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1 **Implementing lung health interventions in low- and middle-income countries – a FRESH AIR**
2 **systematic review and meta-synthesis**

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

1 **Abstract**

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

7 This systematic review followed Cochrane methodology and PRISMA reporting standards. We
8 searched eight databases without date- or language restrictions in July 2019, and included all relevant
9 original, peer-reviewed articles. Two researchers independently selected articles, critically appraised
10 them (using CASP/MetaQAT), extracted data, coded factors (following CFIR), and assigned levels of
11 confidence in the factors (via GRADE-CERQual). We meta-synthesized levels of evidence of the
12 factors based on their frequency and the assigned level of confidence.
13 (PROSPERO:CRD42018088687)

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

20 To conclude, this study identified implementation factors for lung health interventions in LMICs,
21 weighted their level of evidence, and integrated the results into an implementation tool for practice.
22 Policymakers, non-governmental organizations, practitioners, and researchers may use this FRESH
23 AIR Implementation tool to develop evidence-based implementation strategies for related
24 interventions. This could increase interventions' implementation success, thereby optimising the use
25 of already-scarce resources and improving health outcomes.

26
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28

29 Trial Registration Number: The FRESH AIR study is registered under trial registration number:
30 NTR5759. <http://www.trialregister.nl/trialreg/admin/rctsearch.asp?Term=23332>
31

32 Author's contributions: EB was lead researcher; EB & DV designed the study and developed the
33 protocol, including the search (helped by those acknowledged). They performed the screening
34 process, data extraction and analysis under supervision of RvdK and NC. EB wrote the manuscript,
35 RvdK reviewed it at each stage. HP & DV provided input throughout the process. All others reviewed
36 the manuscript and helped translating the findings to meaningful practical recommendations. All
37 authors approved the final version.
38

39 Data sharing: All data and meta-data can be shared upon reasonable request. This includes the study
40 protocol, meeting minutes describing considerations for data analysis. Within reasonable time after
41 email request data will be shared via a secure webbased system.
42

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46

1 Introduction

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

12 However, implementation – the act of carrying an intervention into effect[26] – is complex. Throughout
13 the entire implementation process, from the dissemination of an intervention to its sustained use,[27]
14 numerous factors determine success or failure. These implementation factors are often interacting
15 and influential at multiple levels. To better understand the factors so that they can be adequately
16 addressed in implementation strategies, factors can be pragmatically structured. The Consolidated
17 Framework for Implementation Research (CFIR) integrated 42 implementation factors from existing
18 implementation theories,[18] and categorised them in five domains: 1) innovation characteristics (e.g.
19 the adaptability of an intervention); 2) outer setting (e.g. understanding the needs of local users); 3)
20 inner setting (e.g. resource availability); 4) characteristics of individuals (e.g. self-efficacy); and 5)
21 process (e.g. engagement of stakeholder). The importance of each factor depends on the context.[28,
22 29] Hence, implementation strategies are more successful when context-specific factors are known
23 and addressed.

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

32

33 Methods

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

40

41 All steps of the review process were performed by two researchers (EB & DV) independently. Results
42 were compared, and discrepancies solved through discussion. A third researcher (RvdK) was
43 consulted when consensus could not be reached. We systematically applied validated tools
44 throughout the entire process, to enhance the reproducibility and transparency of our outcomes
45 (Figure 1).

46 *Search strategy and selection criteria*

47 We developed the search strategy together with a certified medical librarian; it contained (synonyms
48 of) implementation, LMICs, and CRD or specific relevant interventions such as 'smoking cessation'
49 (Appendix 1). We focused on asthma and COPD as the most prevalent chronic lung diseases. In
50 PubMed, Embase, Global Health Database, Cochrane, PsycINFO, Emcare, Web of Science, and
51 CINAHL we searched without language restriction for articles published by Oct 23, 2017, and updated
52 our search on July 10, 2019. We included all relevant, original, peer-reviewed articles focusing on the
53 implementation of interventions targeting CRD in LMICs (as classified by the World Bank[42]). As
54 recommended for studying implementation, quantitative, qualitative, and mixed-method articles were
55 considered relevant.[26] Articles were excluded if they focused on legislation at a national

1 governmental level (e.g. implementation of tobacco taxes) or on hypothetical interventions (e.g.
2 theoretical willingness to adopt an intervention), if no factors were reported, or if no full text was
3 available after contacting the authors. Our orienting search resulted in a disproportionate number of
4 articles on the implementation of clean cooking interventions targeting household air pollution. To
5 avoid this specific intervention dominating all review findings, we decided to split our review into two
6 parts. This first review regards the implementation of all but clean cooking interventions, while the
7 second (to be published later) will be exclusively dedicated to those.
8 Full operationalisation of the search criteria is presented in Appendix 1. In addition, we manually
9 searched Google and Google Scholar for the full articles from identified conference abstracts and
10 study protocols, and screened all references from relevant reviews and the included articles.

