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The efficacy of smoking cessation interventions in low- and middle-income countries: a systematic review and meta-analysis

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ABSTRACT

Aims To summarize evidence for the efficacy of smoking cessation interventions in low- and middle-income countries (LMICs). **Design** Systematic review and meta-analysis of randomized controlled trials. **Setting** LMICs as defined by the World Bank. **Participants** Adult current cigarette smokers residing in LMICs. **Interventions** Behavioral and/or pharmacotherapy smoking cessation interventions. **Measurements** PubMed MEDLINE, EMBASE (embase.com), Cochrane Central Register of Controlled Trials (Wiley), PsycINFO (Ebsco), SciELO, WHO Global Index Medicus and Scopus were searched from inception to 4 April 2018. Only studies with at least 6 months of follow-up were included. We used the most rigorous assessment of abstinence reported by each study. Effect sizes were computed from abstracted data. Where possible, a meta-analysis was performed using Mantel–Haenzel random-effect models reporting odds ratios (OR) and 95% confidence intervals (CI). **Findings** Twenty-four randomized controlled trials were included. Six investigated the efficacy of pharmacological agents. Four trials that compared nicotine replacement therapy (NRT) to placebo found NRT improved cessation rates (n : NRT 546, control 684, OR = 1.76, 95% CI = 1.30–2.77, $P < 0.001$, $I^2 = 13\%$). Eight trials found that behavioral counseling was more effective than minimal interventions (e.g. brief advice); n : Counseling 2941, control 2794, OR = 6.87, 95% CI = 4.18–11.29, $P < 0.001$, $I^2 = 67\%$). There was also evidence of the benefit of brief advice over usual care (n : Brief advice 373, control 355, OR = 2.46, 95% CI = 1.56–3.88, $P < 0.001$, $I^2 = 0\%$). **Conclusion** Nicotine replacement therapy, behavioral counseling and brief advice appear to be effective in aiding smoking cessation in low- and middle-income countries. There is limited rigorous research on other smoking cessation interventions in these regions.

Keywords Developing countries, low- and middle-income countries, meta-analysis, smoking cessation, systematic review, tobacco use.

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INTRODUCTION

In 2015, 6.4 million deaths were attributable to cigarette smoking [1], making it the leading cause of preventable death globally [2–4]. Approximately 80% of the world's 1 billion smokers reside in low- and middle-income countries (LMICs) [5]. It is projected that, if this trend continues, by the year 2030 70% of the estimated 10 million smoking-related deaths will occur in LMICs [5].

The scale-up of tobacco control, occasioned by the 2003 World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) [6] and 2008 MPOWER initiatives [7], has resulted in significant reductions in global smoking prevalence during the past decade [1]. Article 14 of the FCTC stipulates that member nations develop evidence-based guidelines and provide treatment to help current smokers to quit [6]. To kick-start treatment for smoking cessation, LMICs are adopting and adapting

therapies recommended in high-income countries [8–10]. Our inability to predict the efficacy of these interventions in the diverse cultural, clinical and economic settings of LMICs has prompted local research in these regions [9,11]. While studies of LMICs populations were included in recent systematic reviews [12,13], they constitute only a small fraction of included studies. The rising prevalence of smoking in LMICs and the unique challenges of implementing smoking cessation in these regions mandate a specific focus on the efficacy of interventions for smoking cessation in LMICs in order to guide smoking cessation treatment efforts in these regions. Our aim was to conduct a systematic review and meta-analysis of randomized controlled trials evaluating recommended smoking cessation interventions (in high-income countries) that were carried out in LMICs.

METHODS

This systematic review is reported using the Preferred Reporting Items for Systematic Reviews (PRISMA) [14] (Fig. 1). The protocol for the systematic review is registered in PROSPERO (CRD42017067114).

Search strategy

Searches were conducted in PubMed MEDLINE, EMBASE (embase.com), Cochrane Central Register of Controlled Trials (Wiley), PsycINFO (Ebsco), SciELO, WHO Global Index Medicus and Scopus from inception to 4 April 2018, using search strategies that were collaboratively developed by the first author (M.O.A.) and librarian (L.C.O'D.). The search utilized randomized controlled trial (RCT) filters to identify

