwork	3 (1·4)	4 (1·9)	2 (1·0)	19 (9·0)	1 (0·5)	0 (0·0)	0 (0·0)	0 (0·0)	2 (5·0)	0 (0·0)
Stress	20 (9·8)	24 (11·5)	22 (10·5)	5 (2·4)	13 (6·5)	2 (4·9)	1 (2·4)	2 (5·0)	2 (5·0)	0 (0·0)
Diet or alcohol intake	9 (4·4)	13 (6·2)	8 (3·8)	14 (6·7)	1 (0·5)	0 (0·0)	2 (4·8)	1 (2·5)	0 (0·0)	0 (0·0)
Medical negligence	2 (1·0)	4 (1·9)	3 (1·4)	2 (1·0)	2 (1·0)	1 (2·4)	0 (0·0)	0 (0·0)	1 (2·5)	1 (2·4)
Cardiovascular	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	2 (4·9)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Ageing	0 (0·0)	0 (0·0)	1 (0·5)	1 (0·5)	0 (0·0)	1 (2·4)	0 (0·0)	1 (2·5)	0 (0·0)	0 (0·0)
Hereditary	12 (5·8)	10 (4·8)	14 (6·7)	19 (9·0)	4 (2·0)	5 (12·2)	3 (7·1)	5 (12·5)	2 (5·0)	2 (4·9)

FIGURE 4: Perceived most important cause for chronic respiratory symptoms
Answers to the open question in the survey what was perceived as the most important cause for the chronic respiratory symptoms in the vignette. Infection included a virus, germ, cold, or the flu. Data in table are n (%). Community members n=1035. Health-care professionals n=204.

Interviewer: "Could you show me where you smoke? [points at a drafted house map]."
Man: "Everywhere, except for the rooftop, as it's hard to climb up [laughs]."
Vietnam: focus group with men (aged 30–60 years; FG 4)

The Roma also stated openly that second-hand-smoke exposure in their house was very common, also to children.

"Inside, also our babies smoke."

Roma: focus group with women (FG 6)

The survey confirmed that the majority of smokers were male (three [100·0%] in Uganda, 38 [100·0%] in the Kyrgyz highlands, 44 [95·7%] in the Kyrgyz lowlands, 48 [90·6%] in Vietnam, and 19 [63·5%] in Greece) and exposed others to their smoke (two [66·7%] in Uganda, 25 [65·8%] in the Kyrgyz highlands, 27 [58·7%] in the Kyrgyz lowlands, 43 [81·1%] in Vietnam, and 36 [69·2%] in Greece; table 3). The majority of smokers wanted to quit (table 3), but among others, cultural norms refrained them from doing so (theme 3).

Besides tobacco smoking, participants in each setting perceived air pollution to cause chronic respiratory symptoms. The perceived sources of pollution reflected what people encountered in their daily lives, such as traffic (Vietnam, Greece), nearby factories (Kyrgyzstan, Vietnam, and Greece), livestock (Kyrgyzstan and Vietnam), burning plastic (Vietnam and Roma), and dust, particularly dusty roads (Uganda and Vietnam).

Many community members were at risk of HAP exposure due to daily solid fuel use (Uganda 198 [95·7%], Kyrgyz highlands 201 [95·7%], Kyrgyz lowlands 127 [60·5%], Vietnam 89 [42·4%], and Greece 29 [14·5%] for cooking; table 3). HAP was less frequently mentioned by community members compared to health-care professionals, and with less consistency and conviction compared to other sources of air pollution.

"Even if smoke from firewood causes problems, it cannot be compared to cigarettes because the cigarettes have a lot of things that cause tuberculosis, but the firewood doesn't contain a lot of chemicals."

Uganda: Focus group men (aged ≥30 years; FG 6)

HAP was perceived to cause chronic respiratory symptoms also in Greece, because during the recent economic crisis, many people were pushed back into burning wood or olive pits as a cheaper source of domestic heating. Roma commonly burned poor-quality wooden pallets for heating and sometimes for cooking; electricity was available from expensive generators only for several hours daily. Although most people were aware of the harm of burning these materials, they reported that cleaner alternatives were unaffordable. The pallets observed in the Roma camp were often covered with paint and other chemicals. The effect of HAP exposure on children was rarely considered in the six settings. However, children's health was perceived as very important and regarded as a trigger to change risk behaviour.

Besides shared perceived causes for chronic respiratory symptoms, culturally specific causes were identified (table 3; figure 5). These ranged from witchcraft in Uganda, to the Evil eye in

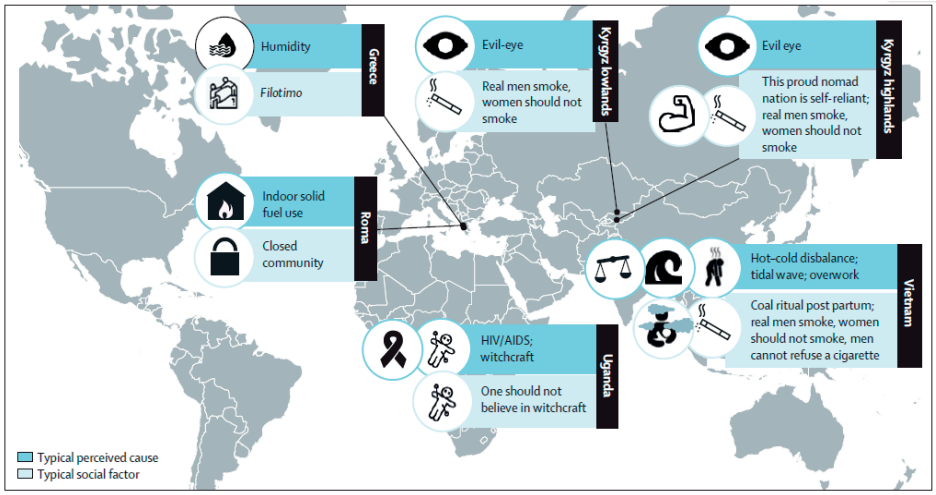


FIGURE 5: Typical perceived cause for CRD and social factors determining CRD-related behaviour Overview of the context-specific traits per setting. Causes and behaviour are not necessarily related. CRD=chronic respiratory disease.

Kyrgyzstan, a hot–cold disbalance in Vietnam, humidity in Greece, and burning poor quality wooden pallets in the Roma camp. We illustrate two such perceived context-specific causes; the examples are not exhaustive.

In Uganda, although none of the informants openly stated they believed in supernatural powers, all confirmed that others in their community did. For example, the lady in the vignette might believe she is bewitched. The local (Lusoga) term used for witch doctors was *omuyiwa*, *wamawembe* and according to the informants this means the one who heals or the one who thinks on your behalf (Uganda, focus group men). By our team members, fluent in Lusoga and English, this term was translated as witch doctor. Different wordings were used for traditional healers and herbalist.

Woman: "She thinks she was bewitched, her friends might be bewitching her."
Interviewer: "Can Nangobi [the lady in the vignette] also seek help from the traditional healers?"
Chorus: "No [all laugh]."
Woman: "That's impossible, that is wasting time."

Uganda: focus group with women (aged ≥30 years; FG 2)

Notably, most survey participants indicated to (strongly) disagree with witchcraft causing symptoms, while 235 (22·6%) of the 1037 community members and 16 (7·9%) of 204 health-care professionals indicated to (strongly) agree (figure 3).

In Vietnam, a prevailing perceived cause for illness was a hot-and-cold disbalance in the body. Therefore, eating cold or hot food, showering in the morning (cold) versus later during the day (warmer), breathing cold air versus smoking a hot cigarette were all believed to relate to the presence of symptoms.

"I get a sore throat when I am smoking too much, it is the heat inside the body."
Vietnam: focus group with men (aged 30–60 years; FG 4)

Vietnamese community members and health-care professionals also mentioned overwork relatively frequently as a perceived cause (figure 4). Qualitative data explained that the Vietnamese word for tuberculosis, *Lao*, resembles the word for overwork, *Lao Lực*, which inflicted a perceived relationship between overwork and respiratory symptoms.

Theme 3 was local social factors related to health keeping and health seeking. Local social structures, norms, and traditions strongly influenced (CRD related) health-keeping and health-seeking behaviour across the settings. Three such local norms are highlighted here, for prevailing social factors, see table 3 and figure 5.

Local beliefs in Vietnam about the cold–hot disbalance were also reflected in norms regarding post-partum care. Midwives and family members prescribed women and their newborns to stay in bed for a month while burning coal underneath their bed and limiting all ventilation. Doing so is perceived to protect mother and child from (respiratory) disease later in life. This custom leads to high levels of HAP exposure to mother and baby during a decisive period in the baby's lung development.

Interviewer: "Is it risky when lots of smoke is generated?"
Women: "I'm not sure... This is a habit from generation to generation, we don't even question it."
Vietnam: focus group with women (aged ≥60 years; FG 3)

One of our highly educated local team members highlighted the social pressure to comply to the custom. Although she perceived it as harmful to health, she had also complied to avoid social condemnation. A local university professor explained his perceived origin of the tradition during an interview: mothers lose blood during the delivery which decreases their body temperature. Burning coal restores the balance.

In the Kyrgyz highlands, a prominent social value related to health seeking behaviour was self-reliance.

"We are a nomad nation. We used to herd cattle and didn't see any doctors. And in fact, we didn't have doctors. It is in our blood. It is just possible to drink hot tea, or sheep fat—it [the nomad lifestyle] stays in our blood. They [our ancestors] did not consult doctors. This habit is in our blood. We have gotten used to this and think that the illness will pass by itself."

Kyrgyz highlands: focus group with men (aged 30–60 years; FG 2)

A feldsher (physician assistant) explained that self-reliance was essential in the region; access to health care and medication were geographically limited.

Key informants and health-care professionals characterised the Roma as a population with an inward-facing social structure. Roma were perceived to distrust outsiders of their community; the key informants and health-care professionals had needed years to gain their trust.

"...when we started [working] here 10 years ago, it was very difficult, all this, because they didn't know us, we had not developed this kind of confidence. Now, after 10 years, approaching them is easier and it is easier for them now, addressing us."

Roma: Social worker in Roma community (key informant 4)

Providing health support was perceived as challenging because Roma would arrive late for appointments or not show up at all. Also (health) illiteracy formed a barrier to access health care, because in the social structure, girls would often not attend school or drop out prematurely. On the other hand, multiple Roma shared that they felt ignored and discriminated in their attempts to access health care.

Almost all community members across the settings (1026 [98·9%] of 1037) indicated that they would seek help if they had symptoms like the person in the vignette. Most Ugandan community members would seek help from a community health worker (126 [60·9%] of 207), Kyrgyz and Vietnamese community members from a general practitioner (402 [95·7%] of 420 Kyrgyz and 177 [84·3%] of 210 Vietnamese community members), and Greek community members from a specialist (141 [70·5%] of 200; appendix 4 p 38).

DISCUSSION

This mixed-methods study explored community members' and health-care professionals' beliefs and behaviours regarding CRDs across diverse low-resource settings. Use of a consistent method based on the same theoretical framework enabled us to identify three themes that consistently played an important role in each setting, and which should be addressed when implementing CRD-related interventions, (1) the locally perceived identity of CRD, (2) local be-

liefs about the causes, and (3) local social values and structures that determine health behaviour. These themes showed both similar and context-specific traits across the settings.

In all settings but Greek, long-lasting respiratory symptoms were commonly identified as infections, particularly as tuberculosis. Asthma and COPD and their chronic, non-communicable nature were relatively unknown, especially among community members. Tobacco smoking was mostly perceived as an important cause for chronic respiratory symptoms. HAP was less frequently cited. Context-specific perceived causes were diverse, and ranged from witchcraft in Uganda to a hot– cold disbalance in Vietnam. Each setting had social factors that shaped behaviour related to CRD; such as the norm that real men smoke (Kyrgyzstan and Vietnam) or a common distrust in medical help from outside the community (Roma). Awareness of these shared and context-specific traits is crucial for designing the right interventions that people adhere to over time.5,7,8,34

To our knowledge, this is the first study that systematically mapped communities' beliefs and behaviours regarding both asthma and COPD this extensively. Regardless of their actual burden, CRD were not perceived to play an important role in the communities. This implies that, despite earlier calls for action over the past decades,35,36 health policies have yet failed to adequately raise awareness on CRD. In addition to our study among communities, previous studies reported that knowledge and awareness were poor even among CRD patients.37–39 Awareness of tuberculosis was much higher compared to CRDs in our study. We hold several explanations. First, communicable diseases have traditionally burdened LMICs more than non-communicable diseases (and in some settings, they still do—although CRD are on the rise while tuberculosis and respiratory infections are in decline).15 This could still be deeply rooted in communities' perceptions. Second, it is a self-fulfilling prophecy; the lack of awareness of CRD among health-care professionals (and the lack of spirometers and skills needed for their interpretation) results in the underdiagnosis of CRD.20 Hence, CRD are perceived to play a less significant role. Third, WHO's active campaigns to eliminate tuberculosis over the past decades seem to have successfully increased awareness among communities and their health-care professionals.40 Fourth, communicable diseases cause more public fear and prioritisation (also in high-income settings), as the relationship between infections and symptoms is acute and conspicuous.36 The current COVID-19 pandemic probably raised fear for infections even further. Although a silent one, CRDs are also a pandemic, especially in LMICs. Therefore, health policies and funding should equally treat CRDs and their preventable risk factors as a health priority, and increase efforts to promote awareness.41,42

One such preventable risk factor that requires more awareness is HAP.43 Although most participants indicated to (strongly) agree with HAP as a cause for chronic respiratory symptoms, a substantial part also indicated to (strongly) disagree or perceive the risk as neutral. Awareness

of the harm to children and of intrauterine smoke exposure was particularly low. Similar limited awareness among community members and health-care professionals was reported in other settings.44,45 WHO's Breathe Life campaign for clean air launched in 2016, and WHO's clean household energy toolkit (CHEST), will potentially increase HAP awareness and provide solutions to address this risk factor.

