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REVIEW ARTICLE

Smoking-Cessation Interventions in Appalachia: A Systematic Review and Meta-Analysis

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Context: Appalachia, a socioeconomically disadvantaged rural region in the eastern U.S., has one of the nation's highest prevalence rates of smoking and some of the poorest health outcomes. Effective interventions that lower smoking rates in Appalachia have great potential to reduce health disparities and preventable illness; however, a better understanding of effective interventions is needed.

Evidence acquisition: This review included trials that evaluated the impact of smoking-cessation programs among populations living in Appalachia. The search was carried out on October 9, 2018 and comprised the Cochrane Central Register of Controlled Trials, Medline, Embase, and Scopus for academic journal articles published in English, with no date restrictions. After preliminary screening, potentially relevant full-text articles were independently reviewed by the authors with a Cohen's κ of 0.72, leading to the final inclusion of 9 articles.

Evidence synthesis: Eligible studies were assessed qualitatively for heterogeneity and risk of bias. Six of the 9 included studies had extractable data related to dichotomous smoking status and reported a measure of association suitable for inclusion in a meta-analysis. For those 6 studies, the pooled RR and pooled OR were estimated using random effects models, with an I^2 index demonstrating substantial heterogeneity. A funnel plot of the 6 trials appeared relatively symmetric.

Conclusions: Participation in smoking-cessation interventions increased the probability of smoking abstinence among Appalachian smokers by an estimated 2.33 times (pooled RR=2.33, 95% CI=1.03, 5.25, p=0.04). Given the low number of studies, their substantial heterogeneity, and high risk of bias, the evidence of the effectiveness of smoking-cessation interventions in Appalachia must be interpreted with caution.

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CONTEXT

Smoking is widely recognized as the leading, yet preventable risk factor for the development of disease, as well as premature mortality in the U.S.[1] Owing to concerted public health campaigns and legislative efforts, smoking rates among adults have dropped from approximately 43% in the 1960s to 16% in 2016.[2] However, this tremendous success has not been distributed uniformly. Smoking rates have remained substantially higher in populations of lower socioeconomic status (SES), such as those with lower educational attainment and individuals living in poverty.[2] Appalachia is a heterogeneous and socioeconomically disadvantaged region in the eastern U.S. spanning several states. Although Appalachia includes large urban and suburban areas like Pittsburgh, PA, 42%

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of Appalachia's population are rural, compared with 20% nationally.[3] There is considerable economic heterogeneity within Appalachia, with poverty rates approaching 25% of the population in Central Appalachian counties, whereas counties in the metropolitan areas of Appalachia are close to the national average.[4] Appalachia has one of the highest prevalence rates of smoking in the U.S.[5] and some of the worst health outcomes in the U.S. as well, associated with a 2.4-year gap in life expectancy compared with the rest of the U.S.[6]

In national surveys, up to 69% of smokers are interested in quitting smoking, and 42% attempted to quit smoking in the previous year.[7] Yet, only 55% of these attempts lead to sustained abstinence.[7] Therefore, effective interventions that lower smoking rates in Appalachia have great potential to reduce health disparities and preventable illness in this socioeconomically disadvantaged population. Given the challenges of reducing smoking rates in populations of lower SES, a better understanding of effective interventions is needed. The aim of this systematic review is to collect and summarize the evidence on smoking-cessation programs specifically targeting individuals living in Appalachia and associated changes in (smoking-related) health outcomes.