11 *Critical appraisal*

12 To critically appraise the included articles on relevance, reliability (reporting quality), validity and
13 applicability, we used the validated Meta Quality Appraisal Tool (MetaQAT)[43] (Appendix 2), and as
14 recommended we embedded the Critical Appraisal Skills Programme (CASP) into it.[44] Results
15 served as input for the assessment of level of evidence of the identified factors (see data-analysis).

16 *Data extraction*

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

27 *Data analysis*

28 For our meta-synthesis (weighting of the factors) we used content analysis, in which all data are
29 categorised into themes and the frequencies of the themes are determined. Content analysis is
30 suitable for both qualitative and quantitative evidence.[45]
31 First, we categorised all identified implementation factors by deductive coding using the CFIR.[18] We
32 inductively added several codes to the CFIR (such as 'language' or 'role model') when our extracted
33 factors did not match existing codes (Appendix 3). Second, we used the Grading of
34 Recommendations Assessment, Development and Evaluation-Confidence in the Evidence from
35 Reviews of Qualitative research (GRADE-CERQual) tool to determine the level of confidence in the
36 importance of the coded factors. The GRADE-CERQual tool has four components (Figure 1), and the
37 results of the critical appraisal served as input for scoring those (e.g. a high MetaQAT score for
38 relevance translated into 'no to very minor concerns' in the GRADE-CERQual component
39 'relevance').[46] Third, each factor was awarded a maximum of four points per component per study
40 in which it appeared (four points for 'no to very minor concerns' regarding the component in that
41 specific study, three for 'minor concerns', two for 'moderate concerns', and one for 'substantial
42 concerns'). Hence, factors were awarded higher scores when they appeared in more studies (the
43 principle of content analysis), and when the components methodology, relevance and adequacy of
44 the study were appraised as high. The fourth GRADE-CERQual component 'coherence' was not
45 rated, because the number of studies in which the factor appeared already accounted for coherence.
46 To conclude, the higher a factor scored, the higher the level of evidence to regard it as an important
47 factor.

48 *Role of the funding source*

49 This study was funded by the EU Research and Innovation program Horizon2020 (Health, Medical
50 research and the challenge of ageing) under grant agreement no. 680997. The funders had no role in
51 study design, data collection, data analysis, data interpretation, or writing of the report. All authors had
52 full access to all the data and EB, DV, RvdK and NC, the guarantor, had the final responsibility for the
53 decision to submit the study for publication.

54 *Reflexivity*

55 Members of our research team came from diverse backgrounds (researchers and clinicians from
56 psychology and medicine, with work experience in high-income countries, LMICs, or both). In these
57 roles, we had experienced working conditions characterised by many of the factors we identified, such

1 as lack of resources and personnel. We recognised that we were potentially more receptive to factors
2 we had experienced ourselves, so adhered to our standardised extraction procedures.

3

4 **Results**

5 *Search results*

6 Our search resulted in 9111 unique articles. After full-text screening we included 37 articles derived
7 from 33 different studies (Figure 2, Table 1). One article was excluded from the analysis,[47] as its
8 factors were based on the exact same study data as another article which scored higher in the critical
9 appraisal.[48]

10 *Study characteristics*

11 The studies resulting from our search were conducted in 17 different LMICs across five geographical
12 regions: Latin-America (Brazil,[49-53] the Dominican Republic,[54] Mexico,[55] Surinam[56]), Africa
13 (Malawi,[57] South-Africa[58-60]), the Middle East (Lebanon[61], Syria[62]), Asia (China,[63-67]
14 India,[47, 48, 68-73] Indonesia,[71, 74] Malaysia,[75] Nepal,[76, 77] Pakistan,[78] Russia,[79]
15 Thailand[80-82]), and Oceania (Fiji[83]) (Table 1, Figure 3). Most studies were based in healthcare
16 settings (n=17; primary care (n=9), secondary care (n=5), primary/secondary care combined (n=3)),
17 followed by schools (n=13), and the community (n=6). The majority of the study interventions focused
18 on tobacco (n=27; cessation (n=10), prevention (n=8), both (n=2) and control (i.e. smoking-free
19 setting) (n=7)). Three studies focused on interventions to improve the implementation of guidelines.
20 One study focused on quality improvement of COPD management, one on delivery of integrated
21 asthma/COPD care, and one on the adaptation of post-partum rituals using biomass smoke to
22 'protect' newborns. Three articles used quantitative methods for determining implementation factors,
23 31 used qualitative methods, and two used both.