A successful global public health programme that targeted risk awareness and implemented preventive measures is WHO's Framework Convention on Tobacco Control.46 Also in our settings awareness of tobacco's harmful effects was high. Nevertheless, awareness alone is generally insufficient to change health behaviour.9–11,46 Most the smokers in our study said they desired to quit, but encountered various barriers to do so, of which local cultural norms played an important role. For example, an offered cigarette—a way to open a conversation—cannot be refused (Vietnam), or real men smoke (Kyrgyzstan and Vietnam). Therefore, beyond addressing awareness, such norms and other contextual factors should be addressed in implementation strategies to enhance their success.34

This study responds to the urgent calls from numerous international parties for more and better implementation evidence in LMICs, especially for non-communicable diseases.1–4 We consistently applied the same method19 across six settings in four countries on three continents, enabling comparison from a global perspective. Using a robust mixed-methods approach we triangulated qualitative findings (from 340 informants in over 200 interviews, focus groups, and observations), with findings from a quantitative survey. To further optimise internal data validity, two researchers independently applied the rigorous Framework Method. Local community researchers in the team ensured excellent knowledge of local themes and networks. They additionally facilitated trust and openness from the communities, resulting in deeper insights. To promote practical relevance of the study and uptake of our findings, the study was grounded in the local context and co-designed with our stakeholders.47

To limit sources of bias, we took a broad range of measures—eg, we addressed participants' self-serving and social desirability bias by triangulating interviews with observations, confirmation, and culture bias by a diverse research team, and selection bias by a solid random sampling approach. Nevertheless, possible sources of bias remained, such as observation bias during health-care professional consultations, or survey-selection bias because more women than men were at home during the daytime. Another study limitation was the use of different languages. Despite careful translation procedures for the research materials and having researchers fluent in both the local language and English, nuance might have been lost in translation. Additionally, qualitative findings from the Roma setting could not be triangulated; the qualitative research activities taught us that conducting a survey was not feasible in the Roma camp within our budget and timeframe. Lastly, during our RAP we reached saturation on many themes, yet we

cannot provide an exhaustive description of each setting. For further in-depth exploration, a more time-consuming approach is recommended.

Our study findings were translated directly into practical leverage points in the implementation strategies of FRESH AIR health interventions19—eg, communities' limited awareness of the harm of HAP exposure required us to deliver an extensive awareness programme48 before the cleaner cooking programme49 was implemented. This awareness programme emphasised the risks of HAP to children, which we had learned was a trigger to change behaviour. Our cooking programme achieved above-average adoption rates of cleaner cookstoves.49 Similarly, we highlighted the benefits of exercise to patients in our Vietnamese pulmonary rehabilitation programme, to overcome the locally perceived risks of overwork. Meanwhile, in the Greek pulmonary rehabilitation programme we embraced the *filotimo* norm; we capitalised on the positive social pressure to exercise together as a group and not let down the others by missing a training.50 The post-partum coal-burning ritual in Vietnam could possibly be addressed by preserving the element of heat while avoiding smoke exposure.

Beyond the FRESH AIR implementation research project, these findings could serve implementation efforts globally. The mapped settings ranged from deprived slums in Uganda, to highly risk-burdened Kyrgyzstan, rapidly developing Vietnam, austerity-impacted rural Greece, and a hard-to-reach Roma camp. The same three themes turned out to play a role across the settings suggesting high generalisability; therefore, we recommend these themes be considered and addressed in the implementation of CRD-related interventions in other low-resource settings.

Furthermore, some specific beliefs and behaviours within a theme were reported to occur in settings with similar characteristics, such as the coal-burning ritual (Indonesia)51 or that real men smoke (China and Indonesia).52,53 Therefore, by looking at the main characteristics (table 3) and the associated health beliefs and behaviours, one could carefully infer what beliefs and behaviours might prevail in new settings with similar characteristics. Also, our findings of where people seek medical help in each setting can help determine who to involve in future health programmes.

This overview of CRD-related beliefs and behaviours could be complemented by insights from new settings. It could expand beyond CRD, to serve as a starting point for mapping contexts for other (non-communicable) diseases—eg, limited perceived chronicity might be applicable to cardiovascular or mental illnesses. It is plausible that this context-mapping approach and some of the findings could also be generalised to high-income settings, yet this remains to be assessed.

Our data emphasise the importance of raising public awareness on asthma and COPD, their chronic nature, and their preventable risk factors. Whole-system approaches are needed, includ-

ing public education on how we breathe and how risk factors affect breathing; health-care professional training on preventing, detecting, and treating CRD; and training policy makers on interpreting the underdiagnosis in their country data and on effective measures to combat risk factors. Second, our data demonstrate the importance of understanding the local context. We recommend relevant beliefs and behaviours be elicited before every intervention, because it will help tailor the implementation strategy at population and individual level. The SETTING-tool, as used in this study, can be a helpful instrument for doing so. It was easily adaptable to and effective in a diverse range of settings, as long as the core elements (the six steps) remained intact.[19]

In conclusion, to facilitate a successful implementation process of CRD-related interventions in low-resource settings, implementers should address the locally perceived identity of CRD, local beliefs about causes, and local social values and structures that influence health behaviour. Therefore, we recommend these beliefs and behaviours be mapped before every intervention to design tailored implementation strategies. Such strategies can reduce the risk of implementation failure, which in turn can optimise the use of resources in settings where they are scarce already. Ultimately, this can improve health outcomes.

Contributors EAB led the conceptualisation and design of the study, supported by RMJJvdK, CCP, NHC, MRC, and RR. PLA, MA, BK, CL, TS, and SWa ensured alignment of the design with the corresponding setting. EAB coordinated data collection and further conduct of the study across the sites, together with MA, PLA, LHTCH, TS, and SWa for the corresponding sites; all coauthors supported. SWi contributed to the formation of the stakeholder engagement groups through the network of the International Primary Care Respiratory Group (IPCRG). RR trained the team and supervised application of the qualitative methodology on the ground in the first site. EAB led qualitative data collection at each site, supported by CCP. RMJJvdK contributed to data collection in Uganda, MM in Kyrgyzstan, LTTO and LHTCH in Vietnam, and MA in the Roma camp. All authors had access to all study data. EAB, RMJJvK, and RR analysed the qualitative data, verified by CCP, MRC and NHC (all sites), and PLA, MA, BK, MM, TS, and SWa for the corresponding sites. PLA, LHTCH, MA, TS, and SWa supervised the quantitative data collection, EAB and RMJJvdK quantitatively analysed data, verified by RR and NHC. NHC was the principal investigator of the overall FRESH AIR project. EAB wrote the Article, RMJJvdK, SWi, CCP, and RR provided feedback. All authors critically reviewed the Article and approved its final version.

Declaration of interests We declare no competing interests.

Data sharing All deidentified data and meta-data, which are not already available in appendix 4 of this Article and the preceding open access methodology paper,[19] will be available on reasonable request to the corresponding author (EAB) within a reasonable timeframe.

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CHAPTER 2

IMPLEMENTING A CONTEXT-DRIVEN AWARENESS PROGRAMME ADDRESSING HOUSEHOLD AIR POLLUTION AND TOBACCO – A FRESH AIR STUDY

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ABSTRACT

Most patients with chronic respiratory disease live in low-resource settings, where evidence is scarcest. In Kyrgyzstan and Vietnam, we studied the implementation of a Ugandan programme empowering communities to take action against biomass and tobacco smoke. Together with local stakeholders, we co-created a train-the-trainer implementation design and integrated the programme into existing local health infrastructures. Feasibility and acceptability, evaluated by the modified Conceptual Framework for Implementation Fidelity, were high: we reached ~15,000 Kyrgyz and ~10,000 Vietnamese citizens within budget (~€11,000/country). The right engaged stakeholders, high compatibility with local contexts and flexibility facilitated programme success. Scores on lung health awareness questionnaires increased significantly to an excellent level among all target groups. Behaviour change was moderately successful in Vietnam and highly successful in Kyrgyzstan. We conclude that contextualising the awareness programme to diverse low-resource settings can be feasible, acceptable and effective, and increase its sustainability. This paper provides guidance to translate lung health interventions to new contexts globally.

INTRODUCTION

Chronic respiratory diseases (CRDs) are a major burden to health worldwide, with chronic obstructive pulmonary disease (COPD) being the third leading cause of death.(1) The vast majority of deaths related to CRD occurs in low- and middle-income countries (LMICs).(2-4) While the prevalence of major risk factors to CRD – smoking and household air pollution (HAP) – is commonly high in LMICs, means to combat the risks are low.(5-10) Preventing CRD is the most affordable and effective strategy for decreasing the burden.(4) This would involve solutions such as smoking cessation and providing alternatives for cooking and heating on solid fuels in poorly ventilated homes. However, for decades, implementation of such interventions in local communities has demonstrated to be challenging.(11-14)

An important reason for implementation failure is the misalignment of local knowledge and beliefs with the interventions offered and their implementation strategies.(15-19) If there is no locally perceived need for change, motivation for behaviour change is low.(20, 21) Particularly in rural areas of LMICs, awareness about CRDs and the risks of tobacco- and biomass fuel smoke is low. COPD as a disease, and the implications of asthma, are often unknown to local community members, policy makers and health workers.(4, 22) This affects the quality of care and prevents communities from taking simple steps to avoid smoke exposure.(5, 23-27) Additionally, the use of biomass fuels is determined by poverty.(28, 29) Motivating low-income household to purchase cleaner stoves and fuels is generally beyond their means.(28, 30, 31) Therefore, for successfully reducing risk behaviour, preventive interventions are needed that understand and address these barriers to behaviour change.

An intervention to raise awareness about CRDs and empower communities with realistic measures to reduce exposure to risk factors was conducted in Uganda.(32) The programme was underpinned by the Capability, Opportunity, Motivation, -Behaviour (COM-B) model. Changing behaviour of individuals, groups or populations involves addressing one or more of the COM-elements.(33) By raising knowledge and awareness of CRD and the harms of smoke exposure (capability), and providing realistic, affordable solutions to prevent exposure (opportunity), participants were stimulated (motivation) to reduce risk behaviour (behaviour). This awareness programme had a cascading train-the-trainer structure, and started with healthcare workers with medical knowledge (HCWs), who then trained community health workers with limited medical knowledge (CHWs), who trained their communities. CHWs were considered the key players in raising awareness. They are chosen from their own community, and play a crucial role in providing primary healthcare in low-resource settings; often, they are the only ones available to provide direct medical assistance in their community.(34, 35) The programme demonstrated to be feasible, acceptable and effective.(32) Potentially, this programme could be widely applicable to other settings across the world.

However, effectively translating evidence-based interventions to other settings is considered by the World Health Organization as among the biggest challenges of the 21st century.(36) Failure to adequately translate and implement interventions can seriously comprise their effectiveness.(37, 38) Practical guidance on how to translate a preventive programme addressing awareness on CRD and empowering communities to change is unavailable. Therefore, our aim was to study the feasibility, acceptability and effectiveness of translating an awareness programme targeting risks to CRD to two completely different contexts in Kyrgyzstan and Vietnam, and provide lessons learned from this process.

METHODS

Study design

This prospective implementation study was conducted between 2016 and 2018 within the FRESH AIR (*F*ree *R*espiratory *E*valuation and *S*moke-exposure reduction by primary *H*ealth c*A*re *I*ntegrated *gR*oups) research project.(39) Reporting of this study was guided by the Standards for Reporting Implementation Studies (Supplementary Methods).(40) The programme itself and the implementation strategy are detailed in Box 1, and the programme's design is detailed in Figure 1.

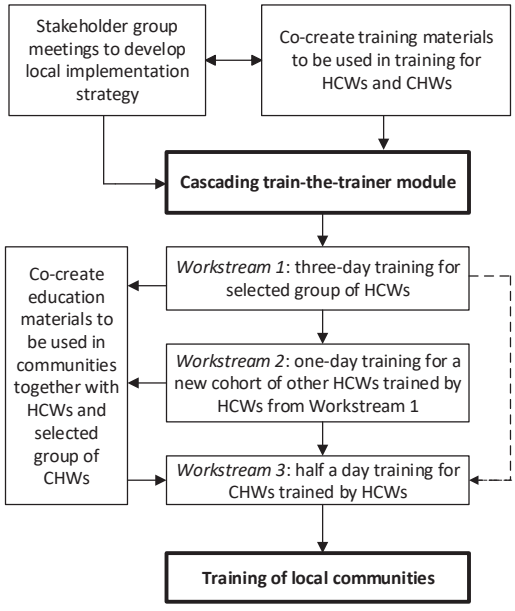

FIGURE 1: Design of the awareness programme
HCWs: Healthcare workers; CHWs: community health workers; § workstream 2 is optional.

Box 1. The awareness programme and its implementation strategy

The awareness programme

The programme aimed to increase local knowledge on CRDs and major risk factors (tobacco- and biomass smoke), and to empower communities to reduce exposure to the risk factors. This included awareness on feasible and acceptable behavioural change interventions for smoking cessation and second hand smoke exposure to, among others, optimise perinatal and child health.(46) It also included specific measures to reduce household air pollution, targeting 1) the source of the smoke (promoting clean fuels and improved stoves), 2) the living environment (improving ventilation and kitchen design), and 3) the user (drying fuel, using pot lids, maintaining the stoves well, keeping small children (and if possible pregnant women) away from the smoke, and cooking outdoors).(47)

The programme followed a cascading train-the-trainer approach: HCWs first received an intense three-day training. Besides the content above, the training also included co-creation of programme materials by HCWs and the team and instruction how to use those. Lastly, training skills were addressed, such as different training techniques and methodologies for adult learners, and community mobilisation techniques. Next, HCWs trained other HCWs (one day), who subsequently trained CHWs (half day), who in turn trained their communities (Figure 1). An overview of the content and how it addressed the COM-B elements is displayed in the Supplementary Methods.

Co-development of the implementation strategy

Ensuring to embed our programme in the local existing health infrastructure, we co-developed the implementation strategy with local influential and knowledgeable stakeholders (ranging from a popular national artist, to community members, to district health officers (Supplementary Table 2)). During a series of meetings, contextual factors (Supplementary Table 2) were discussed. Together we defined the programme's exact aim, intended outcomes, and delivery method. Stakeholders in both settings endorsed the train-the-trainer implementation strategy and considered the programme outline (Figure 1) used in Uganda also appropriate for their own setting.

Co-creation of the training materials

Training materials included posters for clinics and other public places, flip-over charts for HCWs and CHWs (with pictorial messages for communities and instructions for HCWs and CHWs on the back), brochures and seminar materials (Supplementary Methods). Materials used in Uganda (32) were first translated to Vietnamese and Russian. Together with the stakeholders we then contextually adapted the materials to local conditions while maintaining essential elements. For example, we continued to address tobacco, but made changes to the type of tobacco smoked. We also adapted the house, skin colour and background (Figure 2). Illustrations were made by the art department of local universities. The Kyrgyz Ministry of Health and the Vietnamese Center for Health Communication and Education approved the materials for national use.

Setting

We purposively selected Kyrgyzstan and Vietnam, as they represented two distinct low-resource settings with a high prevalence of CRDs and exposure to biomass- and tobacco smoke.(31, 41) In the highlands of Kyrgyzstan, more than 95% of households use wood or dung as their main fuel for their stoves (for cooking and heating); in the lowlands approximately 30% use wood or coal.(31, 42) Tobacco consumption is 26% (50% for men, 4% for women).(43) In the Long An province of Vietnam, 75% of the households use solid fuels (65% use wood) for cooking.(42) Their tobacco consumption is 23% (47% for men, 1% for women).(43) Pre-FRESH AIR field work (31, 44) had revealed poor awareness on CRD in these countries. The exact settings were based on opportunity and the relationship already established with communities during earlier work. Further information on the settings is detailed in the Supplementary Methods.