EVIDENCE ACQUISITION

The methods described for this review were based on the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions.[8]

This review included studies published in English that evaluated the impact of smoking-cessation programs in populations living in Appalachia as defined by the Appalachia Regional Commission as belonging to this area.[3] According to this definition, Appalachia includes all of West Virginia and select rural counties in Alabama, Georgia, Kentucky, Maryland, Mississippi, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, and Virginia (Figure 1). A complete list of the counties comprising Appalachia can be found on the Appalachia Regional Commission's website.[9]

Studies that examined individuals in other states, as well as those belonging to the Appalachian region, were included only if the data were reported separately by region. Studies included all types of smoking-cessation interventions (i.e., programs that were administered in person or online) administered to any population (i.e., no restrictions by age, gender, or ethnicity of participants) in any setting (i.e., including community-based

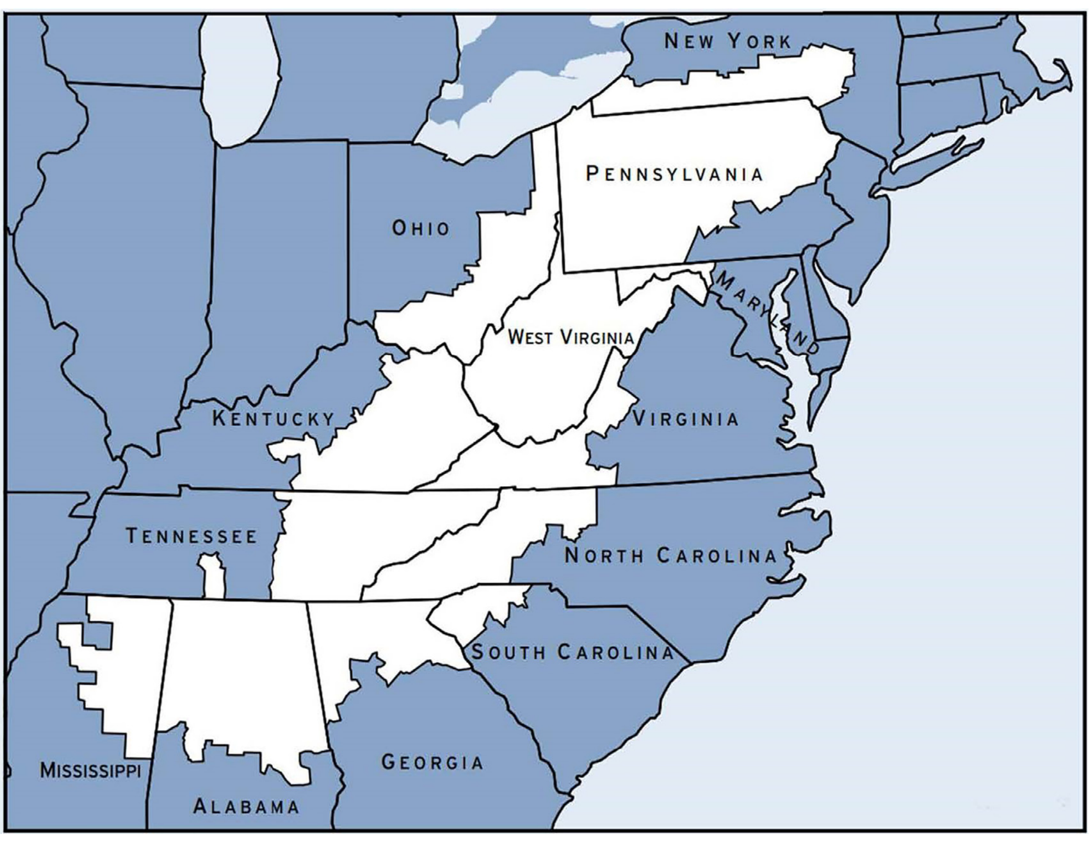

Figure 1. Map of the Appalachian region (as defined by the Appalachian Regional Commission[3]).

or hospital-based interventions). Appendix Table 1 provides more details on the eligibility criteria according to the Population, Intervention, Comparison, Outcome, and Study design/type (PICOS) framework. Both studies with smoking-cessation programs as the primary intervention of interest, as well as studies with smoking-cessation interventions as part of a package of health-related interventions, were included if smoking rates or a smoking-related health outcome were reported in the publication as primary or secondary outcomes. This review was limited to individual and cluster randomized interventions and excluded observational studies.