24 *Critical appraisal of the studies*

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

32 *Implementation factors*

33 Forty-five implementation factors were identified, with a large variation in factors' levels of evidence
34 (Appendix 5). The factors with the highest level of evidence are described in further detail below,
35 these belonged to CFIR domains *Process*, *Inner setting*, and *Outer settings* (Figure 5). A full overview
36 of all weighted factors, their definitions, and illustrations of how they occurred in the included studies
37 is detailed in Appendix 6.

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

51 *Compatibility* was another factor with a high level of evidence, coded 48 times across 23 articles.
52 Categorised in the subdomain *Implementation Climate* (domain *Inner setting*), compatibility is defined
53 as the degree of fit between meaning and values attached to the innovation and of the involved
54 individuals, and how the innovation fits with existing workflows and systems.[18] Implementation
55 success was often attributed to embedding interventions into local, existing infrastructures (e.g. the

1 primary care infrastructure), carried out by people in already established networks (e.g. community
2 health workers), and when aligned with local cultural values. This can, for example, be achieved in
3 highly participant-centred interventions. “Perhaps the most important lesson was eventually letting go
4 of some of our own techniques and agendas and allowing an indigenous culture to develop their own
5 program.” The local participants developed their own programme and implementation strategy,
6 aligned with their local context, and hence, implementation was highly successful.[83]

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

18 Another notable factor was understanding and accurately prioritising on the *Needs of local users*
19 (*Outer setting*). For example, deliverers in one study realised that Chinese parents did not necessarily
20 feel a need for smoking cessation. They also recognised the parents’ need for connecting with their
21 child (and children had a unique position in the Chinese one-child families). Deliverers then educated
22 the children on smoking and cessation, which eventually helped to motivate their parents to quit.[64]
23 Level of evidence was also high for *Cosmopolitanism* (networks of the organization with external
24 organizations; *Outer setting*) and *Networks and Communications* (*Inner setting*).





































25 Notably, all factors appeared strongly interrelated; e.g. engaged stakeholders provided adequate
26 knowledge about the needs of those served by the organization, which improved compatibility, which
27 in turn increased the perceived advantage of the intervention, etc. Also, when comparing the
28 implementation factors and their level of evidence across the geographical regions, findings were
29 highly similar.¹ Only for China, factors related to the *Outer setting* (e.g. *External policies and*
30 *incentives*) were reported less frequently compared to the other regions.





























31 To facilitate future implementors in the translation of the comprehensive overview of all factors to
32 practice, we summarised the factors in a practical, simplified, and manageable implementation tool
33 (Figure 5 and Appendix 7). The tool contains factors prioritised by their level of evidence, and
34 illustrates those factors with examples of how to address them.
35

¹ 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.

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	 1			
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	 1			
Assanang-kornchai, 2014	Qualitative (action research)	Thailand	Primary healthcare setting; healthcare workers (nurses, administrators, directors)	Tobacco, alcohol, and substance use screening and brief intervention	 1			
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	1    
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	1    
Chatterjee, 2017	Qualitative	India	Rural villages; community members (programme managers, coordinators, health workers and stakeholders at village level)	Tobacco-free village	1    
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	1    
Elsay, 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	1    
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	1    
Groth-Marnat, 1996	Qualitative	Fiji	Traditional village; community members	Tobacco cessation	1    
Ishaak, 2014	Mixed-method, factors derived from qualitative data	Suriname	Urban junior high school; management and teachers	Tobacco and other drug prevention	1    
Khan, 2019	Mixed-method, embedded in RCT, factors derived from qualitative data	Pakistan	30 Primary and secondary level public healthcare facilities; care providers (15	Integrated COPD/asthma care	1    

			received intervention, interviews in 4 of the centres)		
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	1    
Marsiglia, 2014	Qualitative for the factors reported, within a quantitative study	Mexico	Urban public middle schools; teachers	Tobacco and other substance use prevention	1    
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	1    
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)	1    

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	 1
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	 1
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	 1
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	 1
Persai, 2015	Qualitative	India	At district level; senior district officials	Tobacco control	 1
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	 1

				(Furthermore, interventions on governmental level, n.a. to our study)	
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	 1
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	 1
Vitavasiri, 2010	Quantitative questionnaire	Thailand	676 Thai hospitals; personnel	Smoke-free hospitals	 1
Wang, 2008	Qualitative	China	County-level hospitals; health professionals, hospital president, director of preventive health, representatives of the hospitals	Smoke-free hospitals	 1
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	 1
Ziedonis, 2012	Qualitative	China	Hospital-based mental health centre; personnel and patients	Smoke-free hospitals	 1

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. *¹Findings 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.