Study population

Any HCW, CHW and community member was eligible to participate in the programme; there were no additional in- or exclusion criteria. The group of HCWs to initiate the train-the-trainer cascade was selected with help from locally influential stakeholders with expert knowledge of the context, such as district health officers. These HCWs then conveniently selected other HCWs or CHWs, usually within their vicinity. Subsequently, the CHWs trained (almost all) community members living in their village.

Outcomes

We considered translation of the programme 'feasible' when it could be implemented with reasonable effort, budget and time, and 'acceptable' if those delivering or receiving the programme responded emotionally and cognitively collaborative.(45) 'Fidelity' was considered to be high if the steps in programme were adhered to as intended (Figure 1). Effectiveness was assessed at multiple levels; the immediate effect on CRD-related awareness (psychological capability in the COM-B) was assessed by knowledge questionnaires. The longer-term effect was expressed in degree of acceptability of improved stoves distributed in a subsequent FRESH AIR programme, and behaviour (adequate use of the stoves).(42) In this latter programme, households could select a locally manufactured improved cookstove/heater that they considered most suitable.

Data collection and instruments

Data on the feasibility and acceptability of the programme, and lessons learned, were collected during face-to-face and online discussions throughout the entire implementation process. We discussed these topics until consensus was reached. The short-term effectiveness was assessed by a questionnaire for HCWs, and one for both CHWs and community members. All HCWs and CHWs were invited to fill out the questionnaires as part of the training. Questionnaires contained several true/false/I-don't-know statements relating to the programme's content (Supplementary Methods). They were filled out before and after the training. Respondents were

instructed to choose 'yes'/'no' when confident about an answer, and to choose 'I-don't-know' otherwise. The questionnaires were adapted according to lessons learned in Uganda.(32) They were translated to Russian and Vietnamese respectively, back-translated to English, compared with the original versions, and tailored accordingly. Acceptability and adequate use of improved stoves of the subsequent FRESH AIR programme were assessed by questionnaires and observations of stove stacking respectively.

Analysis

Feasibility and acceptability of the programme, and lessons learned, were qualitatively analysed, guided by the *modified Conceptual Framework for Implementation Fidelity*.(48, 49) This framework focuses on adherence to complex health interventions, potential moderators, and identifying 'essential components' for achieving the intended outcome (Table 1, left column). Effectiveness on awareness was determined by changes in people's mean score on the pre- and post-training knowledge questionnaire, analysed by the Wilcoxon signed-rank tests (IBM SPSS Statistics version 25, Armonk, NY, USA). *P*-values <0.05 were considered statistically significant. Indications for longer-term behavioural effectiveness (acceptability and adequate use of improved stoves) were calculated using descriptive statistics.

Sample size and selection

We pragmatically aimed for 400 pre- and post-training community questionnaires. This number was chosen based on the maximum number of households that the budget allowed. Community members were randomly invited, stratified by gender, by the CHWs who gave the training. For the effect on acceptability and adequate use, 20 households in Kyrgyzstan and 76 in Vietnam were randomly invited in a subsequent FRESH AIR programme for distributing improved stoves, after they would have participated in this awareness programme.(42)

Ethics

The study complied with all relevant ethical regulations and was approved by the research ethical review board of the University of Medicine and Pharmacy in Ho Chi Minh, Vietnam (188/DHYD-HD;06/27/2016) and the National Center of Cardiology and Internal Medicine Ethics Committee in Bishkek, Kyrgyzstan (5;03/03/2016). Participation by HCWs and CHWs in the programme was within their existing job descriptions. Participation in the knowledge survey was anonymous and voluntary. All participants provided written informed consent, or in case of illiteracy, provided a thumb-printed consent instead.

All participants [of the stove programme] provided written informed consent, or in case of illiteracy, provided a thumb-printed consent instead. In accordance with the ICommunity members that only attended the training and provided

Reflexivity

Our team was diverse in terms of gender, age, professional background and nationality, contributing to diverse perspectives and richer data. To avoid hierarchy being at play, we emphasized that every person's input during evaluations was equally valuable.

TABLE 1: Costs of the awareness programme, compared to Uganda

		Kyrgyzstan	Vietnam	Uganda
Intervention				
PowerPoint	translation	700	850	1530
Posters	translation & printing	1000	n.a.	660
Flip-overs	translation & printing	700	750	830
Training HCWs		500	1000	3830
Training CHWs		500	1900	1050
Training community		500	3300	0
Travel costs training		3000	600	360
Media campaign		1000	n.a.	2060
Other:	refresher course	0	1000	680
	planning	0	650	0
	accommodation	3000	0	0
Total		**10900**	**10050**	**11000**
Study activities				
Preparation final report		*	400	*
Pre- and post-test HCWs		500	*	24
Pre- and post-test CHWs		500	350	46
Pre- and post-test community		500	4000	1450
Travel costs pre- and post-test		3000	200	480
Total		**4500**	**4950**	**2000**
Intervention + study				
TOTAL		**15400**	**15000**	**13000**

Costs are in euros. HCWs: healthcare workers; CHWs: community health workers; n.a.: not applicable. *Not tracked separately. Note, the pilot study in Vietnam that was conducted due to a miscommunication is not included in this overview.

RESULTS

Details on the awareness programme and the deployed implementation strategy are provided in Box 1. A structured evaluation of the programme's feasibility, acceptability and fidelity is detailed in Table 2.

Feasibility

The awareness programme was implemented as planned, without delays within the three-year timeline of the FRESH AIR project (Table 2). Costs remained within the budgeted €11,000 per

setting, although there were local variations (Table 1). For example, travel costs were high in Kyrgyzstan, with rough mountainous terrains. In Vietnam, norms in the health infrastructure prescribed that all additional training time for health workers had to be financially compensated.

Fidelity

Generally, the steps of the programme were adhered to as intended (Figure 1, Table 2). We co-developed the local implementation strategy with local stakeholders, co-created the programme's materials (Figure 2), and completed a train-the-trainer cascade. We slightly deviated from the planned delivery method in Kyrgyzstan; the relatively long travel times due to rough terrains in Kyrgyzstan resulted in an adapted structure in our cascade.

Essential components of the implementation strategy

Adequate knowledge of the local context was essential to successful programme implementation. This included knowledge of the health- and political infrastructure, to ensure embedment of the programme into it. For example, capitalizing on the vital role of CHWs demonstrated to be an effective and sustainable delivery strategy. CHWs were already trusted by communities and trained to deliver knowledge; the programme simply additionally equipped them with relevant medical knowledge to spread. This also included knowledge of local beliefs and behaviours regarding respiratory symptoms and risks. For example, a polite Vietnamese habit to invite a male stranger to a conversation is offering him a cigarette. The programme hence needed to address how to join a conversation without having to smoke the cigarette.

We also considered it crucial to collaborate with local authorities, promote community participation, and engage local knowledgeable and influential stakeholders (Supplementary Methods). Engaging stakeholders from the beginning enabled us to learn about the local context, and also created the sense of ownership needed for sustained use of the programme. Although the bureaucratic approval process of the programme's materials by national authorities resulted in a delay of several months, this collaboration with local authorities was needed for a sustained implementation.

We did not reach consensus on the necessity to train through a full cascading structure. The local Kyrgyz team believed omitting workstream 2 (Figure 1) would increase implementation success, while the coordinating team had the impression that for efficiency and sustainability of the programme, preferably all workstreams should be involved.

Lastly, flexibility was an important component. Many important stakeholders or contextual factors only revealed themselves along the way; the programme and delivery should be highly adaptable to continue to promote compatibility with the context.

Table 2: Implementation fidelity of the awareness programme

Elements of fidelity	Kyrgyzstan	Vietnam
Adherence (was the programme implemented as it was designed?)		
Content	We used the session content template addressing elements of the COM-B model (Appendix 3) in each training of HCWs in workstream 1. A concise version was used for the training of the health workers in workstream (2 and) 3.	
	The content displayed on flip-overs & posters (Appendix 4) was aligned with the session content template.	
		A tradition of constantly burning coal around a new-born during one month turned out to be also relevant, but was not addressed.
Coverage	Direct reach: 10 HCWs were trained first. We had planned to train 50 health workers from different levels (e.g. CHWs and social workers). Due to high enthusiasm of trained health workers, we trained 90. Trained health workers reported to have been in contact with 80-160 community members each month, training ~15,000 community members within 6 months	Direct reach: 17 HCWs were trained first (one per health centre). Each centre covered 3-7 villages, resulting in 77 trained CHWs. Each CHW reported to have contact with 100-150 community members and so reached ~10,000 community members directly within 6 months.
	Number of drop-outs was not registered.	
Frequency/ duration	Initial training was two days shorter than in Uganda, due to experience facilitating the training in Uganda and because the materials were in a further development stage.	
	Initial group of HCWs was trained for 3 days, CHWs and social workers were then trained for half a day within 3 months after HCW training.	Initial group of HCWs was trained for 3 days, new group of HCWs trained for 1 day within 3 months and CHWs trained for half a day within another 3 months.
	Outside of the programme, the training was used to train HCWs from neighbouring countries during an international conference (IPCRG in Bishkek, 2018).	
	Training of communities is ongoing to date. Using the materials, training continues to take place to patients and their families during visits to health facilities.	
Moderators (factors which have influenced the degree of fidelity)		
Intervention complexity	Simplicity was enhanced by accompanying the training materials with short, explicit explanations and illustrations, e.g. specific instructions on the back of flip-overs with main messages to be addressed.	
	The module and training materials were translated in the local languages.	
	We co-created training materials together with health workers and other stakeholders to ensure easy understanding.	
Facilitation strategy	We strategically engaged stakeholders through collaboration meetings, and hence enhanced 1) compatibility with the local context by co-developing the delivery strategy with them, 2) continuation of the programme through their support and ownership of the programme.	

Elements of fidelity	Kyrgyzstan	Vietnam
	We adapted the strategy and programme materials to the local settings in collaboration with local stakeholders, HCWs, CHWs, and community. Key messages remained identical.	
	An active session was held on the national state TV channel, supplemented by messages on the radio and newspapers.	The budget for a media campaign was exchanged for refresher courses of the trainers.
	HCWs and CHWs were trained on how to train. Training was supported by materials: both local FRESH AIR teams chose to use a PowerPoint for the health workers training, flip-overs for training the community, …	
Quality of delivery	… and brochures + posters to be distributed health centres/public spaces.	… and printed flip-overs instead of posters as the budget did not allow printing of additional brochures. The local team also delivered refresher courses for monitoring and feedback.
Participant responsiveness	HCWs and CHWs reported and demonstrated to feel ownership due to the co-creating process. The enthusiastic participation of communities and observed behaviour change (e.g. adoption of changed cooking practices) motivated the health workers to continue the process.	
	CHWs (and social workers) reported high numbers of community members reached, which was confirmed by triangulation with the number of collected knowledge questionnaires.	
Recruitment	All participants were recruited within the existing health infrastructure.	
	District health managers with expert knowledge on the local context selected the first HCWs to be trained.	
	Some of our research team members participated in this first group of HCWs. The local FRESH AIR team explained that they were more easily available than regular HCWs to travel (which took relatively long in Kyrgyzstan due to the rough terrains). Also for the sake of travel time, these HCWs trained other health workers (CHWs and social workers) directly instead of via workstream 2 (Figure 1).	One HCW per ward (the head of the health station) was selected for the initial training. They selected the next group based on convenience.
	CHWs were purposely selected based on convenience (living in villages in vicinity of health centres), in collaboration with local HCWs.	
	Community members were recruited during regular health events.	CHWs and the local team organised health sessions.
Context	Local context was well known due to preliminary explorative FRESH AIR field-work, due to close collaboration with the stakeholders and because our team consisted of local and international team members.	
		Due to a miscommunication with the local and coordinating team, a costly pilot study was conducted assessing the frequency of biomass fuel use. However, the high frequency of use reassured the relevance to the selected setting.
	Compatibility with the local context was enhanced by adapting interventions in collaboration with local stakeholders, HCWs and CHWs, and by embedding the intervention within the local healthcare system.	

COM-B model = capability, opportunity, motivation – behaviour model. HCWs: healthcare workers; CHWs: community health workers; structured by the *modified Conceptual Framework for Implementation Fidelity*

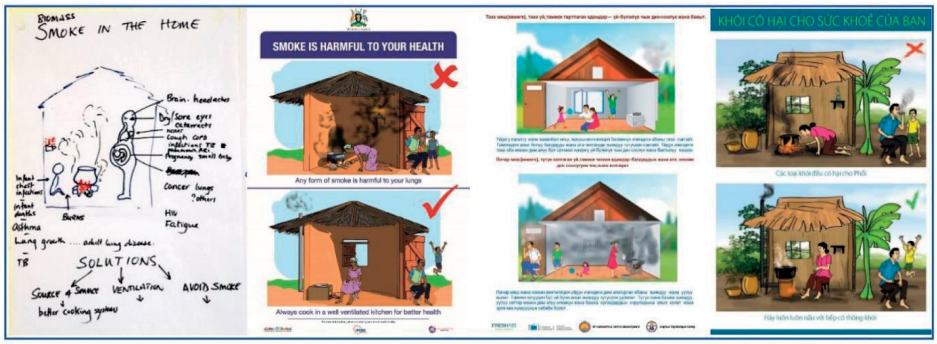

FIGURE 2: Development of the illustrations, from the first draft (left) to the final version used in Uganda, Kyrgyzstan and Vietnam. The illustrations show solutions to smoke exposure (use of improved stoves, improve ventilation by opening a window or installing a chimney, quit smoking, etc.). Illustrations were made by the art department of local universities.

Effectiveness

On the immediate psychological capability level in the COM-B, the percentage of questions answered correctly on the knowledge questionnaire improved significantly among all groups in both countries (Figure 3 and Supplementary Results). Knowledge was initially lower in Kyrgyzstan; improvements were larger in Kyrgyzstan too. Notably, in Kyrgyzstan we did not assess the initial group of HCWs as this group included local FRESH AIR team members.