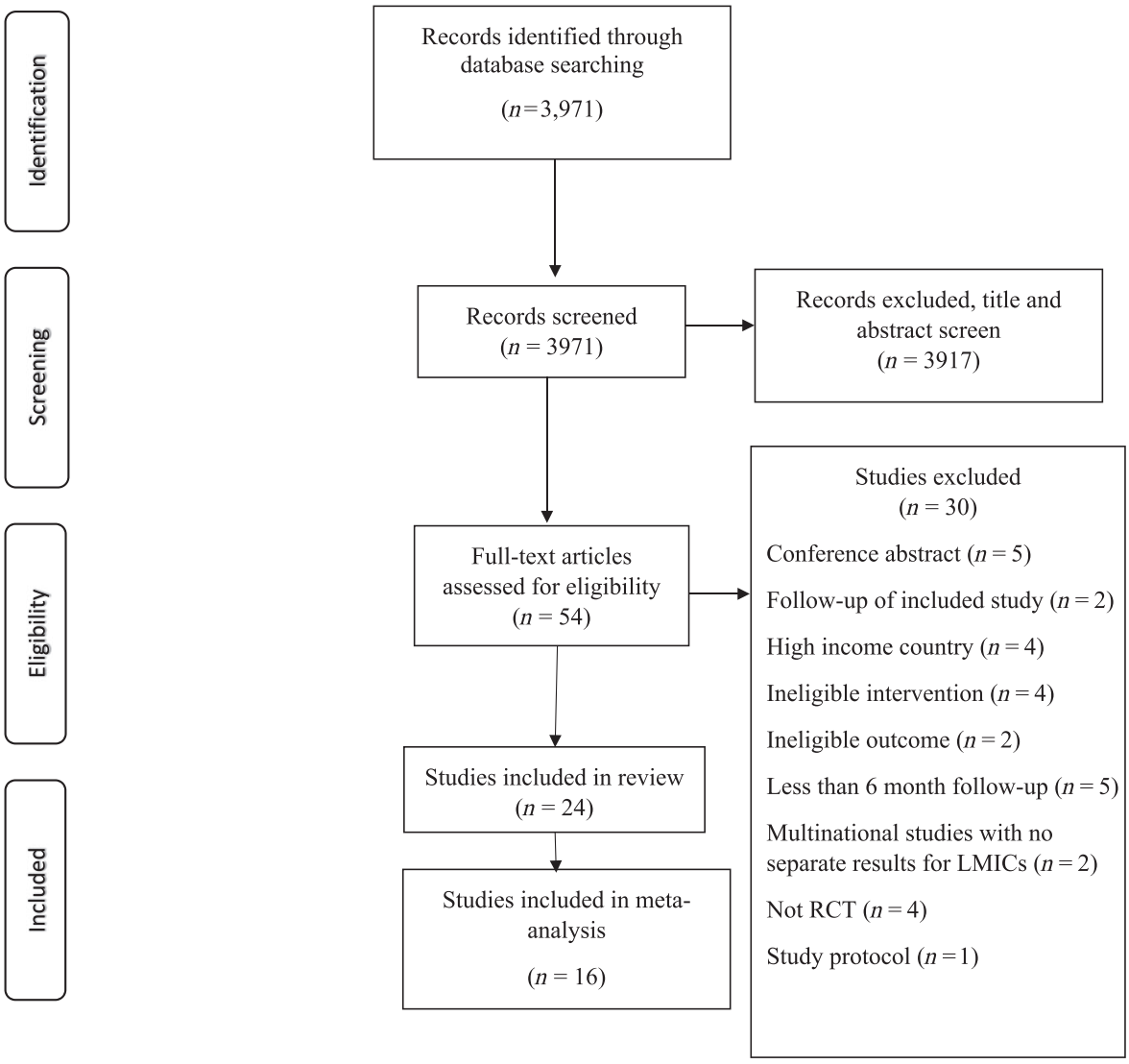

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) flow diagram of study selection

titles on smoking cessation in LMICs. Search terms included 'smoke', 'smoking', 'smoking cessation', 'tobacco', 'tobacco use', 'tobacco products', 'tobacco use cessation products' and term variants, in combination with countries identified as LMICs if the per-capita gross national income was below $12 235, based on the most recent World Bank classification [15]. The full list of search strategies is available in Supporting information, S1.

Inclusion and exclusion criteria

We included RCTs of individual-level smoking cessation interventions recommended by national guidelines [16,17]. Recommended interventions fell into two groups: (1) pharmacotherapy; and (2) behavioral interventions (brief advice, behavioral counseling, tailored self-help materials). First-line pharmacotherapies are nicotine replacement therapies (NRT), bupropion and varenicline. Some national guidelines recommend nortriptyline or clonidine [16]. A combination of behavioral intervention and pharmacotherapy is also recommended. Although delivery of smoking cessation interventions by mobile phones are yet to be recommended, we included mobile phone interventions because of their potential to improve access to smoking cessation services in LMICs [18]. Comparators included usual care, placebo or a less intense smoking cessation intervention(s). Study participants were adult current cigarette smokers residing in LMICs. Studies were required to have at least 6 months' follow-up from the start of the intervention until outcome assessment. We excluded policy-level interventions, mass media campaigns or interventions targeting someone other than the smoker.

Outcome measure

Our primary outcome of interest was abstinence ≥ 6 months after starting the intervention, preferably continuous abstinence with biochemical verification in an intent-to-treat (ITT) sample (i.e. non-responders were coded as smoking). If a self-reported abstinence outcome was available for a later time-point than the bioverified outcome, we nonetheless used the shorter duration (that was still ≥ 6 months) with the bioverified outcome. In the absence of a bioverified outcome, the longest duration of self-reported abstinence was used. If the authors only reported a 'responders' analysis (i.e. outcomes limited to those who completed treatment and/or provided follow-up data), we calculated the ITT abstinence rates based on the proportion confirmed abstinent out of the baseline randomized sample, wherein non-responders were coded as smoking.

Data collection and processing

Search results were saved into Endnote files by the librarian (L.C.O'D). All Endnote files were collated and transferred into Covidence [19] for subsequent processing. Two reviewers (M.O.A. and A.J.C.) independently reviewed the titles and abstracts. A third reviewer (C.A.) resolved conflicts. Extraction of data from included studies was carried out independently by M.O.A. and A.J.C. using a data extraction template designed by the investigators. Information extracted included: study identification, year of publication, country, study sample, type of study, setting, number of participants, intervention type and delivery method, abstinence verification method and the most stringent quit rates reported for each treatment arm.

Methodical quality assessment

The quality of included studies was assessed using the Cochrane quality of study and risk of bias assessment tool [20]. The Cochrane risk of bias tool assesses the quality of studies across seven domains: random sequence generation, blinding of study participants and key personnel, blinding of outcome assessment, selective outcome reporting, allocation concealment, incomplete outcome data and presence of bias from other sources [20]. In each of these domains, each study was assessed as low, high or unclear risk. Two investigators (M.O.A. and A.J.C.) independently assessed the quality of included studies and discrepancies were resolved by consensus.

Statistical analysis

Meta-analysis was performed using the Review Manager version 5.3 software. The overall effect for each intervention on smoking abstinence at 6 months (or longer) post-initiation of intervention was presented as a pooled odds ratio (OR) and 95% confidence interval (CI). We used the Mantel–Haenzel random-effect models for our analyses. Statistical heterogeneity was assessed using the Higgins I^2 [21]. Evaluation for bias using a forest plot was not completed because it is not recommended if fewer than 10 studies are included in a meta-analysis due to low power. Interventions for which only one study was available, or those for which more than one study was available but used different methodologies and so could not be combined in a meta-analysis, were presented as a narrative synthesis.

RESULTS

The electronic search retrieved 4812 titles (PubMed 2056, Embase 298, CENTRAL 386, PsycINFO 279, Scopus 1500, WHO Global Index Medicus 8 and SciELO 255). After removal of duplicates, there were 3971 titles. Figure 1 shows the selection process of included studies. Full-text screening was carried out on 54 articles, from which 30 studies were excluded. The list of excluded studies and reasons for

exclusion is shown in Supporting information, S2. Twenty-four studies are included in this review [22–46].

Characteristics of the included studies are presented in Table 1. The studies included a total of 13 141 participants from 11 countries. Seven studies (29%) were carried out in China [27,29,35,36,38,44,45], three (13%) each in India [39,42,46], Brazil [30,32,40] and Iran [22,26,33], two (8%) each in Malaysia [28,31] and South Africa [24,37] and one (4%) each in Pakistan [41], Syria [43], Thailand [23] and Turkey [34]. Four studies recruited participants from the community, one from a prison, and the remaining 19 recruited participants from medical clinics.