The search included the Cochrane Central Register of Controlled Trials (CENTRAL), as well as Medline (1966−2018), Embase (1980−2018), and Scopus (2004−2018), for academic journal articles published in English, from the start of each database to October 9, 2018 (i.e., no restrictions on publication dates), searching title, abstract, and MeSH Terms/author keywords. Before conducting the search, the systematic review protocol was preregistered on PROSPERO (registration number CRD42018112135). Appendix Table 2 shows search sets and terms; Appendix Table 3 details the search code used, and Appendix Tables 4−7 provide detailed results by database.

The following stepwise approach was used during the screening and reviewing process. First, the database search was conducted as outlined above, generating a total number of articles generated from each repository. All duplicates were then removed from searches across multiple repositories using Zotero, version 5.0.569, followed by a manual review of titles and abstracts to determine remaining duplicate entries. In the next step, one member of the team (SG) randomly assigned 50% of the articles to NB, SF, CS, and AG, who independently screened titles and abstracts to identify papers potentially related to the research question and eligibility criteria. Thus, each article was screened separately by 2 team members. Once the preliminary screening was completed, one team member (SG) received the results of each rater's screening and calculated inter-rater reliability using a κ statistic for the screening to this point. It was determined in advance that a poor inter-rater reliability (κ<0.6)[10] would result in a re-examination of eligibility criteria and screening by the whole team, and a repeat of preliminary screening procedures until inter-rater reliability improved above that set threshold. Team member SG served as a tiebreaker for any articles for which the 2 preliminary screeners were not in agreement about inclusion. After the screening was complete, the full text of the articles identified in the previous step was retrieved; any article whose full text could not be obtained was excluded from the review. Each full-text article was independently reviewed by 2 team members to determine if the study met the eligibility criteria. Whenever there was disagreement about whether a study should be included, SG read the article and made a final decision. Finally, after the full-text review of the initial articles, the references of all eligible articles were hand searched for additional, potentially eligible articles. These articles were then reviewed, and eligibility was determined according to the process outlined above.

The risk of bias was assessed using the Cochrane "Risk of Bias 2.0" tool from the Cochrane Handbook for Systematic Reviews of Interventions.[8] For each study selected for review, 2 team members independently rated the risk of bias by applying 3 categories of risk ("high risk," "some concern," or "low risk" of bias) across the different domains of bias found in the tool. If there was disagreement between the 2 team members, a third team member performed an assessment using the Cochrane "Risk of Bias" tool and served as a tiebreaker.

After assessing eligible articles for homogeneity of outcomes and outcome assessment methods, a meta-analysis focused on evaluating the effect of smoking-cessation interventions on smoking abstinence was performed using the 6 eligible full-text articles with extractable tabular data. Where information on both self-reported and biochemically validated smoking abstinence outcomes were available, data for the biochemically validated outcomes were used in the meta-analysis. Because both cluster and individually randomized trials were included in this systematic review, the ratio estimator approach developed by Rao and Scott[11] was used to adjust for clustering before estimating the pooled parameter of interest in the meta-analysis. In the ratio estimator approach, observed cell frequencies are divided by the estimated design effect of the study to account for dependence among observations belonging to the same cluster.[11,12] The design effect was estimated as $1+(\overline{m}-1)\widehat{\rho}$, where $\overline{m}$ represents the average cluster size across study arms, and $\widehat{\rho}$ is an estimate of the intraclass correlation coefficient (ICC).[12]

For the 3 individually randomized trials included in the meta-analysis (Harris et al.,[13] Wewers and colleagues,[14] and Stoops et al.[15]), the average cluster size was equal to 1, and the ICC was also equal to 1. As a result, the observed cell frequencies were unchanged after adjusting for clustering in these 3 studies. Because the average cluster size and the sample ICCs were not reported for the 3 cluster randomized trials, the number of participants the authors aimed to enroll in each cluster and the ICC described in the sample size estimation sections of each paper were used to estimate design effects. No information regarding the ICC was provided in Schoenberg and colleagues,[16] so the ICC estimate from Wewers et al.[14] was used to estimate the ICC for this study (overview provided in Appendix Table 8). Sensitivity analyses were performed to explore if using a different estimate of the ICC in Schoenberg and colleagues[16] affected the results of the meta-analysis (see Appendix Table 9). The range of external ICC estimates used in the sensitivity analyses was selected from a school-based smoking prevention trial[17] and a community trial evaluating cardiovascular health that included smoking-related health outcomes.[18]