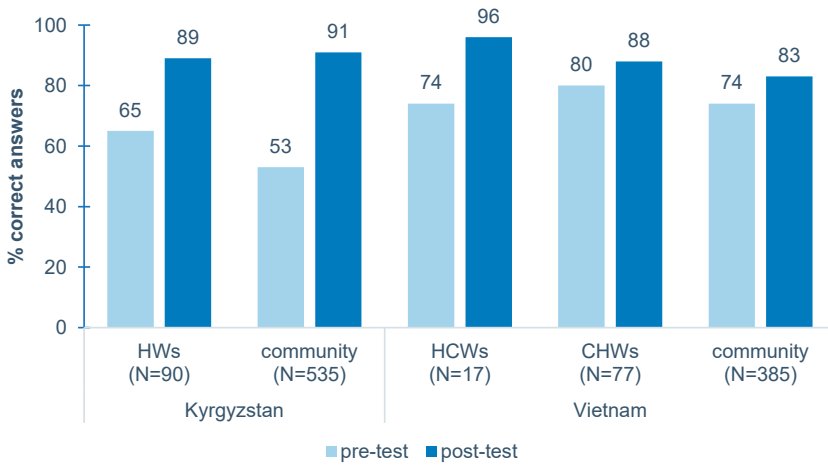

FIGURE 3: Knowledge questionnaire scores

HWs: health workers (CHWs and social workers), HCWs: healthcare workers, CHWs: community health workers. All differences between pre- and post-training scores were significant ($P<0.05$; Wilcoxon signed-rank tests). In Kyrgyzstan, the 10 HCWs were not included, as some members were part of the FRESH AIR team.

On the longer-term behavioural level, acceptability of the improved stoves was high: 100% of the stove users in Kyrgyzstan and 89.8% in Vietnam recommended the new stove to others. Stove stacking occurred in 15% of the Kyrgyz households, and 85.5% of the Vietnamese.(42) In Vietnam, most of the improved cookstoves were considered too small: 44% used the traditional cookstove for cooking every day, and 36% several times a week.

DISCUSSION

In this study, we translated an awareness programme on the risks of biomass fuel- and tobacco smoke to lung health, proven effective in Uganda, to two completely different low-resource settings: Kyrgyzstan and Vietnam. We demonstrated that the implementation of the programme was highly feasible and acceptable in both new settings. It was highly effective in Kyrgyzstan and moderately effective in Vietnam. Essential determinants for implementation success were 1) adequate knowledge of the local context and embedding the programme into it (using existing health infrastructures), 2) collaborating with local influential stakeholders and motivating communities to actively participate, and 3) flexibility throughout the process.

Other cascading train-the-trainer awareness programmes for lung health have previously demonstrated to be feasible in LMICs.(50, 51) However, these studies mainly focused on tobacco as a risk factor to lung health, while the need to address HAP is increasingly recognized.(52) Interestingly, these other programmes reported several essential factors of the implementation strategy comparable to those we had identified. Where we identified engaging influential and knowledgeable stakeholders, an Indian awareness programme on tobacco similarly defined the involvement of local role models (teachers) and leadership engagement (support from the school principals) as crucial.(50) Where we identified motivating the community, a PALSA study on CRD-guidelines in South-Africa reported actively involving participants in the delivery of the intervention.(51) Costs of these programmes were not reported so cannot be compared. Both studies also reported the importance of compatibility of the intervention and implementation strategy with the local context, although they did not specifically emphasize the importance of embedding the programme into the local health infrastructures. A large overview of reviews on CHW-programmes published in the Lancet in 2018 reported this embedment as a key recommendation for implementation success.(53)

We achieved statistically significant knowledge increases among all groups in both countries. The larger knowledge increase in Kyrgyzstan compared to Vietnam could be due to the lower baseline knowledge in Kyrgyzstan. Vietnam has had a longer tradition of patient education and patient self-management (and has established patient groups already decades ago). This may imply that awareness programmes could cover more advanced content in countries like Vietnam.

Besides a higher increase in knowledge, also the acceptability- and adequate use of cookstoves were higher in Kyrgyzstan compared to Vietnam after the awareness programme. This may indicate, in line with literature, that better knowledge on the risks of HAP to lung health is associated with higher success of clean cooking programmes.(15, 16) Notably, rates for adequate adoption of the stoves were substantially higher in Kyrgyzstan compared to stove adoption rates from other studies. Adoption rates are often not reported in clean cookstove studies; if they are, it is commonly mentioned the rates are 'strikingly low', 'disappointing, or around 4-10%.(11, 54) However, stove stacking occurred substantially more frequently in Vietnam in our study, suggesting that other causes also contribute to inadequate clean cooking practices. For example, characteristics of the stove are known to influence implementation success;(15, 16) Vietnamese participants in the FRESH AIR stove programme considered their stove too small and continued to use their old one concurrently.(42) Hence, with many factors contributing to the adequate use of improved stoves, programme implementation should ideally go hand-in-hand with all favourable factors such as favourable market developments and policies.(15, 16) This gives this cascading train-the-trainer programme a particularly powerful potential when applied by policy makers, health workers and communities together, because then all different factors can be addressed simultaneously.

This study both aligns with the recent WHO-guideline which emphasizes on the role of CHWs in the prevention and treatment of (non-)communicable diseases,(35) and responds to the call to enhance focus on contexts during implementation.(55, 56) Furthermore, we systematically applied and evaluated a uniform programme design in two completely different settings, enabling us to assess its wider applicability. This addresses the challenge of inconsistency in methodology and implementation assessment between training programmes for CHWs.(57) Another strengths is the action research approach involving the whole system (from Ministry of Health to community), while generating real-world evidence. For example, the district health officers appointed the first HCWs to be trained. They supposedly selected the most capable and motivated HCWs, which is precisely what would happen in a non-study setting. Such an approach reduces selection bias and potential underestimations of the programme's effect. Furthermore, the focus on implementation (fidelity) and its context – knowing what is 'in the black box' – combined with effectiveness enabled us to relate the observed effect to the intervention with more confidence.(58, 59) We are also among the few community-based implementation studies that included programme costs as an outcome.(60) The cascading train-the-trainer approach is designed to continue programme activities after the initial project has ended, thus contributing to the development of a sustainable system which builds knowledge and capacity among health workers, and raises awareness in communities.

As a limitation, our budget did not allow for observation of all implementation activities in vivo (precise number of delivered sessions, number of participants reached, etc.). Therefore, we

relied on health workers' self-reported implementation integrity. Social desirability might have tempted workers to overreport their implementation efforts,(61) possibly leading to an overestimation of fidelity. However, the number of completed knowledge questionnaires allowed us to triangulate and confirm the self-reported number of HCWs and CHWs trained, and provide us with the minimum number of trained community members. Furthermore, although the effect was assessed at multiple levels in this study, each had its limitation. Validated questionnaires assessing knowledge about the risks of biomass- and tobacco smoke did not exist to our knowledge. We therefore developed these questionnaires ourselves. Additionally, the results from the questionnaires could be subject to selection bias. Although acceptability of the stoves was very high in both countries and stove stacking was particularly low in Kyrgyzstan,(42) we were unable to conclude whether these longer-term outcomes were causally related to the awareness programme. Many other factors are associated with an adequate use of the stove (15) and there was no control group. Tobacco-related behaviour change was not measured. Also, the financial barrier for behaviour change was less prominent in our study as the people received a small compensation for study participation (the price of the cheapest stove option in Vietnam or a stove donated by the World Bank in Kyrgyzstan). Therefore, conclusions on indications for effectiveness should be interpreted with caution.

Exposure to HAP and tobacco smoke continues to place a high burden on LMICs. Not only through CRD, but also through stroke, cardiovascular disease, ischemic heart disease, pneumonia and lung cancer.(52, 62) Beyond the health burden, there is a substantial socioeconomic burden of CRD in LMICs.(63) Effectiveness of previous lung health programmes is often hampered by implementation failure, further draining resource potential from already resource-limited settings, and leading to poor health outcomes.(11) By demonstrating a feasible, acceptable and effective translation of an awareness programme in Uganda to two completely different settings – in Kyrgyzstan and Vietnam – we provide a potential guide for universal translation to other settings. The programme can be implemented on itself or, as applies to our FRESH AIR project, be an excellent starting point to prepare for smoking cessation programmes(46) or clean cooking interventions.(42) This same implementation strategy of the programme could also be used to address other relevant health topics beyond lung health. We recommend to establish a relation with the community before implementing an awareness programme, for example by conducting a rapid assessment (64) of the local context first. This will help to address the identified essential determinants for implementation success (adequate knowledge of the local context and embedding the programme into it, collaborating with local influential stakeholders and motivating communities to actively participate and flexibility).

To conclude, contextually translating a train-the-trainer awareness programme from Uganda to Kyrgyzstan and Vietnam, and potentially other low-resource settings, can be feasible, acceptable and effective for increasing awareness on lung health and its risk factors. Increased awareness

empowers communities to take action to reduce exposure to biomass- and tobacco smoke, which can ultimately lead to better lung health in low-resource settings.

Data availability statement:

All data and meta-data will be available within a reasonable timeframe upon reasonable request.

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Author contributions:

Co-first author FvG, in collaboration with SW, TS, PA and CdJ, designed this study. Co-first author EB provided input on the local context for the design based on explorative fieldwork. The organisation, including the training, was led by FvG, supported by EB, and conducted by TS, BE, MM and AT in Kyrgyzstan, and PLA, NNQ, LH and TND in Vietnam. The data were acquired by FvG, NNQ and AT and analysed by EB, FvG and CdJ. EB wrote the manuscript together with FvG; CdJ, RvdK and SW revised it. All authors gave input to the final version. EB, FvG, RvdK, SW and CdJ had the final responsibility for the decision to submit the study for publication. All authors had full access to the data.

Conflicts of interest:

None to declare.

Supplementary information:

Provided with the online version of this publication.

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CHAPTER 3

GENERAL DISCUSSION

GENERAL DISCUSSION

Chronic respiratory disease (CRD) constitutes a major burden of disease globally. Evidence-based lung health interventions are often ineffective, as they commonly misalign with their local context and then fail to be implemented into routine practice.[1-4] The aim of this thesis was to generate evidence on how to effectively combat CRD in low-resource settings across the globe, while leveraging characteristics of the local context to facilitate successful implementation. To this end, we first sought to understand the burden of CRD and related risk factors in diverse low-resource contexts. We then focused on how to implement context-driven, evidence-based lung health solutions. This chapter recapitulates the thesis' main findings, discusses how these findings relate to each other, to the literature to date, and to the current major global health challenges. Lastly, it provides recommendations for the four stakeholder groups introduced in the first chapter.

Main findings – the FRESH AIR expedition

Part I – Understanding the problem; exploring chronic respiratory disease in its local context

First, findings from our study on COPD in Kyrgyzstan (**chapter 2**) reinforced the important role of context; mountainous areas faced a significantly higher COPD prevalence and exposure to risk factors compared to neighbouring low altitude areas. Second, typically in low-resource settings the risk factors for developing CRD co-occur and interrelate, such as household air pollution, malnutrition, and a history of tuberculosis. There is increasing evidence that the effects already manifest in-utero. Therefore, in an opinion paper (**chapter 3**), we called for an increased focus on prevention early in life, and for optimising lung health already before birth. Third, besides differences in exposure to risk factors, low-resource settings also remarkably differed from high-resource settings regarding the socioeconomic burden of CRD. In our health economics study across low-resource settings in Uganda, Kyrgyzstan, Vietnam, and Greece (**chapter 4**), we found CRD-related absenteeism to be low compared to presenteeism and activity impairment; CRD-patients commonly showed up at work at the expense of lower productivity. Last, in our systematic review on guidelines for smoking cessation across settings globally (**chapter 5**), the identified similarities and differences illustrated how contextual differences (in health infrastructure, risk factor distribution, medication availability, culture, etc.) may play a role in recommendations for smoking cessation care.

In conclusion, Part I demonstrated a generally high prevalence of CRD and related risk factors in low-resource settings, and it highlighted several contextual differences in which CRD is embedded.

Part II – Towards a solution; facilitating implementation success of lung health programmes by engaging and leveraging their local context

In our systematic review (**chapter 6**) we identified five factors critical to the implementation success of CRD-related interventions in low-resource settings. These were consolidated in a practical implementation tool. While conducting the literature search, not only an abundance of evidence was revealed on the lack of success in implementation of cleaner cooking interventions, but also a clear lack of the *use* of all the evidence. Therefore, we urged in a commentary (**chapter 7**) for the actual use of implementation evidence in future research and practice, and indicated which stakeholders should take on which role. To practice what we preached, we (taking the role of researchers) teamed up with national and international colleagues to create an overview of all available literature; we conducted a systematic umbrella review ('review part B' of chapter 6) resulting in hands-on tools to serve implementers of cleaner cooking solutions in the field. As for the more complex methodology involved in this umbrella review of narrative and systematic reviews, we published the protocol (**chapter 8**) separately from the results (**chapter 9)**. Compatibility of the intervention with the local context, such as beliefs and needs, was identified as a critical factor in both implementation reviews. However, evidence was not available on *how* to map the context to understand it in the first place. Hence, we developed and validated an evidence-based step-by-step guide to doing so: the SETTING-tool (**chapter 10**). We applied the tool in six low-resource settings on three continents in a mixed-method study to identify relevant beliefs and behaviours regarding CRD (**chapter 11**). We found that chronic respiratory symptoms were mostly attributed to infectious disease, while chronic disease was under-recognised. We also identified shared and context-specific perceived causes for CRD and related norms. These findings were used to design the implementation strategy of a subsequent lung health intervention: a train-the-trainer programme promoting awareness about CRD and related risk factors (**chapter 12**). This programme proved to be feasible and acceptable, as well as effective in raising awareness about and taking action against CRD. It laid the foundation for the implementation of a cleaner cooking intervention to reduce household air pollution, which had above-average implementation success rates.

In conclusion, Part II synthesised the literature into several practical tools to facilitate the implementation success of lung health interventions. We also developed and validated a step-by-step guide to systematically map local contexts. Findings of the application of this approach were used to design context-driven strategies of a successfully implemented lung health awareness programme.

Tackling chronic respiratory disease in low-resource settings

Understanding the problem; chronic respiratory disease in its context

Understanding the prevalence

At the start of the FRESH AIR project, reliable data on the prevalence of asthma and COPD in low-and middle-income countries were scarce, and even unavailable for many of our study settings. For example, when we conducted the COPD prevalence study in Kyrgyzstan, lung function reference values for such central-Asian highland populations were lacking. However, they were expected to differ substantially from Caucasian reference values due to the altitude. This made it difficult to determine what to classify as airway obstruction. Fortunately, several large international lung health studies took off over the recent years, such as RESPIRE, Breathe Well, GECo, and Pure Air.[5-8] Their evidence will contribute to understanding the distribution of the burden of CRD across the globe, and hence, to developing strategies to combat CRD and adequately prioritise resources.

Understanding risk factors

Interestingly, when our Kyrgyz prevalence study confirmed household air pollution as a risk factor for COPD, a causal relation between household air pollution and CRD was still being debated.[9,10] Only several years later, the relation became considered as well-established.[11,12] Household air pollution as an established risk factor changed the way we view the solution to COPD; smoking cessation does not protect the many young, non-smoking women who spend hours daily in a smoky kitchen. A systemic approach is needed, including accelerating access to cleaner fuels and alleviating other disadvantageous environmental factors.