Efficacy of smoking cessation interventions

Pharmacotherapy

Pharmacological agents investigated were NRT [23–25,33,43], bupropion [32,41], varenicline [33], nortriptyline [32], naltrexone [25] and clonidine [25].

Four studies investigated the efficacy of NRT. NRT was administered as a patch [24,33,43] or gum [23]. All studies reported biochemically verified smoking abstinence at 6 months from the start of the intervention to confirm point prevalence [23,43] or continuous abstinence from weeks 2 to 24 [33] or from weeks 9 to 24 [24]. Pooled analysis of NRT versus placebo or brief advice favored NRT (Fig. 2).

Two studies investigated the efficacy of bupropion [32,41]. Counseling was provided in all study arms. The primary outcome in both studies was continuous abstinence, defined as abstinence at the 1st and the 6th month [41] or the 3rd and 6th month [32], with biochemical confirmation at both time-points. While Haagstram and colleagues [32] reported that bupropion increased rates of smoking abstinence compared to placebo, the study by Siddiqi [41] did not find a significant difference in smoking abstinence between intervention and control groups. A pooled analysis of these studies did not find bupropion to be superior to placebo or usual care (Fig. 2). Heterogeneity in the pooled analysis may be explained by differences in study design and study population. For example, Siddiqi *et al.* performed a cluster RCT that included hookah users, and observed differences in the efficacy of their intervention in different clusters which they ascribed to possible differences in counseling.

Other studies of pharmacological agents included a study with three arms, by Ahmadi and colleagues [25], that compared NRT to naltrexone or clonidine. Abstinence was highest in the NRT arm and lowest in the naltrexone arm. One study each compared varenicline to brief advice [33] or nortriptyline to placebo [32]. Varenicline increased smoking abstinence when compared to brief advice, but smoking abstinence from nortriptyline was similar to placebo. We had inadequate data for meta-analysis for varenicline, nortriptyline, naltrexone and clonidine.

Behavioral counseling

Eight studies evaluated the efficacy of individual or group behavioral counseling compared to brief advice or usual care. All interventions included face-to-face counseling at baseline, with duration ranging from 5 [36] to 60 minutes [34]. Duration of baseline counseling was not reported in two studies [39,45]. Six of the eight studies provided follow-up counseling through phone calls [29,30] or face-to-face interactions [34,36,42,45]. All but two studies [34,42] reported biochemical confirmation of smoking abstinence. Follow-up duration for all studies was for 6 months except for Lou [36], with a follow-up duration of 4 years. The pooled analysis favored counseling over minimal intervention such as brief advice or usual care (Fig. 2).

Three studies compared 'high-intensity counseling' to 'low-intensity counseling', and two of the three reported higher abstinence rates in the high-intensity group. Blebil [28] evaluated the effect of adding four follow-up telephone calls in the first month compared to baseline counseling with two brief follow-up calls after 2 and 3 months. They reported that the additional telephone calls increased continuous abstinence at 6 months. Among patients with acute coronary syndrome, '5As + 5Rs' (5As = Ask, Advise, Assess, Assist, Arrange; 5Rs = Relevance, Risks, Rewards, Roadblocks and Repetition [47]) counseling was more effective than 5Rs alone in achieving continuous abstinence [38]. In Brazil, De Azevedo [30] found similar abstinence rates among participants randomized to receive either 30 minutes of counseling at baseline plus seven booster sessions via telephone or 15 minutes of counseling at baseline with no follow-up. Due to the heterogeneity of interventions tested, a pooled analysis was not completed.

Pharmacotherapy plus counseling

Three studies evaluated the efficacy of combined pharmacotherapy and behavioral counseling. Interventions evaluated included: counseling plus bupropion versus usual care [26,41], counseling plus bupropion versus counseling only [41], counseling plus bupropion versus brief advice [26] and graded duration of counseling combined with different doses of NRT [40]. The outcome was assessed at 6 months with biological verification in two of the studies [26,41], while for the third study, the outcome was assessed at 1 year by self-reported 7-day point prevalence abstinence [40]. We pooled results of the two studies that compared bupropion plus counseling to usual care, and the result favored the combination over usual care (Table S2). Counseling plus bupropion was more effective than brief advice [26], but was not superior to counseling alone [41]. Lastly, a dose–response pattern was observed between doses of NRT plus duration of counseling [40].

Table 1 Summary of included studies.

Author, year, country	*Sample size*	*Population/setting*	*Counseling*	*Medication*	*Intervention delivery method*	*Outcome measure*	*Abstinence rates (ITT)*
Pharmacotherapy							
Ahmadi, 2003, Iran [25]	171	17–64 y/o males, ≥ 10 CPD, treatment seeking, out-patient medical center patients	None	24 weeks of naltrexone (50 mg; *n* = 57), Clonidine (0.4 mg; *n* = 57), or NRT (2 mg gum; *n* = 57)	Outreach workers	Bioverified ('test verification') 24-week CA at 6 months	Naltrexone: 3/57, 5.3% Clonidine: 11/57, 19.3% NRT: 21/57, 36.8% $P < 0.05$
Areechon, 1988, Thailand [23]	199	< 60 y/o, ≥ 15 CPD, community sample	None	840 pieces (2–3 months) of NRT (2 mg gum; *n* = 98) or placebo (gum; *n* = 101)	Physician(s)	Bioverified (CO) PPA (for 83/93 ppts) at 6 months	NRT: 56/98, 57.1% Placebo: 37/101, 36.6% $P < 0.05$
Haggsträm, 2006, Brazil [32]	156	≥ 18 y/o, ≥ 10 pack-years, FTND ≥ 4, motivated to quit	9, 15-minute FTF CBT sessions (+ 2 by telephone) over 6 months	9 weeks of bupropion (150 mg *n* = 53) or nortriptyline (50 mg; *n* = 52), or placebo (*n* = 51)	1 physician	Bioverified (CO ≤ 10 p.p.m.) CA at 6 months	Bupropion: 22/53, 41.5% Notriptyline: 16/52, 30.8% Placebo: 11/51, 12.6% (Bup > plac, $p < 0.05$)
Heydari, 2012, Iran [33]	272	Tobacco cessation clinic patients	4, 5-minute standard SC sessions over 4 weeks	8 weeks of varenicline (1 mg; *n* = 89), NRT (15 mg patches; *n* = 92) or none (*n* = 91)	1 physician	Bioverified abstinence at 12 months	Varenicline: 29/89, 32.6% NRT: 23/92, 25.0% No medication: 6/91, 6.6% $P < 0.05$
Koegelenber, 2014, South Africa [24]	446	18–75 y/o, ≥ 10 CPD for ≥ 1 y, 7 health-center patients	7, 10-minute standard SC counseling sessions over 6 months	13 weeks of varenicline +14 weeks of NRT (15 mg patches; *n* = 222) or varenicline + placebo (patches; *n* = 224)	Unclear	Bioverified (CO ≤ 10 p.p.m.) 15-week CA at 24 weeks	Varenicline + NRT: 71/222, 32.0% Varenicline + placebo: 42/224, 18.8% $P < 0.05$
Ward, 2013, Syria [43]	269	18–65 y/o, ≥ 5 CPD for ≥ 1 y, primary care patients	3, 30-minute FTF sessions +5, 10-minute telephone sessions over 7 weeks	6 weeks of NRT (patches, dose per CPD; *n* = 134) or placebo (*n* = 135)	5 primary-care physicians	Bioverified (CO < 10 p.p.m.) 12-month CA at 12 months	NRT: 17/134, 12.7% Placebo: 16/135, 11.9% NS