Fixed and random effects models with the Mantel−Haenszel method were used to estimate both the pooled RR and pooled OR of smoking abstinence. Homogeneity was assessed qualitatively using data extracted about each study's population, intervention, and outcome (Appendix Table 10). Homogeneity was also assessed quantitatively using Cochran's Q statistic and the I^2 index. Because both the Q statistic and I^2 index have low power to detect heterogeneity among a small number of studies,[19] a L'Abbé plot was also used to attempt to graphically evaluate homogeneity.[20,21] If there was evidence of a violation of the homogeneity assumption, the pooled effect of smoking-cessation intervention programs on smoking abstinence was estimated from a random effects model. In addition, sensitivity analyses were performed to explore if any one study had an outsize impact on the results of the meta-analysis by iteratively leaving out each trial and estimating the pooled RR of smoking abstinence.[22] Funnel plots were used to attempt to identify potential publication bias. All meta-analysis procedures were performed in R, version 3.5.0, using the package meta, version 4.9-2.[23]

EVIDENCE SYNTHESIS

The search was conducted on October 9, 2018 and resulted in 74 records identified via Medline (PubMed), 14 records identified via Embase, 24 records identified via Scopus, and 3 records identified via the Cochrane Library.

Records were exported from each database and imported into Zotero to organize and remove duplicates. Twenty-one duplicate records were removed using Zotero's automatic tool for detecting duplicates, and an additional 2 duplicate entries were manually removed after sorting by article title and author names.

The remaining 92 articles were randomly assigned to 4 members of the research team (AK, CS, NB, SF) who independently scanned the titles and abstracts to identify papers related to the research question based on the eligibility criteria. The resulting overall agreement was 85.9% (Cohen's κ=0.72), indicating a moderate level of inter-rater reliability.[10] Of the 44 included articles, an additional 4 articles were excluded owing to the nonavailability of full text. The remaining 40 articles were then subjected to a full-text review.

The full-text articles were retrieved and randomly assigned to 4 team members (AK, CS, NB, SF), with each article independently screened by 2 team members. There was 82.5% agreement (Cohen's κ=0.62) at this stage, again demonstrating moderate inter-rater reliability.[10] All disagreements were referred to a third team member (SG) who independently read the articles and made a final decision. Thirty-one full-text articles were excluded at this stage, as these articles did not meet the predefined eligibility criteria. The most common reason for exclusion was the study population living in geographic areas outside the rural Appalachian region, or the trial being conducted in states within and outside the Appalachian region, without data separately reported such that Appalachian subjects could be isolated for this review. Two studies used quasi- and non-randomized trial designs, and hence were excluded from the review. In 4 studies, the measured outcomes were not directly related to smoking cessation or smoking-related health (e.g., the main outcomes of interest for which data were reported were physical activity, with smoking status only noted as a covariate), thereby leading to their exclusion. One study was excluded during the data extraction phase when it was determined to be a substudy of another trial already included. A total of 9 RCTs[13−16,24−28] evaluating the effect of smoking-cessation interventions in populations residing in rural Appalachia were included in the review. The screening process and reasons for exclusion are summarized in Figure 2.

The characteristics of the 9 studies included in the review are summarized in Table 1 (with details provided in Appendix Table 10). Most studies were conducted in rural Ohio, Kentucky, Alabama, and West Virginia. Intervention outcomes included smoking-cessation rates, biochemical validation, adherence to nicotine patches, self-reported cigarettes per day, abstinence rates, and nicotine dependency scores. The number of participants in the studies varied from 17 to 707. Most of the articles were published from 2009 to 2016.