In our analysis, 'altitude' also showed to be an independent risk factor for COPD. We considered the possibility that lower ambient oxygen levels at higher altitudes increase lung volumes (the FVC) more than the airways (the FEV_1),[13] thereby decreasing the FEV_1/FVC ratio (a traditional way to diagnose COPD). We also speculated altitude to be an umbrella risk factor for disadvantageous factors that we had been unable to account for, such as poor nutrition and a history of tuberculosis. Later, a meta-analysis combined our findings with others and confirmed the latter hypothesis: altitude itself was not found to be a risk factor.[14]

Understanding the importance of timing

As simultaneous evidence showed that disadvantageous factors can impair lung development even in-utero, we called for a life-course approach to respiratory health, starting to optimise lung health even before birth. Recent studies about air pollution and the placenta reinforced this call; for example, black carbon particles were found to be able to cross the placenta.[15] The fact that air pollution has in-utero effects fundamentally changes the way to assess the success of lung health interventions, especially regarding the timing of these assessments. The benefits of cleaner cooking solutions may foremostly manifest in the yet unborn generation, as the lungs

in older generations may have already been irreversibly damaged. Also, traditional outcome measures such as 'COPD' should be complemented or replaced by measures that account for the effects of early exposure to air pollution, such as a reduced maximum attained lung capacity. Furthermore, to detect the benefits of cleaner cooking solutions, funding institutes should facilitate longer-term research to evaluate effects beyond the common timespans of only several years.

Understanding the importance of defining

Interestingly, an international expert group recently proposed an operational definition for "early COPD". It was defined as an "age <50 years with ≥10 pack-years of tobacco consumption", combined with one or more spirometry or computed tomography related criteria.[16] This definition does not serve a major part of the world's population, as it ignores the three billion people at risk of CRD due to solid fuel smoke exposure (and relies on diagnostic devices that are largely unavailable in low-resource settings). Use of this definition would lead to wide-scale underdiagnoses in exactly those settings suffering from underdiagnoses already, leading to a vicious circle: CRD does not seem to pose a high burden and is therefore not prioritised by policymakers, research funders, healthcare professionals and communities. Hence, awareness of CRD and available (diagnostic) resources are low, which leads to an underdiagnosis, and so forth. This elite definition of early COPD reinforces the importance of increasing research focus beyond high-income settings, so that its practical implications serve populations globally.

Understanding the indirect burden

Besides the direct burden, data on the indirect burden of CRD are also still scarce. Our FRESH AIR study was the first international study to assess the CRD-related work productivity and activity impairment (WPAI) across low-resource settings.[17] Of note, the WPAI-questionnaire was applied so scarcely in low-and middle-income countries, that its validated form turned out to be suboptimal in practice. For example, those who answered negatively to the question 'Do you work for pay?' were excluded from the further questionnaire. However, in low-and middle-income countries many work informally, for example in subsistence farming, and were unnecessarily excluded. We reported our learnings and discussed these with colleagues from the RESPIRE research project,[5] who could timely adapt their questionnaire.

Enhancing implementation success by engaging and leveraging the local context

As described in the introduction of this thesis, we interpreted 'context' broadly as a set of characteristics and circumstances that surround the implementation effort.[18] These characteristics entailed many aspects, ranging from the political climate to geographical influences to health infrastructures. Both our implementation reviews pointed out that alignment with the local beliefs, perceptions and behaviours is a critical implementation factor.[19,20] We chose this contextual aspect as a further focus of study.

Leveraging the local context to fuel implementation

Uncovering CRD-related beliefs, perceptions, and behaviours in low-resource settings in Uganda, Kyrgyzstan, Vietnam, and Greece resulted in shared- and context-specific themes. An example of a context-specific norm that we identified in Greece was *filotimo* (to help those around you). We learnt to capitalise on this norm for the pulmonary rehabilitation programme. Patients did not want to miss a single rehabilitation session in order to be there for their peers, which resulted in a high participation rate.[21] In our Vietnamese settings, we discovered that exercise was perceived to cause lung disease (the Vietnamese word *Lao* for tuberculosis resembled the word *Lao Lực* for overwork). We needed to address this belief before patients were open to participation in the pulmonary rehabilitation programme. These examples, and the others presented throughout the chapters of this thesis, illustrate how contextual factors can be used to fuel the implementation success of lung health programmes.

Addressing the poor awareness about chronic respiratory disease and engaging stakeholders

Our context-mapping study also revealed an important theme that was shared across the different FRESH AIR contexts: the relatively poor awareness about CRD compared to infectious disease. As mentioned earlier, the vicious circle of poor awareness, underdiagnosis, and inadequate prioritisation for CRD must be broken. In FRESH AIR, we tried to do so by engaging important stakeholders (a critical implementation factor[19]) throughout the entire process. Our local team and our consortium partner, the International Primary Care Respiratory Group (IPCRG), had managed to engage the Kyrgyz Ministry of Health in our FRESH AIR stakeholder group. Discussing the high COPD prevalence we had found in our study in combination with the CRD-related work productivity loss in Kyrgyzstan made a strong case for action. Consequently, the IPCRG, the Ministry, and the local FRESH AIR team collaboratively organised the first central-Asian conference to raise CRD awareness. Nurses, physicians, and other professionals were empowered to take action through context-driven, affordable measures. Such measures ranged from teaching local communities about how to prevent exposure to risk factors, to establishing pulmonary rehabilitation programmes. Besides the national Ministry, FRESH AIR also engaged with the World Bank as an international stakeholder, who committed to distributing 14.000 cleaner cooking stoves in Kyrgyzstan to reduce exposure to HAP and improve lung health.[22]

Think globally, act locally

By mapping the local settings and demonstrating how findings can be used to improve implementation success, we aimed to provide knowledge and tools that can be used globally to combat CRD. In the FRESH AIR study, we were able to immerse at the local levels and leverage our contextual findings effectively, thanks to the collaboration between local community workers and (inter)national academic workers. A limitation of this approach was the use of multiple languages. On the other hand, the involvement of the community researchers provided us

with the necessary trust from the communities, and thorough awareness of important local networks, needs, and prevailing themes. The academic team members ensured to underpin the research activities with evidence-based methods and frameworks. The international researchers helped to point out remarkable themes that were considered normal by the national and community researchers.

Concurrently, our collaboration has built and strengthened research capacity in the settings. Throughout the FRESH AIR study, multiple local researchers have enrolled in international PhD-trajectories, and the Department of Respiratory Medicine at the National Center for Cardiology and Internal Medicine in Bishkek has opened a FRESH AIR research centre.

The challenge of implementing the implementation tools

The evidence-based tools we had developed were a response to repetitive calls for more and better implementation research in low-resource settings,[23-26] underpinned by adequate frameworks,[27] and the need to align interventions and their implementation strategy with the local context.[28-30] We are not naïve to believe that these tools will implement themselves, their actual implementation remains challenging. We use the tools' own contents to support their implementation process: the publication in a journal with a wide reach (contributing to "facilitating access to knowledge and information"[19]) is certainly not enough. Especially not for the local targeted settings where – even if locals can read in English – a 'European Respiratory Journal' would not be on top of their list of sources. Collaboration with "engaged stakeholders" to "facilitate access to the knowledge" and "align with the local needs" is essential. The use of the tools has already been facilitated by liaising with other teams and actively sharing knowledge, for example as was done for the implementation of a Ugandan study into music and dance as a means of pulmonary rehabilitation.[31] Together with a large international party in the field of cleaner cooking we are currently exploring a collaboration of how to transfer the evidence of the related tools into a user-friendly format (helped by communication experts), and get them into use.

Tackling chronic respiratory disease in the context of the world's major health challenges

The world is currently facing two major global health challenges: a COVID-19 pandemic, and even larger, a climate emergency. Below, the findings of this thesis are discussed in light of these challenges.

Chronic respiratory disease and the COVID-19 crisis

The COVID-19 pandemic has reinforced the need for broad, life-course approaches to improving health. Like for CRD, mortality for COVID-19 is higher where education levels are lower, air quality is worse, and poverty levels are higher.[32-35] A pessimist would say that due to the

pandemic awareness about CRD has been even further overshadowed by awareness about infectious disease. An optimist would believe that a focus on strengthening health systems and tackling COVID-19's risk factors, which largely overlap with those of CRD, would benefit both communicable and noncommunicable diseases. However, as this thesis demonstrated for COPD and asthma, high-income settings are much better equipped to do so than low-and middle-income settings. At the time of writing, the Netherlands is administering COVID-19 booster shots ('the third dose', or second dose in case of the Janssen vaccination), while only 3.5% of all people in low-income countries have received a first dose;[36] many healthcare workers across the globe are still attending their patients unprotected. Not only does the unequal distribution of resources deny the global goal to "leave no one behind" [principle two of universal values of United Nations Sustainable Development Goals]. It also allows for more COVID-19 mutations and complicates attempts to control the pandemic, also in high-resource settings.[37] Global collaboration should be promoted and to do this effectively, context-driven strategies are needed locally, leveraging local beliefs. Evidence from this thesis could contribute to designing and implementing such strategies.

Fortunately, the COVID-19 crisis also provides hope; it has demonstrated the ability of humankind to rigorously and rapidly adapt behaviour to improve health once the sense of urgency is sufficiently high.

Chronic respiratory disease and the climate crisis

How the climate crisis impacts chronic respiratory disease

Besides the 'acute' COVID-19 crisis, findings from this thesis may also be used to approach the much larger 'chronic' health crisis. The climate crisis is considered "code red for a healthy future"[37-40] and the "single biggest health threat facing humanity."[41] This September, more than 230 medical journals called for emergency action, as the climate crisis is a health emergency that affects all human health indicators.[42]

Chronic respiratory health is impacted by this crisis via numerous direct and indirect pathways. For example, CO_2 emissions from burning fossil fuels are coupled to emissions of air pollutants.[37-39,41,42] Extreme weather events, hotter temperatures, and drought are contributing to more intense and more frequent wildfires, thunderstorms, and sandstorms.[43] This also leads to air pollution. Besides, higher temperatures result in higher levels of ground-level ozone pollution and longer, more intense pollen seasons, triggering asthma exacerbations. The climate crisis also affects other health outcomes, thereby increasing the likelihood of contracting comorbidities such as cardiovascular disease and affecting mental wellbeing. Comorbidities further deteriorate CRD-related outcomes. Moreover, the climate crisis threatens food security, and inflicts poverty and inequity, leading to poorer access to adequate care.[37] Hence, respiratory health heavily relies on a healthy climate.

Towards a solution: tackling shared risk factors

Solutions to CRD and the climate crisis often go hand in hand, yet complex dynamics play a role.[44] Limiting fossil fuel use reduces greenhouse gas emissions and concurrently reduces a major risk factor for CRD: air pollution. However, certain types of particulate matter in the atmosphere can protect the earth from warming up.[39] WHO launched new air quality guidelines in September 2021 recommending lower levels of key air pollutants.[45] Additionally, household air pollution is currently on its decline globally as people escaping from poverty switch to cleaner fuels.[12] This means that with lower levels of air pollution we will have to further intensify our efforts to target global warming.

The dynamics between the other main risk factor for CRD – tobacco – and the climate crisis are also complex. First, the life cycle of tobacco (from cultivation to disposal) involves 84 Mt of CO_2 equivalent (eq) emissions yearly, 0.2% of the global total.[46] Second, tobacco cultivation increasingly competes with essential commodities for resources such as land and water, placing pressure on food security. While the global population is rising, a changing climate is increasing crop failure and higher ambient CO_2 levels are decreasing the nutritional yield per crop.[37] Third and foremost, speculatively the largest part of tobacco's footprint would be revealed when accounting for the healthcare-related emissions caused by tobacco. To my knowledge, the global tobacco-related healthcare emissions have not yet been assessed, but these would be significant. Tobacco smoking is the second largest risk factor for disease burden,[47] and the healthcare sector is estimated to be responsible for 4.4-5% of the total global CO_2 emissions (ranging from the production of medication to transportation of patients).[48,49]

To summarise, combatting air pollution and tobacco use will mutually benefit CRD and the climate crisis. This could be done using a broad, life-course approach as outlined in this thesis, engaging important stakeholders. This thesis' tools may also contribute to designing implementation strategies for global collaborative action against the climate crisis; local, context-driven action is required to achieve a global mission.

Towards a solution: tackling the paradoxical harm of chronic respiratory disease treatment

Lastly, beyond tackling shared risk factors for CRD and the climate crisis, an important medical opportunity lies in CRD treatment. The world's ageing population causes the global number of CRD patients to rise.[50] To combat CRD, we strive to make inhaler treatment widely accessible, including in lower-resource settings. However, the commonly used pressurised metered dose inhalers (pMDIs) contribute substantially to greenhouse gas emissions.[51] pMDIs contain gases with fluorinated compounds; these are highly potent greenhouse gases that remain in the atmosphere for years.[52] Approximately 800 million pMDIs were used globally in 2018 – equalling the average annual use of almost 4 million USA passenger cars – and numbers are increasing every year.[53] To most patients, the environmentally-friendly dry powder inhalers (DPIs) are

equally effective and acceptable options, and can even be cheaper.[54] A systemic approach is required to ensure that the treatment of CRD patients does not pose healthy people at risk of developing CRD. Hence, all stakeholders must encourage the use of DPIs rather than pMDIs when clinically acceptable. Of note, the ERS position statement on asthma and the environment launched in May 2021[43] refrains from making this recommendation. This could be a missed opportunity, considering the urgency of the climate crisis and its consequences for CRD. Especially healthcare professionals have the duty to protect health and to do no harm in the first place: *primum, non nocere*. Healthcare professionals have a unique position in society to advocate for stronger measures: they reach most of the world's population, and, as a large representative poll in the United Kingdom indicated, healthcare professionals are regarded the most trusted professionals to tell the truth.[55]

Recommendations

Findings from this thesis demonstrate the crucial importance of engaging relevant stakeholders in both conducting the studies and in implementing lung health programmes. The knowledge generated in this thesis can serve policymakers, healthcare professionals, researchers, and community members in the evidence-based implementation of lung health interventions (figure 1). Importantly, like in the FRESH AIR study, these different stakeholders should continuously interact to exchange needs and solutions. Speculatively, our findings can also support the context-driven design of implementation strategies for interventions targeting the COVID-19 and climate crisis.

Of note, our studies have focused on several factors that were proven critically important to successful implementation, but these factors were not comprehensive. As reported in chapter 6, other factors should also be considered, such as the setting's political climate or the local health infrastructure. Additionally, it would be interesting to gain knowledge on a 'dose-response' relation: to what extent does a contextual factor need to be studied to successfully design an implementation strategy, and to obtain which degree of success?