(*Continues*)

Table 1. (Continued)

Author, year, country	*Sample size*	*Population/setting*	*Counseling*	*Medication*	*Intervention delivery method*	*Outcome measure*	*Abstinence rates (ITT)*
Counseling							
Blebil, 2014, Malaysia [28]	231	≥ 18 y/o, willing to quit, out-patient smoking cessation clinic patients	Extra counseling (+4, 10–15-minute telephone sessions; n = 120) or Standard counseling (6 FTF sessions +2 telephone over 2 months; n = 111)	2 weeks of NRT (gum)	Counselors who were experts in smoking cessation	Bioverified (CO < 7 p.p.m.) 4-week PPA at 6 months	Extra counseling: 86/120, 71.7% Standard counseling: 57/111, 48.6% $P < 0.05$
Chen, 2014, China [29]	190	≥ 18 y/o, ≥ 1 CPD for ≥ 100 days, SC medication-naive, COPD clinic patients or healthy community sample (separate analyses for COPD versus healthy sample)	Counseling (1, 20-minute individual FTF counseling session +9, 10-minute phone counseling; n = 94) or Advice to quit (n = 96)	None	Two doctors with experience in smoking cessation treatment	Bioverified (CO < 10 p.p.m.) 5-month CA at 6 months	Counseling: 22/94, 23.4% Advice: 10/96, 10.4% $P < 0.05$ Also sig. among COPD (40.5 versus 18.6%), not among healthy (9.5 versus 3.8%)
De Azevado, 2011, Brazil [30]	273	≥ 18 y/o, ≥ 1 CPD, public university hospital inpatients (consecutively admitted)	High intensity (30-minutes tailored SC counseling +7, 10-minute telephone calls over 6 months; n = 141) or Low-intensity (15 minutes standard SC counseling; n = 132)	None	Trained smoking cessation counselors (4 psychologists, 2 nurses, 1 occupational therapist)	Self-reported 7-day PPA at 6 months	High-intensity: 48/141, 34% Low-intensity: 45/132, 34% NS
Koyun, 2016, Turkey [34]	80	20–49 y/o females, ≥ 1 CPD, family health-center patients	Transtheoretical model counseling (5, 45–60-minute FTF sessions; n = 40) or interviews only (5, 15–20 minutes; n = 40)	None	Unclear	Self-reported PPA abstinence at 6 months	Transtheoretical: 9/40, 22.5% Control: 1/40, 2.5% $P < 0.05$
Lou, 2013, China [36]	†2735	≥ 35 y/o, ≥ 1 CPD with < 3 months abstinence in past 1 year, COPD diagnosis, health-care center patients (k = 14)	Brief counseling (5–8-minute sessions + weekly or monthly home visits; k = 7, n = 1423) or usual care (COPD treatment; k = 7, n = 1273)	None	136 general practitioners trained in SC counseling	Bioverified (CO ≤ 10 p.p.m.) 42-month CA at 48 months	Month 6: Counseling: 79/1444, 5.7% Usual care: 3/1291, 0.2% $P < 0.05$

(*Continues*)

Table 1. (Continued)

Author, year, country	*Sample size*	*Population/setting*	*Counseling*	*Medication*	*Intervention delivery method*	*Outcome measure*	*Abstinence rates (ITT)*
							Months 24–30: Counseling: 610/1444, 42.2% Usual care: 63/1291, 4.9% $P < 0.05$
Louwagie, 2014, South Africa [37]	†388	≥ 18 y/o, current smoking, new TB diagnosis with ≤ 1 month tx, TB clinic patients	Counseling (motivational interviewing, 1, 15–20-minute session; $n = 194$) or brief advice to quit ($n = 194$) and handout	None	Lay health care workers (at least 1 year experience)	Bioverified (CO ≤ 10 p.p.m.) 6-month CA at 6 months (verification only for 165 ppts)	Counseling: 24/194, 12.4% Advice: 11/194, 5.7% $P < 0.05$
Luo, 2017, China [38]	†319	18–80 y/o with ACS, ≥ 1 CPD for ≥ 6 months, not ready to quit, heart center in-patients	High-intensity counseling (5As + 5Rs; 1 in-hospital 30–45-minute session + 2 in-hospital 10–30-minute + 15 telephone f/u; $n = 160$) or low-intensity counseling (5Rs; 1 in-hospital 10–15 minutes + 6, 5–20-minute telephone f/u; $n = 160$)	Varenicline recommended but not provided per protocol	8 cardiologists	Bioverified (CO ≤ 10 p.p.m.) 16-week CA at 6 months	High-intensity: 38/159, 23.9% Low-intensity: 24/160, 15.0% $P < 0.05$
Naik 2014, India [39]	600	Males, current or occasional tobacco use, prisoners with ≥ 1 year left to serve	Counseling (motivational interviewing; $n = 300$) or control ($n = 300$)	None	Unclear	Bioverified (CO; cut-off not reported) abstinence at 6 months	Counseling: 48/300, 16.0% Control: 6/300, 2.0% $P < 0.05$
Thankappan, 2013, India [42]	224	≥ 18 y/o males with diabetes, smoked within past 1 month, diabetes clinic patients	Physician advice + counseling (5As + 5Rs; 3, 30-minute sessions over 3 months; $n = 112$) or physician advice + psychoeducation only ($n = 112$)	None	Physicians and diabetes educators	Self-reported 7-day PPA at 6 months	Counseling: 58/112, 51.8% Psychoeducation: 14/112, 12.5% $P < 0.05$