1 Discussion:

2 *Main results*

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

11 *Strengths and limitations*

12 To the best of our knowledge, this systematic review is the first to focus on factors critical to the
13 implementation of diverse CRD-interventions. It focused on LMICs, precisely where the burden of
14 disease is highest, while evidence is fragmented and often poor for these settings. This review had a
15 rigorous design and conduct, following Cochrane methodology and PRISMA reporting standards.[39-
16 41] Every step was standardised and performed independently by two researchers. Validated tools
17 were applied at each stage,[18, 43, 44, 46] with a transparent description of their operationalisation.
18 Moreover, we adopted a comprehensive approach with an extensive search in eight databases with
19 no language/date restrictions. We synthesised real-world evidence from highly diverse settings and
20 countries in the included studies, resulting in a high generalisability of the findings to other
21 settings.[84] In fact, the LMICs in this review were broadly representative of the population distribution
22 across the worlds' continents, among others with many studies conducted in China and India.

23 However, several relevant types of interventions were underrepresented or even absent in the
24 implementation literature, such as patient education, self-management, or pulmonary rehabilitation.
25 Due to the small number of existing studies that focus on such interventions, we were unable to
26 assess whether their implementation factors meaningfully differed from tobacco-related interventions.
27 However, as the desired implementation behaviour is focussed on a similar health goal in similar
28 settings, we assume that there will be at least some overlap in implementation factors. Meanwhile, the
29 high representation of tobacco-related studies in literature remains welcome, with 80% of the world's
30 smokers living in LMICs.[85] As another limitation, we recognise along with other authors that
31 implementation studies are poorly indexed and we possibly missed relevant studies.[86] Yet, data
32 saturation was still achieved in the identified factors and the hierarchy of their level of evidence.
33 Notably, absence of evidence (factors not reported) should not be interpreted as evidence of absence
34 (factors not important);[45] we could only determine the level of confidence in the importance of
35 factors, for which we relied on the existing evidence.

36 *Comparison to previous literature*

37 Our findings partly overlap with implementation factors considered important for clean cooking
38 interventions as reported in two reviews.[87, 88] First, our factors 'Compatibility' and 'Understanding
39 local users' needs' correspond to 'user needs' (e.g. the ability of clean cookstoves to give the food the
40 right taste or save fuel). Second, our factors 'Engaging' and 'Access to knowledge and information'
41 correspond to 'community involvement' and 'user training'. The authors of these studies similarly
42 observed that barriers could turn into facilitators when these are adequately addressed and vice
43 versa. They also concluded that factors should be addressed simultaneously because they all
44 interrelate. The overlap between their findings and ours may not be surprising, as clean cooking
45 interventions similarly target CRD in LMICs. Possibly, this supports the assumption mentioned earlier
46 that implementation factors would not differ substantially for those chronic lung health interventions in
47 LMICs that have not yet been studied.

48 Implementation is a relatively unexplored topic in LMICs, and we predominantly relied on qualitative
49 articles. Qualitative studies allow for a deeper understanding of the *how, what and why* of
50 implementation processes.[89] As opposed to in quantitative studies, the concept 'high level of
51 evidence' cannot be quantified or tested on significance in qualitative studies. Therefore, a
52 combination of qualitative with quantitative (mixed-method) evidence would be highly welcome; such
53 studies are still largely unavailable. The need for more high-quality implementation evidence for
54 LMICs has been highlighted repeatedly.[25, 34-37, 90] Systematic reviews are particularly scarce.

1 *Interpretation and implications for implementation initiatives*

2 Our findings could serve future implementation initiatives, especially those initiatives targeting CRD in
3 LMICs. To facilitate the design of effective implementation strategies for CRD-related interventions,
4 we have developed a comprehensive overview of all implementation factors, their level of evidence,
5 and examples of how they played a role in the included studies (Appendix 6). In addition, we
6 translated factors from the comprehensive overview into a more pragmatic and hands-on tool for
7 practice (Figure 5). Throughout the implementation process, implementors should address these
8 factors in their strategy, and should continuously monitor the effectiveness of their strategy to improve
9 it accordingly.[91]