Other questions that remain unanswered are to what extent the approaches can be used for mapping contexts for other chronic diseases, or for high-income settings. Plausibly, also high-income settings could draw lessons from this thesis given that similar risk factors and factors influencing potential solutions occur. For example, 23% of all particulate matter in the Netherlands is attributable to woodstove use, surpassing particulate matter emissions from road traffic.[56] Also in this high-income country, woodstove use is strongly related to cultural beliefs and traditions. Lastly, now that settings have been mapped and evidence-based tools have been developed, a clear challenge remains as described above: embedding these tools in practice.

Conclusion

Overall, this thesis has navigated from context-assessment (epidemiology, health economics, anthropology, comparison of guidelines) to the development of evidence-based tools to design context-driven implementation strategies for CRD programmes in low-resource settings. It has demonstrated how the application of the approach can enhance implementation success. Additionally, we have developed an overview of the FRESH AIR study settings' characteristics with shared and context-specific themes to be considered prior to the implementation of CRD programmes.

FIGURE 1. Recommendations for different stakeholders; all stakeholders should continuously communicate and collaborate.

Data have been collected using the same method in highly diverse settings across the globe, enhancing their generalisability. Our findings regarding the burden of CRD and the risk factors

can help to adequately prioritise scarce resources. Other contextual findings and the implementation tools serve to improve the implementation success of CRD programmes, thereby preventing the waste of scarce resources and ultimately optimising health outcomes. This thesis responds to repetitive calls for implementation evidence about non-communicable disease in low-resource settings, where the burden of disease is highest, yet research quality and quantity are lowest. Now the challenge remains to implement the evidence into practice; we aim to promote this using the implementation evidence that the tools themselves contain. We will, therefore, continue to collaborate with both locally and internationally engaged stakeholders and employ context-driven strategies.

Of note, understanding the context also means understanding how everything is interrelated: risk factors are related to socioeconomic factors and hence to prevalence, prevalence to the socioeconomic burden and to health beliefs and behaviours. It is simply impossible to target one aspect, such as household air pollution, and ignore the others, such as poverty and nutrition. A broad life course approach to tackling CRD is needed, starting preconception. Everyone in society has a role; policymakers can enhance clean air policies, educators can raise the CRD awareness of healthcare professionals, which they, in turn, can spread among their communities. Lastly, it is important to see CRD in relation to the COVID-19 and climate crisis. This means we should increase efforts to tackle the shared risk factors air pollution and tobacco. We should also treat CRD in a climate friendly manner, promoting inhaler use without greenhouse gases when clinically acceptable. Policymakers, healthcare professionals, researchers, and community leaders should speak up to spread awareness about CRD in relation to the COVID-19 and climate crisis. They should express concerns without polarising our society, and propose solutions. To leave no one behind, we rely on strong global collaborations. Moreover, we rely on context-driven approaches to achieve a global mission. Only then we can effectively tackle CRD in low-resource settings in light of the current major global health challenges.

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CHAPTER 14

SUMMARY

SUMMARY

Chapter 1, the introduction, outlines the relevance of this thesis. The global burden of chronic respiratory disease (CRD) is high; the two leading CRDs, COPD and asthma, are responsible for 74.4 and 21.6 million DALYs respectively. COPD has become the third leading cause of death and is killing more people than HIV/AIDS, malaria, and tuberculosis combined. Particularly burdened by CRD are low-resource settings where exposure to risk factors such as tobacco and air pollution is high, while disease awareness and means to combat it are low. Evidence for effective approaches to target CRD is also limited for low-resource settings. However, health programmes are likely to fail when implementation strategies misalign with their local context. Therefore, the aim of this thesis is to generate evidence on how to combat CRD in low-resource settings across the globe. To this end, we first seek to understand the context around CRD in diverse low-resource settings. We then focus on how to implement lung health interventions, aligning their implementation strategy with their local context to facilitate successful implementation.

Of note, many of the studies are part of the Horizon 2020 Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups (FRESH AIR) research project. FRESH AIR studies the implementation of preventive, diagnostic, and therapeutic interventions targeting CRD in low-resource settings in Africa (Uganda), Asia (Kyrgyzstan and Vietnam), and Europe (rural Greece and a Roma camp).

Part I – Understanding the problem; exploring chronic respiratory disease in its local context

In Part I, the context around CRD is explored in diverse low-resource settings globally, focusing on the direct and indirect burden of disease, on exposure to risk factors, and on how diverse settings approach the risk factor tobacco in their guidelines.

First, the epidemiological study in Kyrgyzstan, **Chapter 2**, compares the prevalence of COPD and its risk factors between a highland (~2050 m above sea level) and a lowland setting (750 m). Earlier studies had reported conflicting results about the relation between altitude and COPD. However, most studies had not accounted for household air pollution. Household air pollution is caused by cooking or heating with solid fuels (such as wood, dung, or coal), as 3 billion people do daily. None of the studies had objectively measured pollution levels. In randomly selected households, we objectively measured both lung function (using spirometry) and personal exposure to household air pollution (particulate matter with an aerodynamic diameter <2.5 μm [$PM_{2.5}$]). We administered a questionnaire on other COPD risk factors like tobacco. COPD was more prevalent among the 199 highlanders than the 193 lowlanders (36.7% *versus* 10.4%; p<0.001). Average $PM_{2.5}$ exposure was also higher in the highlands (290.0 *versus* 72.0 μg·m–3;

p<0.001). High levels of $PM_{2.5}$ exposure (OR 3.174, 95% CI 1.061–9.493), pack-years of smoking (OR 1.037, 95% CI 1.005–1.070) and age (OR 1.058, 95% CI 1.037–1.079) contributed to a higher COPD prevalence among highlanders. In addition, high altitude independently predicted COPD (OR 3.406, 95% CI 1.483–7.825). Findings demonstrate how contexts of neighbouring settings can differ significantly in terms of risk exposure and disease burden. Preventive interventions seem especially warranted in these low-resource, highland settings. Of note, this was among the first spirometry-based prevalence studies in Central Asia.

Chapter 3, an opinion paper, details a then-novel perspective on the origins of COPD in low-resource settings. It explains how risk factors for COPD in these settings typically co-occur and interrelate, leading to a 'false start' in lung function. A complex interplay of disadvantageous factors early in life, such as intra-uterine exposure to household air pollution, malnutrition, or a history of tuberculosis, affect lung development. This increases the likelihood of developing COPD later in life. The trajectory leading to COPD for these patients is not (only) through the 'traditional' accelerated decline of a normal lung function, but through the physiological decline in the function of lungs that never attained their potential maximum value. A low socioeconomic status can further deteriorate lung health, as it is associated with factors like poor access to healthcare, poor nutrition, low birth weight, and poor sanitation. COPD caused by a false start implies that risks should be tackled at much earlier stages, starting before birth, and these approaches should later be combined with 'regular' preventive methods. As risk factors are diverse, the measures should be embedded in a wide, intersectoral approach. Awareness about COPD and its early origins should be raised among communities, health workers, and policymakers, along with awareness on affordable measures to prevent and treat disease. Lastly, a false start also implies a fundamentally different perspective on how to study the effects of interventions targeting household air pollution on lung function. Currently, the effects of interventions are often studied in lungs that have already been irreversibly damaged; effects should also be studied in the yet unborn generation.

Next, the health economics study in **Chapter 4** demonstrates that besides differences in exposure to risk factors, low-resource settings remarkably differ from high-resource settings regarding the socioeconomic burden of CRD. We estimated the work productivity and activity impairment due to CRD across four diverse low-resource settings, and studied modifiable risk factors for impairment. We conducted a cross-sectional, observational study in the four FRESH AIR countries: Uganda, Kyrgyzstan, Vietnam, and Greece. Of the 1040 spirometry confirmed CRD patients, a median [interquartile range] of 40.0% [20.0–60.0] reported impairment in daily activities. The 459 employed patients reported an overall work impairment of 30% [1.8–51.7] and decreased productivity (presenteeism) of 20.0% [0.0–40.0]. Of note, work time missed (absenteeism) was 0.0% [0.0–16.7]. Potentially modifiable risk factors for CRD-related impairment were severity of breathlessness (MRC-scale) (B = 8.92, 95%CI = 7.47–10.36), smoking (B = 5.97,

95%CI = 1.73–10.22), and solid fuel use (B = 3.94, 95%CI = 0.56–7.31). The low absenteeism compared to the substantial presenteeism and activity impairment could be explained by social security systems that are often missing in low-resource settings; patients commonly showed up at work at the expense of lower productivity. This was the first large international study assessing CRD-related work productivity and activity impairment in low-resource settings. Results warrant healthcare workers, policymakers, patients, and employers to increase awareness, take preventive actions, and enhance clinical management of CRD in low-resource settings.

Last, the systematic review in **Chapter 5** focuses on a major risk factor for CRD in different contexts; it compares primary care smoking cessation guidelines across the globe. We identified the guidelines using an online inventory of national guidelines (on treattobacco.net) and by consulting colleagues through the network of the International Primary Care Respiratory Group. Out of 43 identified guidelines from 39 countries, 26 guidelines from 22 countries were relevant for primary care with the guidelines and/or key recommendations (made) available in English. There was almost universal agreement on the need to identify smokers, offer brief advice to quit, assess motivation to quit, and offer assistance with behavioural and pharmacological support. Discrepancies between the guidelines were most prominent for specific recommendations regarding the specific content and delivery format of behavioural support, and the provision of pharmacotherapy. This was likely to be due to different contextual health environments (health infrastructures, risk factor distribution, medication availability, cultures, etc.), or different interpretations of the evidence. Based on these findings, we developed a universal checklist of guideline recommendations for primary care professionals and future guideline developers.

Part II – Towards a solution; facilitating implementation success of lung health programmes by engaging and leveraging their local context

Part II focuses on generating evidence on how to combat CRD in low-resource settings, the development of practical tools and a methodology, and on studying the application of this evidence in practice.

It starts with a systematic literature review and meta-synthesis in **Chapter 6** to identify critical factors to the implementation of interventions targeting CRD in LMICs, and to weigh the level of evidence. After searching eight databases without date or language restrictions in July 2019, we included 37 articles out of 9111 screened. Studies were broadly representative of the population distribution across the world's continents, and conducted in community settings, healthcare settings and schools. Studies regarding cleaner cooking interventions to reduce exposure to household air pollution were so numerous that we decided to separate these from the current review and dedicate a separate review exclusively to this topic (Chapter 9). Many of the 37 (remaining) studies regarded tobacco related interventions, while pulmonary

rehabilitation, patient education, and self-management interventions were underrepresented or even absent. Factors identified with a high level of confidence were 1) Understanding needs of local users; 2) Ensuring compatibility of the intervention with the local context; 3) Identifying influential stakeholders and applying engagement strategies; 4) Ensuring adequate access to knowledge and information; and 5) Addressing resource availability. These real-world findings were consolidated in a hands-on implementation tool for practice. Policymakers, nongovernmental organisations, practitioners, and researchers can use this 'FRESH-AIR Implementation tool' to develop evidence-based implementation strategies for interventions targeting CRD in low-resource settings.

While conducting the literature search above, not only an abundance of evidence was revealed on the implementation of cleaner cooking interventions, but also a lack of the *use* of all the evidence. Therefore, **Chapter 7** concerns a commentary that reflects on decades of substantial discrepancies between the disappointing adoption rates of cleaner cookstoves, and the subsequent failure to adapt implementation strategies accordingly. Several solutions to overcoming this evidence to practice gap are proposed. Above all, the commentary urges all stakeholders to use existing evidence in the design and execution of implementation strategies for improved stoves. First, researchers should consolidate the existing bulge of implementation evidence into a practical tool. Implementors should use this tool, and collaboratively with researchers ensure to continuously update it. They should connect to large network organisations (the World Health Organization, the Clean Cooking Implementation Science Network), which should in turn promote and distribute the tool to make it widely available. In addition, funders, nongovernmental organisations, and development institutions should exclusively grant support for projects with adequate implementation strategies addressing the tool's critical implementation factors. Lastly, carbon credit (offset) projects should not incentivise on the number of stoves distributed, but on the number of stoves adopted. All stakeholders should constantly network to ensure everyone is on the same, up-to-date page. Ultimately, successful implementation would both improve health and benefit the planet, as cleaner combustion requires less fuel use and reduces deforestation.

To practice what we preached, we teamed up with national and international colleagues as a first step. We collaboratively conducted the systematic review dedicated exclusively to cleaner cooking (Chapter 9) to develop this practical implementation tool. An umbrella review, a review of reviews, was considered a more suitable methodology to analyse the evidence of the more than 400 of individual studies we had identified. For full transparency, the updated study protocol in **Chapter 8** details this relatively complex methodology.

Chapter 9, the resulting systematic umbrella review, consolidates evidence from 31 cleaner cooking implementation reviews. Critical factors regarding the implementation of improved

solid fuel cookstoves supported by the highest level of evidence included 'Costs', 'Knowledge & beliefs about the innovation', and 'Compatibility'. Factors for cleaner fuels included 'Costs', 'Knowledge & beliefs about the innovation', and 'External policy & incentives'. The factors were synthesised into the Cleaner Cookstove Implementation Tool (CleanCIT) and the Clean Fuel Implementation Tool (CleanFIT). To bridge the gap from science to practice, we are currently exploring possibilities together with large relevant networks for how to prepare the tools for practical use and disseminate them.

A critical factor identified in both implementation reviews is the compatibility of the intervention with the local context, among which the local beliefs and needs. However, no evidence was available on *how* to map the context to understand it in the first place. Therefore, the methodology paper in **Chapter 10** details the development and prospective validation of a systematic methodology to map local health beliefs and behaviours: the Setting-Exploration-Treasure-Trail-to-Inform-ImplementatioN-strateGies-(SETTING) tool. Together with an expert panel and local end-users we co-created this six-step approach: 1) Co-set study priorities with local stakeholders; 2) Combine a qualitative rapid assessment with a quantitative survey (a mixed-method design); 3) Use context-sensitive materials; 4) Collect data involving community researchers; 5) Analyse pragmatically and/or in-depth to ensure timely communication of findings; and 6) Continuously disseminate findings to relevant stakeholders. We applied the tool in six low-resource settings in the four FRESH AIR countries on three continents; the methodology proved highly feasible, acceptable, and effective in each setting.