The studies were relatively heterogeneous, each using different interventions to promote smoking abstinence and each focusing on different populations in Appalachia, including pregnant women, nonpregnant women, people living with HIV/AIDS, and adolescents. Five of the studies were individually randomized, whereas 4 were cluster randomized, each with different units of randomization (church, school, county, and physician). However, 6 of the 9 included studies had extractable data related to dichotomous smoking status (abstinent versus not abstinent), and each reported a measure of association or provided enough information in their study publication to allow for

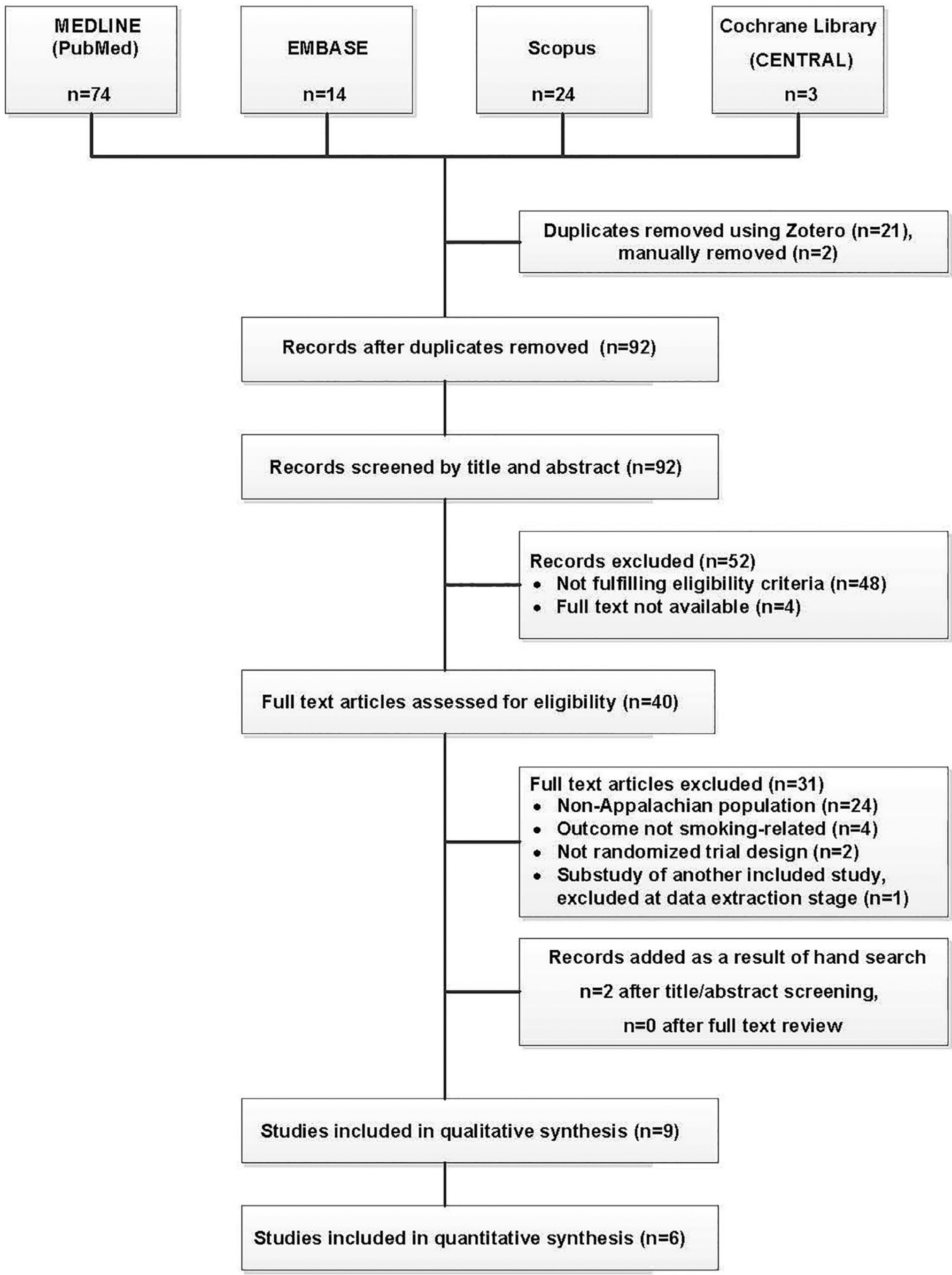

Figure 2. Flowchart of the search process and results.

creation of a contingency table of smoking abstinence by intervention arm. Therefore, these 6 studies were included in a quantitative meta-analysis.