(*Continues*)

Table 1. (Continued)

Author, year, country	*Sample size*	*Population/setting*	*Counseling*	*Medication*	*Intervention delivery method*	*Outcome measure*	*Abstinence rates (ITT)*
Zheng, 2007, China [45]	225	≥ 18 y/o, ≥ 100 life-time cigarettes and current smoking, community sample	Group counseling (5 sessions over 3 weeks; n = 118) or brief advice (n = 107)	None	3 health education professionals	Bioverified (urine cotinine < 25 ng/ml) 6-month CA at 6 months	Counseling: 33/118, 28.0% Advice: 3/107, 2.8% $P < 0.05$
Combination of pharmacotherapy and pharmacotherapy + counseling							
Aryanpur, 2016, Iran [26]	183	≥ 18 y/o, newly diagnosed TB, health-center patients	Counseling (5As; 4 sessions over 2 weeks) or brief advice (4 sessions standard SC counseling) or usual care (TB treatment)	9 weeks of bupropion (n = 60) or no medication (n = 62) or usual care (TB treatment; n = 61)	6 trained physicians (1 per health center) delivered all interventions	Bioverified (CO < 7 p.p.m.) CA at 6 months	Counseling + bupropion: 43/60, 71.7% Advice: 21/62, 33.9% Usual care: 6/61, 9.8% $P < 0.05$
Otero, 2006, Brazil [40]	1199	19–59 y/o, > 5 CPD, motivated to quit, community sample	Brief 1, 20-minute group CBT session (a) or 1–2, 60-minute weekly group CBT sessions (b), or 3–4, 60-minute weekly group CBT sessions (c)	8 weeks of NRT (21 mg, 14 mg, or 7 mg patches per FTND score; brief n = 189; 1–2 n = 204; 3–4 n = 204) or none (brief n = 194; 1–2 n = 203; 3–4 n = 205)	Physicians, nurses and psychologists trained according to National Tobacco Control Program	Self-reported 7-day PPA at 12 months	With NRT: Brief: 57/189, 30.2% 1–2: 68/204, 33.3% 3–4: 68/204, 33.3% All $Ps < 0.05$ Without NRT: Brief: 39/194, 20.1% (ref. group) 1–2: 35/203, 17.2% 3–4: 48/205, 23.4% Both NS
Siddiqi, 2013, Pakistan [41]	†1947	≥ 18 y/o, ≥ 1 CPD, suspected TB, urban health-center patients (k = 33)	Behavioral counseling (5As, 30-minute PQ + 10-minute TQD) or usual care (self-help leaflet)	7 weeks of bupropion (150 mg; k = 11, n = 654) or none (k = 11, n = 639) or usual care (k = 11, n = 654)	Paramedics (+ physicians for medication)	Bioverified (CO ≤ 9 p.p.m.) 6-month CA at 6 months	Counseling + bupropion: 275/654, 42.0%, $P < 0.05$ Counseling: 254/639, 39.7%, $P < 0.05$ Usual care: 52/654, 8.0% (ref. group) (counseling + bupropion versus counseling, NS)

(***Continues***)

Table 1. (Continued)

Author, year, country	*Sample size*	*Population/setting*	*Counseling*	*Medication*	*Intervention delivery method*	*Outcome measure*	*Abstinence rates (ITT)*
Brief advice							
De Silva, 2016, Malaysia [31]	80	Males, current smoking, undergraduate students who the university medical clinic	Brief advice to quit (n = 40) or self-help materials (n = 40) to encourage referral to quitline	None	Health-care provider	Self-reported CA at 6 months	Brief advice: 6/40, 15% Self-help: 0/40, 0% (no statistics provided)
Goel, 2017, India [46]	152	≥ 15 y/o, current or occasional smoking, TB diagnosis, Designated Microscopy Centre patients	Brief advice to quit (5-minutes; n = 78) or usual care (TB treatment; n = 74)	None	Health-care workers	Self-reported 2-week CA at 6 months	Brief advice: 57/78, 73% Usual care: 42/74, 56.8%, $P < 0.05$
Lin, 2013, China [35]	126	Male smokers, out-patient medical clinics	Brief advice to quit (< 30 sec; n = 74) or usual care (n = 52)	None	Physicians (multiple fields) w/ <1 hour of training	Self-reported 6-month CA at 12 months	Brief advice: 13/74, 16.6% Usual care: 2/52, 3.8% NS
Wu 2017, China [44]	369	≥ 18 y/o, ≥ 10 CPD in past 1 month, not motivated to quit, out-patient endocrinology and acupuncture clinic patients	Brief advice to reduce/quit smoking (1, 1-minute FTF session +5, 1-minute telephone counseling over 12 months; n = 181) or brief advice to improve exercise and diet (n = 188)	None	Physicians and medical students	Bioverified (CO < 6 p.p.m.) CA at 12 months	SC advice: 26/181, 14.4% Exercise and diet advice: 13/188, 6.9% $P = 0.02$
Mobile phone intervention							
Augustson, 2016, China [27]	8000	Nokia cell phone users, community sample	6 weeks of high-frequency text messages (1–3×/day; n = 4000) or low-frequency (1×/week; n = 4000)	None	Text messages (adapted from NCI)	Self-reported 7-day PPA at 6 months	High-frequency: 1108/4000, 27.7% Low-frequency: 1109/4000, 27.7% NS

$P < 0.05$: significant differences between intervention and control group(s); NS = not significant. [†]Sample size adjusted for deaths. Outcome at month 6 except otherwise stated. ITT = intention to treat; k = clusters; y/o = years old; CPD = cigarettes per day; TB = tuberculosis; COPD = chronic obstructive pulmonary disease; PQ = pre-quit; TQD = target quit day; SC = smoking cessation; FTF = face-to-face; NRT = nicotine replacement therapy; CO = carbon monoxide; p.p.m. = parts per million; PPA = point prevalence abstinence; CA = continuous abstinence; NCI: National Cancer Institute; 5As = Ask, Advice, Assess, Assist, Arrange [61]; 5Rs = Relevance, Risk, Reward, Roadblocks, Repetition [61].