Application of the tool is demonstrated in the observational mixed-methods study in **Chapter 11**, aiming to map local beliefs and behaviours regarding CRD across the six diverse low-resource settings in Uganda, Kyrgyzstan, Vietnam and Greece. Qualitative data were collected from 340 informants in more than 200 interviews, focus group discussions, and observations, and findings were triangulated with a quantitative survey among 1037 community members and 204 healthcare professionals. Three key themes were identified that consistently played a key role in CRD-related beliefs and behaviours: 1) Perceived CRD identity (community members in all settings except the rural Greek strongly attributed long-lasting respiratory symptoms to infection, predominantly tuberculosis); 2) Beliefs about causes (65.8% of the community members strongly agreed that tobacco smoking causes symptoms, this was 19.1% for household air pollution; typical perceived causes ranged from witchcraft [Uganda] to a hot–cold disbalance [Vietnam]); and 3) Norms and social structures (such as that 'real men' smoke [Kyrgyzstan and Vietnam]). These key themes should be addressed when designing context-driven implementation strategies for CRD-related interventions across these global settings, each with shared and context-specific beliefs and behaviours. This study also provides an overview of the settings' typical characteristics with their associated prevailing beliefs and behaviours which may serve implementors in settings that share similar characteristics.

Findings of Chapter 11 were then used to design the implementation strategy of a subsequent lung health intervention in an implementation study in **Chapter 12**. We implemented a Ugandan train-the-trainer lung health intervention in Kyrgyzstan and Vietnam, empowering communities to take action against solid fuel- and tobacco smoke. We co-created the design and implementation strategy with local stakeholders, and embedded the programme into existing local health infrastructures. Feasibility and acceptability were considered high; around 15,000 Kyrgyz and 10,000 Vietnamese community members were reached within the budget of around € 11,000 per country. The programme was effective in improving knowledge: scores on lung health awareness questionnaires increased significantly after participation in the programme, to excellent levels in all target groups. Effectiveness was also assessed by behaviour change, namely whether cleaner cooking methods (delivered by a subsequent FRESH AIR intervention study not included in this thesis) were adopted. Adoption was moderately successful in Vietnam, and highly successful in Kyrgyzstan. The current study demonstrates how an implementation strategy for a lung health intervention can be tailored to the context to support implementation success.

The general discussion, **Chapter 13,** reflects on how this thesis navigates from context assessment (epidemiology, health economics, anthropology, comparison of guidelines) to the implementation of context-driven, evidence-based lung health solutions in low-resource settings. Broad, multisectoral interventions are needed that promote lung health even before birth. This thesis demonstrates how exploring, engaging, and leveraging the local context can facilitate implementation success. It also provides an overview of characteristics of the six diverse FRESH AIR study settings in four countries with shared and context-specific themes. These could be considered before implementing a programme targeting CRD in a similar setting. The generalisability of the findings is enhanced as data were collected across the globe. The main challenge that persists is the implementation of this implementation evidence.

CRD in light of the COVID-19 crisis and the climate crisis reinforces the need to take collaborative action globally, using context-driven strategies locally. To "leave no one behind" [UN], we rely on strong global collaborations in which every individual should take a role. Policymakers, healthcare workers, researchers, and others are encouraged to use these findings to effectively implement interventions targeting CRD, thereby optimising the use of resources that are scarce in low-resource settings already, ultimately benefitting health outcomes.

ADDENDUM

NEDERLANDSE SAMENVATTING

In de inleiding, **hoofdstuk 1**, wordt de relevantie van dit proefschrift beschreven. De wereldwijde ziektelast van chronische longziekten (CLZ) is hoog; COPD en astma, de meest voorkomende CLZ, zijn verantwoordelijk voor respectievelijk 74,4 en 21,6 miljoen DALYs. COPD is de derde meest voorkomende doodsoorzaak en doodt meer mensen dan HIV/AIDS, malaria en tuberculose bij elkaar. CLZ zijn vooral problematisch in gebieden waar de middelen schaars zijn, ook wel resource-arme gebieden genoemd. De blootstelling aan risicofactoren zoals tabak en luchtvervuiling is hier namelijk vaak hoog, terwijl men beperkt bewust is van CLZ en weinig middelen heeft om ze te bestrijden. Bovendien bestaat er juist voor deze resource-arme gebieden slechts weinig bewijs over doeltreffende aanpakken voor CLZ. Het is bekend dat gezondheidsprogramma's een grote kans hebben te mislukken wanneer implementatiestrategieën niet aansluiten bij hun lokale context. Het doel van dit proefschrift is om inzicht te krijgen in hoe CLZ wereldwijd kunnen worden bestreden in resource-arme gebieden. Om dit te bereiken onderzoeken we eerst de context van CLZ in verschillende resource-arme gebieden. Vervolgens onderzoeken we de implementatie van verschillende interventies gericht op CLZ, waarbij we de implementatiestrategie afstemmen op de lokale context om een succesvolle implementatie te bevorderen.

Veel van de studies uit dit proefschrift maken deel uit van het EU Horizon 2020 onderzoeksproject *'Free Respiratory Evaluation and Smoke-exposure reduction by primary Health cAre Integrated gRoups'* (FRESH AIR). FRESH AIR bestudeert de implementatie van preventieve, diagnostische en therapeutische interventies gericht op CLZ in resource-arme gebieden in Afrika (Uganda), Azië (Kirgizië en Vietnam), en Europa (het Griekse platteland en een Grieks Roma-kamp).

Deel I - Inzicht in het probleem; verkenning van chronische longziekten in hun lokale context

In deel I wordt de context onderzocht van CLZ in verschillende resource-arme gebieden wereldwijd, met een focus op de directe en indirecte ziektelast, de blootstelling aan risicofactoren, en hoe verschillende gebieden de risicofactor tabak in hun richtlijnen benaderen.

Ten eerste vergelijkt de epidemiologische studie in Kirgizië (**hoofdstuk 2**) de prevalentie van COPD en de risicofactoren tussen een hoogland (~2050 m boven zeeniveau) en laagland regio (750 m boven zeeniveau). Eerdere studies rapporteerden tegenstrijdige resultaten over de relatie tussen hoogte en COPD. De meeste studies hielden echter geen rekening met luchtvervuiling binnenshuis. Deze vervuiling wordt veelal veroorzaakt door te koken of stoken op vaste brandstoffen (hout, mest, steenkool, etc.), zoals 3 miljard mensen wereldwijd dagelijks doen. Geen van de studies had de luchtvervuiling objectief gemeten. Daarom hebben wij bij willekeurig geselecteerde huishoudens zowel de longfunctie (middels spirometrie) als de persoonlijke

blootstelling aan luchtvervuiling binnenshuis objectief gemeten (middels fijnstofmeters voor fijnstof <2,5 µm [$PM_{2,5}$]). Ook namen we een vragenlijst af over andere risicofactoren voor COPD, zoals roken. COPD kwam meer voor bij de 199 hooglanders dan bij de 193 laaglanders (36,7% versus 10,4%; p<0,001). De gemiddelde blootstelling aan $PM_{2,5}$ was ook hoger in de hooglanden (290,0 versus 72,0 $\mu g \cdot m^{-3}$; p<0,001). Hoge niveaus van $PM_{2,5}$-blootstelling (OR 3,174, 95% BI 1,061-9,493), pakjaren roken (OR 1,037, 95% BI 1,005-1,070) en leeftijd (OR 1,058, 95% BI 1,037-1,079) droegen bij aan een hogere COPD-prevalentie onder hooglanders. Bovendien bleek hoogte een onafhankelijke voorspeller voor COPD (OR 3,406, 95% BI 1,483-7,825). De bevindingen tonen hoe de context van aangrenzende regio's aanzienlijk kan verschillen op het vlak van blootstelling aan risicofactoren en ziekte. Voor de hooglanden, met weinig middelen, lijken vooral preventieve interventies geïndiceerd te zijn. Noemenswaardig is dat dit een van de eerste op spirometrie gebaseerde prevalentie studies in Centraal-Azië was.

Hoofdstuk 3, een opinieartikel, beschrijft een op dat moment nieuw perspectief op het ontstaan van COPD in resource-arme gebieden. In de gebieden treden verschillende risicofactoren voor COPD vaak gelijktijdig op en versterken elkaar, wat kan leiden tot een "valse start" in de longontwikkeling. Een complex samenspel van nadelige factoren vroeg in het leven, zoals blootstelling aan luchtvervuiling in de baarmoeder via het bloed van de moeder, (maternale) ondervoeding, of een voorgeschiedenis van tuberculose, beïnvloeden de longontwikkeling. Dit vergroot de kans op het ontwikkelen van COPD later in het leven. Het traject dat bij deze patiënten tot COPD leidt, verloopt dan niet (alleen) via de 'traditionele' versnelde achteruitgang van een normale longfunctie, maar via de fysiologische achteruitgang van longen die hun potentiële maximumwaarde nooit hebben bereikt. Een lage sociaaleconomische status kan de longgezondheid verder verslechteren, omdat deze geassocieerd wordt met factoren zoals slechtere toegang tot gezondheidszorg, slechtere voeding, lager geboortegewicht en slechtere sanitaire voorzieningen. Bij COPD die veroorzaakt wordt door een valse start moeten de risico's in een veel eerder stadium worden aangepakt, te beginnen al vóór de geboorte. Deze aanpak moet dan later in het leven worden gecombineerd met de conventionele preventieve methoden. Aangezien de risicofactoren uiteenlopen, moeten maatregelen worden ingebed in een brede, intersectorale aanpak. Gemeenschappen, gezondheidswerkers en beleidsmakers moeten bewust worden gemaakt van COPD en het vroegtijdige ontstaan ervan, en van betaalbare maatregelen om de ziekte te voorkomen en te behandelen. Tenslotte impliceert een valse start ook een fundamenteel andere kijk op hoe de effecten van interventies tegen luchtvervuiling binnenshuis worden bestudeerd. Momenteel worden de effecten van interventies vaak bestudeerd in longen die al onomkeerbaar beschadigd zijn; effecten zouden ook in de nog ongeboren generatie moeten worden bestudeerd.

Vervolgens toont de gezondheidseconomische studie in **hoofdstuk 4** dat naast verschillen in blootstelling aan risicofactoren tussen resource-arme en resource-rijke gebieden, er ook

opmerkelijke verschillen bestaan in de sociaaleconomische ziektelast van CLZ. In vier verschillende lage-inkomenslanden maakten we een inschatting van de beperkingen in arbeidsproductiviteit en activiteiten ten gevolge van CLZ, en identificeerden we modificeerbare risicofactoren voor beperkingen. We verrichtten een cross-sectionele, observationele studie in de vier FRESH AIR-landen: Uganda, Kirgizië, Vietnam, en Griekenland. Van de 1040 door spirometrie bevestigde CLZ-patiënten, rapporteerde een mediaan van 40,0% [interkwartiel bereik: 20,0-60,0] beperkingen in dagelijkse activiteiten. De 459 deelnemende patiënten met een baan rapporteerden een totale arbeidsongeschiktheid van 30,0% [1,8-51,7] en een verminderde productiviteit (presenteïsme) van 20,0% [0,0-40,0]. De gemiste werktijd (absenteïsme) was 0,0% [0,0-16,7]. Potentieel modificeerbare risicofactoren voor CLZ-gerelateerde beperkingen waren de mate van kortademigheid (MRC-schaal) (B = 8,92, 95% BI = 7,47-10,36), roken (B = 5,97, 95% BI = 1,73-10,22), en gebruik van vaste brandstof (B = 3,94, 95% BI = 0,56-7,31). Absenteïsme was dus laag in vergelijking met het substantiële presenteïsme en de beperkingen in activiteiten. Dit zou kunnen worden verklaard door de vaak ontbrekende socialezekerheidsstelsels in resource-arme gebieden; patiënten kwamen vaak opdagen op het werk ten koste van een lagere productiviteit. Dit was de eerste grote internationale studie die CLZ-gerelateerde beperkingen in de arbeidsproductiviteit en activiteiten in resource-arme gebieden onderzocht. De resultaten vragen om meer bewustzijn van de (indirecte) kosten en lasten van CLZ onder zorgverleners, beleidsmakers, patiënten en werkgevers. Zij dienen preventieve maatregelen te nemen en de klinische behandeling van CLZ in resource-arme gebieden te verbeteren.

Tenslotte richt de systematische literatuurstudie van **hoofdstuk 5** zich op een belangrijke risicofactor voor CLZ in verschillende contexten; we vergeleken wereldwijd Stoppen-met-roken richtlijnen in de eerstelijnszorg. We identificeerden richtlijnen middels een online inventarisatie van nationale richtlijnen (op treattobacco.net) en het raadplegen van collega's via het netwerk van de International Primary Care Respiratory Group. We vonden 43 richtlijnen uit 39 landen. Hiervan bleken 26 richtlijnen uit 22 landen relevant voor de eerstelijnsgezondheidszorg, met (de aanbevelingen van) de richtlijnen beschikbaar (gemaakt) in het Engels. Er was bijna unanieme overeenstemming over de noodzaak om rokers te identificeren, een kort stoppen-met-rokenadvies te geven, de motivatie om te stoppen te beoordelen, en gedragsmatige en medicamenteuze ondersteuning te bieden. De discrepantie tussen de richtlijnen was het grootst bij specifieke aanbevelingen over de inhoud en vorm van gedragsmatige ondersteuning en de verstrekking van farmacotherapie. Dit was waarschijnlijk te wijten aan verschillende contextuele gezondheidsomgevingen (gezondheidsinfrastructuur, verdeling van risicofactoren, beschikbaarheid van medicatie, cultuur, etc.). Op basis van deze bevindingen ontwikkelden we een universele checklist met richtlijnaanbevelingen voor eerstelijnszorgprofessionals en toekomstige richtlijnontwikkelaars.

Deel II – Op weg naar een oplossing; het bevorderen van implementatiesucces van longgezondheidsprogramma's door hun lokale context te betrekken en te benutten

Deel II richt zich op het genereren van bewijs over hoe CLZ te bestrijden in resource-arme gebieden, op de ontwikkeling van praktische instrumenten en een methodologie daartoe, en op het bestuderen van de toepassing van dit bewijs in de praktijk.

Deel II begint met een systematisch literatuuronderzoek en meta-synthese (**hoofdstuk 6)** om essentiële factoren te identificeren voor de implementatie van interventies gericht op CLZ in laag- en middeninkomenslanden, en om bewijskracht te wegen. We doorzochten daarvoor acht databases zonder datum- of taalbeperkingen in juli 2019, wat resulteerde in 9111 artikelen. Hiervan voldeden er 37 aan de inclusiecriteria. De beschreven studies waren in grote lijnen representatief voor de bevolkingsspreiding over 's werelds continenten, en waren uitgevoerd in gemeenschapsomgevingen, gezondheidszorginstellingen en scholen. We identificeerden een dermate groot aantal studies over schoner koken (om de blootstelling aan luchtvervuiling binnenshuis te verminderen) dat we besloten hier een aparte review aan te wijden (hoofdstuk 9). Veel van de 37 overgebleven studies betroffen tabaksinterventies, terwijl interventies als longrevalidatie, patiënteducatie en zelfmanagement ondervertegenwoordigd of zelfs afwezig waren.