10 Therefore, awareness of the implementation factors requires additional evidence on *how* to
11 adequately address them.[91, 92] A suggestion for how to address the critical factors ‘compatibility’
12 and ‘understanding of needs of local users’, is developing, testing, and disseminating “homegrown”
13 interventions.[93] This was done in another FRESH AIR study by conducting an initial explorative
14 mixed-method rapid assessment of the local context.[94] The results of this assessment informed
15 implementation strategies for improved cookstove interventions in Uganda, Vietnam and
16 Kyrgyzstan.[95] First, the context assessment revealed that communities and their health workers
17 poorly understood the risk of household air pollution and therefore felt no need for change. Hence, the
18 intervention was preceded by an awareness-raising programme. Second, the rapid assessment
19 helped to identify the relevant influential stakeholders in the settings (e.g. village leaders, district
20 health officers). These stakeholders were then involved in the design of the implementation strategy,
21 which ensured high compatibility of the strategy with the local reality, and engaged the stakeholders
22 (the third critical factor) for the subsequent delivery.[96]

23 A creative example of addressing the fourth critical factor, lack of access to knowledge and
24 information and skilled staff, could be introducing task-sharing between physician and non-physician
25 health workers. This proved to be effective in lowering blood pressure in LMICs.[97] The fifth critical
26 factor, resource availability, can be particularly challenging to address. One included study reported
27 that workshop facilitators overcame the barrier of transportation costs by ride-sharing and delivering
28 several sessions per visit to reduce the number of visits.[61] Reducing the impact of the lack of
29 resources generally requires innovative system strengthening.[16]
30 Overall, opinions on how to address implementation factors most effectively turned out to be highly
31 heterogeneous among experts:[98] additional how-to evidence is required.

32 *Implications for implementation research*

33 Studies that systematically evaluate approaches of how to address implementation factors are
34 needed to provide solid and detailed evidence for future initiatives. We are currently working on part
35 two of this review, which focuses on the implementation of clean cooking interventions. However, we
36 argue that future studies should also focus on topics beyond tobacco and clean cooking, such as
37 personalised asthma action plans or pulmonary rehabilitation.[85] The studies included in this review
38 consistently missed economic evaluations, so we recommend future studies to include those.[99]
39 Furthermore, results from the critical appraisal of the studies showed that research quality could
40 generally benefit from more standardised methods and more structured reporting of e.g. context
41 characteristics, implementation strategies, and their conduct. These and additional recommendations
42 are further outlined in an article on improving health-care provider practices for LMICs,[91] and in the
43 STandards for Reporting Implementation Studies.[86]

44 *Implications for practice*

45 Guiding implementation processes by evidence-informed implementation strategies could enhance
46 implementation success. Successful implementation can substantially increase interventions’
47 effectiveness.[17] This could, in turn, optimise the use of already-scarce resources and decrease the
48 high direct and indirect costs associated with CRD in LMICs.[100, 101] Above all, implementation
49 success could improve health outcomes.

50 *Conclusion*

51 In this study, we systematically searched the literature for factors critical to the successful
52 implementation of lung health interventions. We meta-synthesised the factors’ level of evidence and
53 developed an implementation tool for practice. Priority for future implementors should be to
54 understand needs of local users, ensure compatibility of the intervention with the local context,
55 engage influential stakeholders, facilitate adequate access to knowledge and information, and secure
56 sufficient resources. Use of the FRESH AIR Implementation Tool could facilitate policymakers, non-
57 governmental organizations, practitioners, researchers, and community members to design evidence-

1 based, tailored implementation strategies to enhance implementation success. This could hence
2 optimise the use of already scarce resources and, ultimately, improve health outcomes.

3

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1 **Figure 1. Tools used in each phase**

2 Meta-QAT = Meta Quality Appraisal Tool; CASP = Critical Appraisal Skills Programme; CFIR = Consolidated Framework for
3 Implementation Research; GRADE-CERQual = Grading of Recommendations Assessment, Development and Evaluation-
4 Confidence in the Evidence from Reviews of Qualitative research

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22 **Figure 2. Flow diagram of screening process**

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27 **Figure 3. Study settings and interventions**

28 Symbols with 2 colours indicate the study covered both interventions. Half a symbol means half of the study was conducted in
29 this setting, and the other half in another setting.

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34 **Figure 4. Full overview of implementation factors per domain, and the relative level of evidence for
35 the factor**

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40 **Figure 5. FRESH AIR Implementation Tool**

41 *These suggestions are based on the literature specific interventions targeting chronic respiratory disease in low-and middle-
42 income countries, and on additional, general implementation literature. See Appendix 7 for recommended use and details on
43 references.