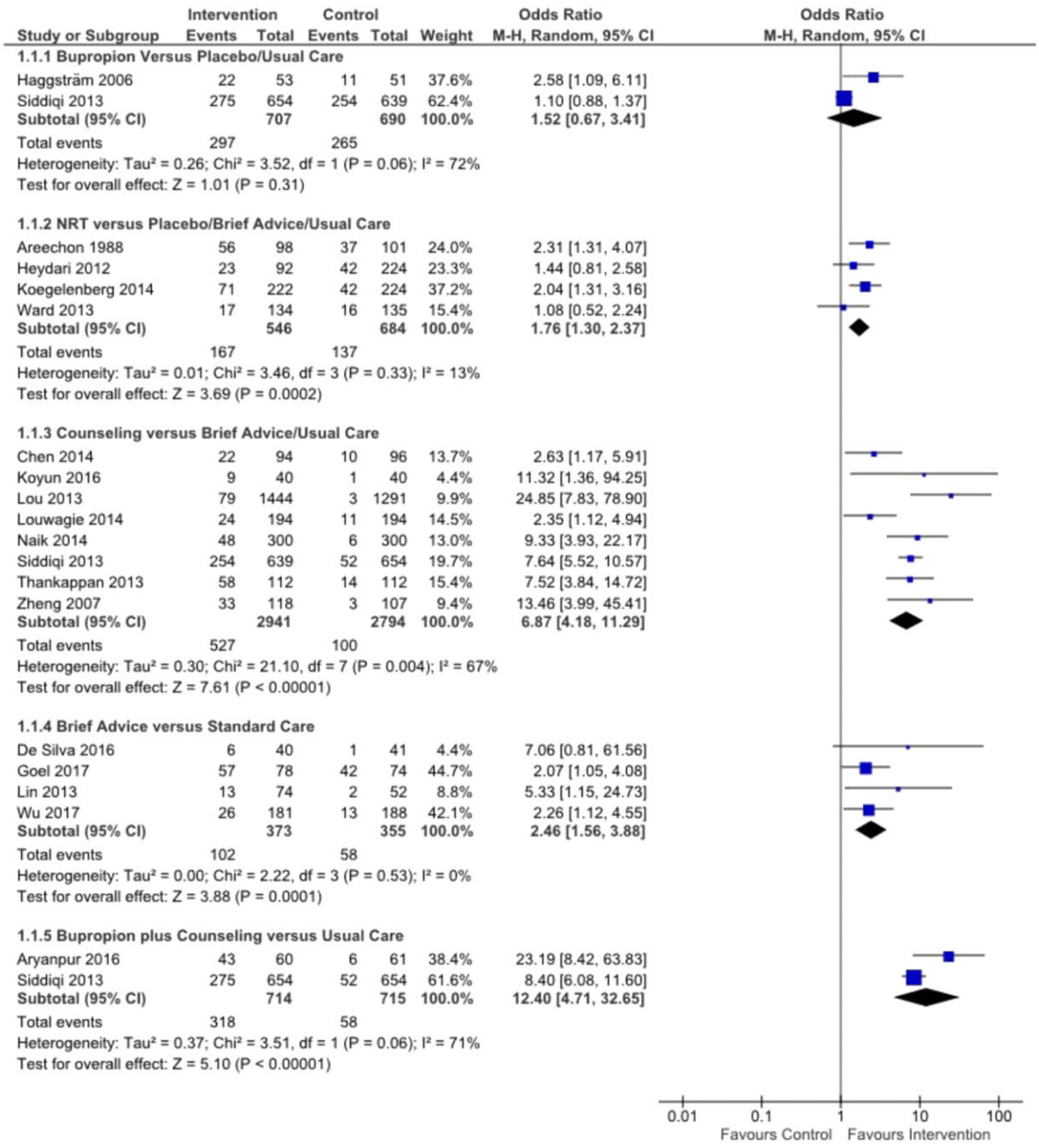

Figure 2 Forest plot of the comparison of randomized controlled trials of recommended smoking cessation intervention in low- and middle-income countries. Outcome: smoking abstinence at 6-month follow-up. Koegelenberg 2014 administered varenicline to both nicotine replacement therapy (NRT) and control groups. With the study excluded the NRT subtotal odds ratio (OR) = 1.59, 95% confidence interval (CI) = 1.04–2.44, I^2 = 29%, P = 0.03. [Colour figure can be viewed at wileyonlinelibrary.com]

Brief advice

Four studies compared brief advice to standard care or educational materials [31,35,44,46]. The duration of brief advice ranged from 30 sec [35] to 5 minutes [46]. Three studies evaluated brief advice in clinic populations during out-patient visits, while one identified smokers among otherwise healthy undergraduate students during routine pre-enrollment evaluation [31]. In all the trials, brief advice was provided by health-care providers. In addition to advice provided at baseline in all trials, Goel and colleagues provided additional brief advice at the 2nd and 5th month during the period of tuberculosis treatment [46]. Control interventions were standard care [35,46], a one-page leaflet on the risk of smoking and quitline access [31] and advice on nutrition and exercise, which is standard care for diabetic patients [44]. All studies assessed smoking abstinence at 6 months by self-report. Outcome measures were self-reported 1-week [35,44] or 2-week [31,46] abstinence. In addition, one study had a 1-year follow-up with

biochemical confirmation at this point [44]. The result of the pooled analysis of these four studies was in favor of brief advice over standard care or educational leaflet (Fig. 2).

Mobile phone intervention

We identified only one RCT of a mobile phone intervention which met our review criteria. It investigated the efficacy of a high- versus low-frequency text message intervention for smoking cessation among 1500 self-identified smokers recruited through text messages via their service provider [27]. The intervention lasted for 6 weeks, with a follow-up duration of 6 months. Study outcome was self-reported (via text message) 7-day smoking abstinence. At 6 months, the same proportion of participants (27.7%) self-reported abstinence in the intervention and control groups. Notably, the dropout rates were high in both arms of the study (high frequency 41.7%, low frequency 43.8%).

Quality of included studies

A summary of the risk of bias among all studies is shown in Figs 3 and 4.

Selection bias

All the included studies were randomized, and the majority of studies (16 of 24; 67%) reported the method of random sequence generation for participant randomization. A smaller number of studies (eight of 25; 32%) reported the method employed for allocation sequence concealment prior to participant enrollment, such as using sequentially numbered opaque envelopes [30,35,37,43,44], pulling numbers out of a box [45] or blinded treatment providers [38,40]. Only one study [42] explicitly reported that allocation sequence was not concealed, as participant folders were flagged with colored stickers.