Factoren die met een hoog niveau van bewijs werden geïdentificeerd waren: 1) Het begrijpen van de behoeften van de lokale gebruikers; 2) Het zorgen voor compatibiliteit van de interventie met de lokale context; 3) Het identificeren van invloedrijke stakeholders en het toepassen van strategieën hen actief te betrekken; 4) Het zorgen voor adequate toegang tot kennis en informatie; en 5) Het adresseren van de beschikbaarheid van nodige middelen. Deze bevindingen werden geconsolideerd in een handzaam implementatie instrument voor de praktijk. Beleidsmakers, non-gouvernementele organisaties (ngo's), onderzoekers of andere uitvoerders kunnen deze 'FRESH-AIR implementatietool' gebruiken om evidence-based implementatiestrategieën te ontwikkelen voor interventies gericht op CLZ in resource-arme gebieden.

Tijdens het verrichten van het literatuuronderzoek hierboven, werd niet alleen een overvloed aan bewijs geïdentificeerd over de implementatie van schoner koken interventies, maar ook een gebrek aan het gebruik ervan. Daarom schreven we in **hoofdstuk 7** een commentaar dat reflecteert op decennia van teleurstellende cijfers over de implementatie van schonere kooktoestellen, en het falen om daar vervolgens de implementatiestrategieën op aan te passen. In het commentaar stellen we verschillende oplossingen voor om de kloof tussen bewijs en praktijk te overbruggen. Er wordt bij alle stakeholders op aangedrongen om gebruik te maken van bestaand bewijs in het ontwerp en de uitvoering van implementatiestrategieën voor schonere kooktoestellen. Ten eerste zouden onderzoekers de bestaande overvloed aan

bewijs over de implementatie moeten consolideren, bijvoorbeeld in een praktisch instrument. Uitvoerders moeten dit instrument vervolgens gaan gebruiken, en er samen met onderzoekers voor zorgen dat het voortdurend wordt bijgewerkt naar de laatste inzichten. Zij moeten zich aansluiten bij relevante netwerkorganisaties (de Wereldgezondheidsorganisatie, het Clean Cooking Implementation Science Network), die op hun beurt het instrument moeten promoten en verspreiden om het op grote schaal beschikbaar te maken. Daarnaast moeten financiers, ngo's, en ontwikkelingsinstellingen uitsluitend steun verlenen aan projecten met adequate implementatiestrategieën die de essentiële factoren van het instrument adresseren. Ten slotte moeten carbon-krediet projecten niet belonen naar het aantal *uitgedeelde* kooktoestellen, maar naar het aantal kooktoestellen *in gebruik*. Alle stakeholders moeten voortdurend met de netwerken in contact blijven om alle neuzen dezelfde, evidence-based kans uit te richten. Succesvolle implementatie kan zowel de gezondheid van de mens als van de planeet bevorderen, aangezien bij een schonere verbranding minder brandstof nodig is en zo de ontbossing beperkt.

Om woord bij daad te voegen, benaderden we nationale en internationale collega's om hierin samen te werken. We verrichtten de systematische literatuurstudie die toegespitst was op schoner koken (hoofdstuk 9). We achtten een overkoepelende review, een review van reviews, een geschiktere methode om het bewijs te analyseren van de meer dan 450 individuele studies. Omwille van transparantie, publiceerden we een bijgewerkt studieprotocol in **hoofdstuk 8** waarin we uitvoerig ingaan op deze relatief complexe methodologie.

Hoofdstuk 9, de resulterende systematische overkoepelende review, consolideert bewijsmateriaal uit 31 reviews van de implementatie van schoner koken. Kritische factoren voor de implementatie van schonere kooktoestellen, ondersteund door het hoogste niveau van bewijs, waren: 1) Kosten; 2) Kennis en overtuigingen over de innovatie; en 3) Compatibiliteit. Factoren voor de implementatie van schonere brandstoffen waren 1) Kosten; 2) Kennis en overtuigingen over de innovatie; en 3) Extern beleid en beloningen. De factoren werden samengevat in de Cleaner Cookstove Implementation Tool (CleanCIT) en de Clean Fuel Implementation Tool (CleanFIT). Om de wetenschappelijke kennis de praktijk in te brengen, exploreren we momenteel samen met relevante netwerken de mogelijkheden om de instrumenten klaar te maken voor gebruik in de praktijk en ze te verspreiden.

Een essentiële factor die in beide implementatie-reviews (hoofdstuk 6 & 9) naar voren kwam, is de compatibiliteit van de interventie met de lokale context, waaronder de lokaal heersende overtuigingen en behoeften. Er was echter geen bewijs voorhanden over hoe de context in kaart moest worden. Daarom wordt in de methodologische studie in **hoofdstuk 10** de ontwikkeling en prospectieve validatie beschreven van een systematische methodologie om lokale gezondheidsovertuigingen en gedragingen in kaart te brengen: de Setting-Exploration-Treasure-Trail-to-Inform-ImplementatioN-strateGies-(SETTING) tool. Samen met een panel

van deskundigen en lokale eindgebruikers ontwikkelden we een aanpak van zes stappen: 1) Stel samen met lokale stakeholders de onderzoeksprioriteiten vast; 2) Combineer een kwalitatieve 'rapid assessment' met een kwantitatieve enquête (een 'mixed-method design'); 3) Gebruik materialen die aansluiten bij de lokale context; 4) Betrek onderzoekers uit de gemeenschap bij de dataverzameling; 5) Analyseer pragmatisch en/of grondig om tijdige communicatie van de bevindingen te verzekeren; en 6) Verspreid de bevindingen voortdurend onder relevante stakeholders. We hebben de SETTING-tool toegepast in zes resource-arme gebieden in de vier FRESH AIR-landen op drie continenten. De methodologie bleek in elke setting haalbaar, aanvaardbaar en effectief.

De toepassing van de SETTING-tool demonstreren we in de observationele mixed-methods studie in **hoofdstuk 11**, gericht op het in kaart brengen van lokale overtuigingen en gedragingen ten aanzien van CLZ in de zes verschillende resource-arme gebieden in Uganda, Kirgizië, Vietnam en Griekenland. We verzamelden kwalitatieve gegevens onder 340 informanten in meer dan 200 interviews, focusgroep discussies, en observaties, en trianguleerden de bevindingen met een kwantitatieve enquête onder 1037 dorpsbewoners en 204 zorgprofessionals. We identificeerden drie hoofdthema's die consistent een sleutelrol speelden in CLZ-gerelateerde overtuigingen en gedragingen: 1) De waarneming van de identiteit van CLZ – dorpsbewoners in alle gebieden behalve op het Griekse platteland schreven chronische luchtwegklachten sterk toe aan infecties, vooral aan tuberculose; 2) Overtuigingen over de oorzaken – 65,8% van alle dorpsbewoners was het sterk eens dat tabaksrook symptomen veroorzaakt, dit aantal was 19,1% voor luchtvervuiling binnenshuis; context-specifieke oorzaken varieerden van hekserij in Uganda tot een warmte-koude disbalans in Vietnam; en 3) Normen en sociale structuren – zoals dat 'echte mannen' roken in Kirgizië en Vietnam. Deze gedeelde hoofdthema's dienen aan bod te komen bij het ontwerpen van context-gedreven implementatiestrategieën voor interventies gericht op CLZ in deze gebieden, elk met gedeelde en context-specifieke overtuigingen en gedragingen. Verder geeft de studie een overzicht van de typische kenmerken van de gebieden met hun bijbehorende heersende overtuigingen en gedragingen. Dit overzicht kan dienen bij de implementatie van CLZ-programma's in gebieden met vergelijkbare kenmerken.

We gebruikten onze bevindingen uit hoofdstuk 11 om de implementatiestrategie van een volgende longgezondheidsinterventie te ontwerpen in **hoofdstuk 12**. In deze implementatiestudie vertaalden we een Ugandees train-de-trainer programma naar gebieden in Kirgizië en Vietnam. Gemeenschappen leerden hoe ze actie konden ondernemen tegen luchtvervuiling binnenshuis door gebruik van vaste brandstoffen en tabak. Samen met lokale stakeholders ontwikkelden we het ontwerp en de implementatiestrategie om het programma in bestaande lokale infrastructuren te bedden. De haalbaarheid en aanvaardbaarheid werden hoog geacht; ongeveer 15000 Kirgizische en 10000 Vietnamese dorpsbewoners werden bereikt binnen het budget van zo'n 11000 euro per land. Het programma was effectief in het verbeteren van relevante kennis:

de scores op kennisvragenlijsten over longgezondheid stegen aanzienlijk na deelname aan het programma, tot uitstekende niveaus in alle doelgroepen. De effectiviteit werd ook beoordeeld aan de hand van gedragsverandering, namelijk of schonere kooktoestellen in gebruik werden genomen (deze werden geleverd door een latere FRESH AIR-interventiestudie die niet in dit proefschrift is opgenomen). Het gebruik was matig succesvol in Vietnam, en zeer succesvol in Kirgizië. De huidige studie laat zien hoe een implementatiestrategie voor een longgezondheids-interventie kan worden aangepast aan de context om implementatiesucces te bevorderen.

De algemene discussie, **hoofdstuk 13**, reflecteert op hoe dit proefschrift navigeert van het onderzoeken van de context (epidemiologie, gezondheidseconomie, antropologie, vergelijking van richtlijnen) naar de implementatie van context-gedreven, evidence-based longgezond-heidsprogramma's in resource-arme gebieden. Dit proefschrift toont dat brede multisectoriële interventies nodig zijn die de longgezondheid al voor de geboorte bevorderen. Het laat zien hoe het onderzoeken, betrekken en benutten van de lokale context implementatiesuccessen kan verbeteren. Ook biedt het een overzicht van de kenmerken van de zes verschillende FRESH AIR onderzoekssettings in vier landen met gedeelde en contextspecifieke thema's. De thema's kun-nen worden overwogen in het ontwerpen van implementatiestrategieën van interventies tegen CLZ in vergelijkbare gebieden. De generaliseerbaarheid van de bevindingen is betrekkelijk groot doordat de gegevens in verschillende gebieden over de wereld zijn verzameld. De belangrijkste uitdaging die blijft bestaan is de implementatie van dit implementatiebewijs zelf.

CLZ in het licht van de COVID-19 -crisis en de klimaatcrisis versterkt de noodzaak tot we-reldwijde samenwerking met gebruik van context-gedreven strategieën op lokaal niveau. Om "niemand achter te laten" [VN], zijn we afhankelijk van sterke wereldwijde samenwerkings-verbanden waarin iedere individu een rol moet spelen. Beleidsmakers, gezondheidswerkers, onderzoekers en anderen worden aangemoedigd om de bevindingen van dit proefschrift te gebruiken om effectief interventies te implementeren die CLZ aanpakken. Daarmee kan het gebruik van middelen die al schaars zijn in resource-arme gebieden geoptimaliseerd worden, wat uiteindelijk ten goede komt aan onze planeet, en aan gezondheidsresultaten.

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2. Anastasaki A, van Bree EM, **Brakema EA**, Tsiligianni I, Sifaki-Pistolla D, Chatzea VE, Crone MC, Karelis A, van der Kleij RMJJ, Poot CC, Reis R, Chavannes NH, Lionis C, on behalf of the FRESH AIR collaborators. Beliefs, Perceptions, and Behaviors Regarding Chronic Respiratory Diseases of Roma in Crete, Greece: A Qualitative FRESH AIR Study. *Frontiers in Public Health*. 2022; 10; B12700
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CURRICULUM VITAE

Evelyn Brakema (the Hague, 1989) completed her PhD with the department of Public Health and Primary Care at the Leiden University Medical Centre in the Netherlands.

Her interest in global wellbeing was sparked at age 16 when she travelled as an ambassador of the Rijnlands Lyceum (graduation 2007) to Kenyan slums to see the benefit of educational projects. She subsequently persued this interest by teaching English to teachers and students in the Peruvian Andes (2007-2008). Later, during her medical studies at the University Medical Centre Utrecht (graduation 2015) she focused further on Global Health with electives in Congo Brazzaville and Nicaragua, and an extra-curricular internship in medical management in Jordan. A year of full-time board membership and several part-time positions with the international student organisation AIESEC showed her the power of international collaboration.

Her passion for global health and international collaboration came together in the Horizon 2020 FRESH AIR project, in which she studied how to implement lung health programmes in low-resource settings, thereby coordinating studies with partners across 14 institutes in nine countries. She was awarded an Erasmus+ Mobility Grant to specialise in implementation science at the University of Edinburgh in Scotland. Her studies have been published in journals such as *The Lancet Global Health*, *The Lancet Planetary Health*, and *the BMJ Global Health*. She has presented her work at over 20 conferences in 14 countries, and served as reviewer for top journals such as *The Lancet*. She was invited to present her findings in the international media, ranging from *the BBC World Services Radio* to a Dutch Podcast for general practitioners. More importantly, her findings were discussed with relevant stakeholders such as the Kyrgyz Minister of Health, the World Bank, and the Clean Cooking Alliance, resulting in hands-on improvements in practice.

Teaching remained an important theme; she co-developed the half minor Global Health Cuba (nominated best half minor 2019), to teach medical students at the Leiden University qualitative research skills in Havana, enabling them to learn from the celebrated Cuban primary care system. She also co-facilitated research courses with the International Primary Care Respiratory Group in Sri Lanka, Romania, and digitally.

Clinically she worked as a medical doctor in a refugee camp in Samos, Greece (Jan/Feb 2017), followed by working in the emergency room of the Flevoziekenhuis, the Netherlands (2020). In 2021 she started the general practitioner training in Leiden, continuing her research concurrently. Throughout her work, she has recognised the need for urgent targeting of the climate crisis as a health crisis, and to mitigate the healthcare sector's contributions to this crisis. This shaped her further career.

She acquired grants for integrating Planetary Health into medical curricula, for supervision of a PhD student (SBOH; lead & Ministry of Health; lead), and for mapping of the ecological impact of certain patient trajectories (ZonMw; co-lead). She co-founded and contributed to several Green Teams and committees before co-founding and chairing the Green Care Alliance (Groene Zorg Alliantie). This alliance unites 30 green committees and over 120 teams across the healthcare sector to catalyse the transition to sustainable healthcare. For these efforts, the alliance won the Best Green Care Idea (Ministry of Health, 2021), and Evelyn was appointed 'Young Talent' by the Dutch *Financieele Dagblad*. She was a panel member of the Dutch launch of *the Lancet Countdown on Health and Climate Change*, and is a regular invited speaker on (inter) national webinars and in the media, such as *Radio 1*, the newspaper *Trouw*, the popular magazine *Libelle*, and the *NOS* 8 o'clock news.

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IPCRG; I am proud of our culture and how we collaborate globally for respiratory health through primary care (and of our dancing!)

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