Performance and detection bias

In the large majority of studies (18 of 24; 75%), blinding participants and/or personnel to study condition was challenging or impossible given that these studies included different counseling content, methodology or intensity. Three studies did not use a placebo control when evaluating pharmacological interventions [25,33,41]. The majority of studies (16 of 24; 67%) used biologically confirmed abstinence methods, although it is notable that some studies only biologically confirmed abstinence for a proportion of their responders [23,36,37] and some did not specify their method [23,25,39]; the remaining 36% relied solely upon self-report of abstinence [27,30,31,34,35,39,40,42,46].

Ten studies (42%) failed to indicate whether their outcome assessors were blinded to study condition [25,29,32–34,36,39–41,45], four studies (17%) reported that their assessors were not blinded to study condition [27,30,37,42] and the remaining 10 studies (42%) reported using blinded assessors [23,24,26,28,31,35,38,43,44,46].

Attrition and reporting bias

Reported attrition rates ranged from 0% [33] to 37.7% [24] for in-person treatments; Augustson [27] had higher rates of attrition (57.2%) for a mobile phone intervention. In three studies, attrition rates were significantly different between study arms [25,30,35]. In six studies, attrition was not reported [26,28–30,32,39]. Most often, study participants lost to follow-up were considered to be smokers (ITT), but five studies either did not specify [28,31] or did not report [30,36,42] ITT outcomes.

DISCUSSION

The purpose of this review was to evaluate the efficacy of recommended individual-level smoking cessation interventions in LMICs. This study is important, because the current evidence supporting the efficacy of smoking cessation interventions emanate from decades of research conducted in high-income countries. Differences in smoking behavior, cultural contexts, health-care access and health-care systems may influence the translation of these interventions to LMICs where smoking prevalence is rising

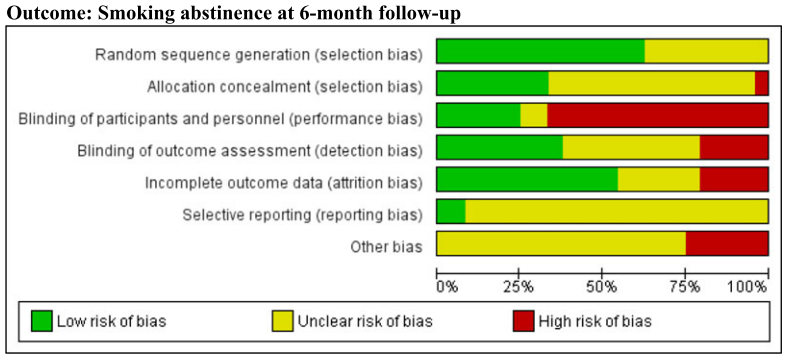

Figure 3 Risk of bias graph: summary of risk of bias across all studies. [Colour figure can be viewed at wileyonlinelibrary.com]

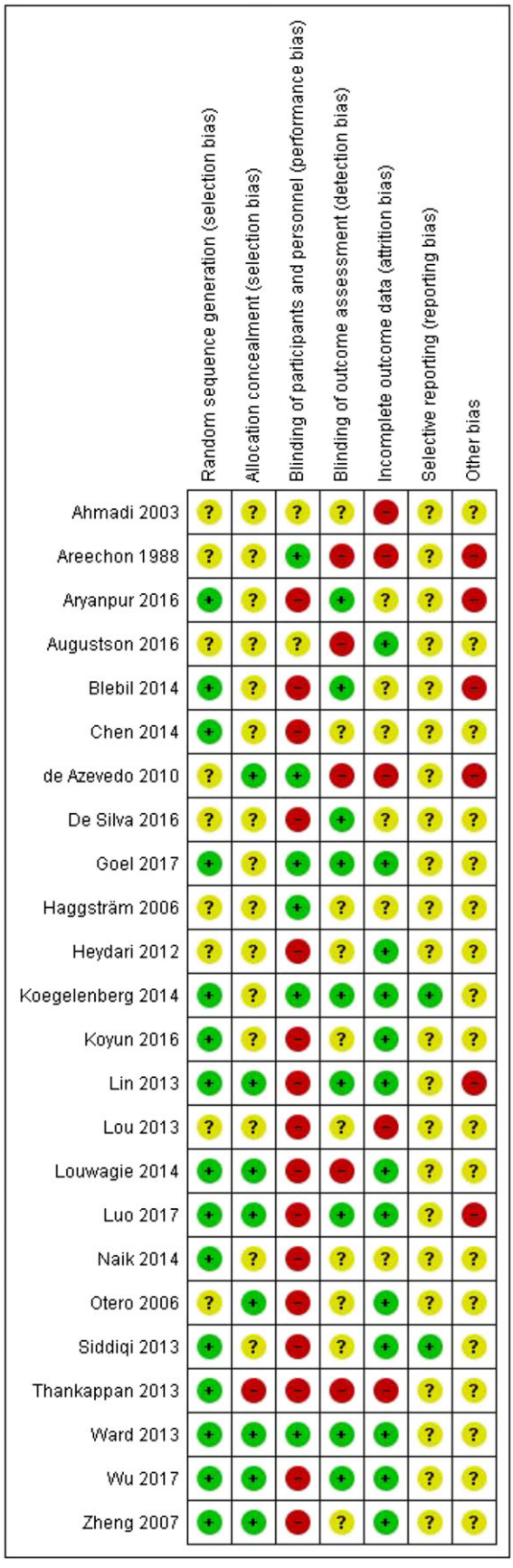

Figure 4 Risk of bias assessment of individual studies. [Colour figure can be viewed at wileyonlinelibrary.com]

[11]. Because of these concerns, smoking cessation research has been recognized as a priority in LMICs [11,18].

We identified 24 RCTs with a follow-up duration of at least 6 months that investigated recommended smoking cessation interventions. The majority of the published studies (76%) reported that the interventions for smoking cessation were efficacious. Results of our meta-analysis showed increased smoking abstinence with NRT compared to placebo/brief advice; counseling compared to usual care/brief advice; the combination of bupropion and counseling compared to usual care; and brief advice compared to usual care. Pooled analysis of two studies that compared bupropion to placebo or usual care, however, did not show that bupropion significantly improved smoking abstinence.

There are still relatively few RCTs of smoking cessation in LMICs compared to high-income countries. We identified five RCTs of NRT (patches, gum), which is one of the most widely studied pharmacotherapies for smoking cessation [12,13]. A recent systematic review of 136 trials of NRT compared to placebo with a follow-up duration of at least 6 months [13] found an effect size of 1.55 (95% CI = 1.49–1.61), similar to the present analysis (OR = 1.76, 95% CI = 1.30–2.37), suggesting that NRT may have similar efficacy irrespective of the country. The low cost and high availability of NRT in LMICs make NRT an ideal pharmacotherapy for smoking cessation compared to other smoking cessation medications [48]. Notably, NRT is the only first-line pharmacotherapy for smoking cessation on the World Health Organization essential drug list [49].

Previous studies have shown that bupropion is effective in aiding smoking cessation [12], and bupropion is widely used for the treatment of depression. We identified two RCTs and compared the efficacy of bupropion to placebo or usual care, with conflicting results. Both studies provided behavioral counseling to both study arms. Siddiqi [41], who found no overall benefit from bupropion, reported that the intervention effects varied across clusters within the study and opined that this may be due to differences in the implementation of the intervention. In addition, this study enrolled patients receiving treatment for tuberculosis. The high pill burden from anti-tuberculosis drugs and bupropion may reduce medication adherence, including bupropion. Nonetheless, in India, bupropion was reported as the most affordable pharmacotherapy for smoking cessation [50], suggesting that it may become a more affordable and more available option in other LMICs in the near future.

We found only one RCT that investigated the efficacy of varenicline for smoking cessation which found varenicline to be more effective than brief advice [33]. Varenicline is the most effective single pharmacological agent for smoking cessation [12]. However, varenicline is not readily available in most LMICs because of its high cost [48],

despite cost-effectiveness analyses in high-income countries suggesting that varenicline may be more cost-effective than NRT or bupropion due to its high efficacy [51–53].

Behavioral counseling was the most commonly investigated intervention. All identified studies reported that behavioral counseling was more effective than minimal contact control (brief advice, usual care or provision of self-help materials). This effect was found in spite of significant diversity, suggesting that it is robust. From our pooled analysis, the efficacy of counseling in LMICs was much higher than previously published [54]. The reason for this is unclear, and requires further evaluation. As expected, counseling plus pharmacotherapy was also more effective than minimal contact controls. One study compared different durations of counseling with or without NRT and suggested that counseling and NRT increased smoking cessation compared to counseling alone [40]. The few studies that investigated brief advice also suggested that it may be more effective than usual care or educational materials alone. In countries with very limited resources, adoption of brief advice as the minimum standard of care should be recommended. Overall, it would be useful to conduct further studies that utilize a standard behavioral counseling protocol (e.g. following the Public Health Service Guidelines) that would be applicable across different settings, countries and patient populations to determine the true effect of a behavioral intervention on smoking cessation in LMICs.

Mobile phone (m-Health) interventions for smoking cessation present unique opportunities that may be suitable for LMICs. The paucity of studies evaluating this intervention delivery method limits adequate assessment of their effectiveness in LMICs. The use of m-Health has the potential to significantly improve access to care and improve health outcomes in LMICs, given that access to mobile phones has increased significantly in LMICs in the last decade, reaching 70–90% of the population in some countries [55]. A recent Cochrane meta-analysis of 12 studies that evaluated m-Health interventions for smoking cessation reported greater quit rates in the intervention group [56]; however, all the included studies were from high-income countries.

Quitline access is one of the stipulations of the FCTC to help current smokers to quit [6]. None of the RCTs identified investigated the effect of quitlines on individual smoking cessation rates. Lin *et al.* [35], while evaluating the effect of very brief physician advice, provided quitline access to both study arms. Smoking cessation rates were similar in intervention arm and control arm. Quitlines are still not widely available in LMICs [48]. As countries in these regions strive to improve access to recommended services for smoking cessation, more countries may make quitlines available. It is important to investigate how best to increase utilization of quitlines to ensure their efficacy.

Our review provides a synthesis of the growing evidence on the effectiveness of smoking cessation interventions across all LMICs. This builds on existing systematic reviews in individual LMICs, notably China [57] and India [58]. To ensure high-quality evidence, unlike previous reviews we included only RCTs with at least 6 months of follow-up. We also focused on cigarette smokers (rather than bidis, smokeless tobacco, hookah, etc.), due to the urgent need to build evidence to support treatment guidelines in LMICs.

Our review had some limitations. Our conclusions on the effectiveness of interventions in this review are constrained by the quality of included studies. Many authors did not provide information on how the trials were protected against bias, as evidenced by the high frequency of 'unclear risk'. As most studies investigated behavioral interventions requiring behavioral interactions, blinding of participants or intervention providers was probably more challenging. In a large number of studies it was unclear if outcome assessors were blinded. Despite searching through relevant databases, we may have missed studies only available in grey literature or unpublished conference abstracts. We also did not contact authors of registered trials, so we may have missed out unpublished trial results. Lastly, due to the limited number of studies evaluating certain interventions (e.g. varenicline), more rigorous evidence using meta-analysis could not be completed for some interventions.

Despite these limitations, our findings have important implications for tobacco control in LMICs. Some interventions recommended in high-income countries are being adapted successfully in LMICs, and most trials suggest that they are effective. There has been concern about the adaptability and efficacy of these interventions in LMICs [10]. The feasibility of integrating smoking cessation interventions into existing health-care infrastructures was also demonstrated. NRT, which is widely available, was the most studied and was found to be effective in aiding smoking cessation. However, very few RCTs of other pharmacological agents and behavioral interventions for smoking cessation have been investigated in LMICs. Potentially low-cost pharmacological agents such as cytisine and nortriptyline [12,59] need to be evaluated in the LMICs. In addition, the widespread use of mobile phones in LMICs, which has facilitated development in various sectors, is yet to be fully exploited to aid smoking cessation.

In conclusion, approximately 80% of the current tobacco users reside in LMICs. Addressing tobacco use in these regions is critical in the global efforts to reduce harm from tobacco exposure. We found some evidence to support the efficacy of NRT and behavioral counseling interventions compared to brief advice or usual care. Limited

studies were available on other pharmacological agents or m-Health approaches for smoking cessation intervention in these regions. Continued research on novel, cost-effective and wide-reaching interventions are needed to treat the growing population of smokers and prevent the projected 1 billion tobacco-attributable deaths in this century [60].

Declaration of interests

B.H. has served on a scientific advisory board for Pfizer and receives varenicline and placebo free of charge from Pfizer for use in an ongoing National Cancer Institute-funded clinical trial. Other authors declare no competing interests.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1 Search strategy.
Table S2 Table of excluded studies and reasons for exclusion.