The 6 trials of smoking-cessation intervention programs resulted in increased smoking abstinence overall; however, the effect was significant in only 1 study (Schoenberg et al.[16]). The pooled RR (Figure 3) and pooled OR (Appendix Figure 1) were estimated using random effects models because the validity of summary estimates from fixed effect models requires an assumption of homogeneity, which did not appear to be satisfied for these studies. The trials included in this meta-analysis were relatively heterogeneous with respect to specific interventions, populations, and unit of randomization (see Appendix Table 10). In addition, the *Q*-test provided evidence of substantial heterogeneity across the 6 studies ($\text{chi-square}_{(5)}=18.86$,

Table 1. Summary of Eligible Study Characteristics

Study characteristics	Number of studies	Total participants
Type of randomization		
Individual	5	489
Cluster	4	1,744
Bias assessment		
Low	1	590
Some concerns	3	1,077
High	2	231
Not assessed	3	335
Study outcomes[a]		
Self-reported smoking abstinence	8	2,165
Biochemical validation of smoking abstinence	6	1,370
Nicotine dependence (e.g., Fagerstrom)	4	709
Reported measure of association[a]		
OR	6	1,898
RR	0	0
Other (difference in means, eta-squared)	3	692
None	1	233
Total	9	2,233

[a]Studies reported multiple outcomes/measures; total >9.

$p<0.01$), and the I^2 index indicated that between-study variability constituted approximately 74% of the total variability across the 6 estimated RRs (I^2=73.5%, 95% CI=39.3%, 88.4%). There was also heterogeneity in the percentage of trial participants who achieved abstinence in intervention groups (2.86%−31.07%) and control groups (0%−28.57%) among the trials (Appendix Figure 2). However, given the small number of studies, the authors also used fixed effects models to estimate the pooled parameters, which yielded similar results to the random effects models described below (Appendix Figures 3 and 4 provide Forest plots of the pooled RR and OR estimates using fixed effects).

The results of the random effects model indicated that participation in smoking-cessation interventions increased the probability of smoking abstinence among Appalachian smokers an estimated 2.33-fold (RR=2.33, 95% CI=1.03, 5.25, p=0.04). The pooled OR estimate was also significant, but the point estimate was slightly further from the null (Appendix Figure 1; OR=2.69, 95% CI=1.05, 6.87, p=0.04). In the sensitivity analyses used to understand the impact of changing the imputed ICC value for 1 of the 3 cluster randomized trials, participation in smoking-cessation intervention programs significantly increased the probability of smoking abstinence as well; as expected, the magnitude of the effectiveness of smoking-cessation programs decreased as the imputed ICC increased (Appendix Table 9).

Potential publication bias was assessed using a funnel plot of the 6 trials included in this meta-analysis (Appendix Figure 5). Although the plot appears to be relatively symmetric, a larger number of studies would improve the ability to discern if there is evidence of publication bias. The precision of Stoops and colleagues[15] was much lower than that of the other 5 trials.

All but one of the 6 trials included in the meta-analysis had at least some concerns related to bias in study design and results reporting (Appendix Table 11). This was especially true with regard to apparent deviations from intended interventions, and missing outcome data, though there were also concerns in 4 of the 6 studies related to randomization processes.

DISCUSSION

In this systematic review of 9 randomized trials of smoking-cessation programs with a total of 2,233 participants carried out in Appalachia, a moderately beneficial effect

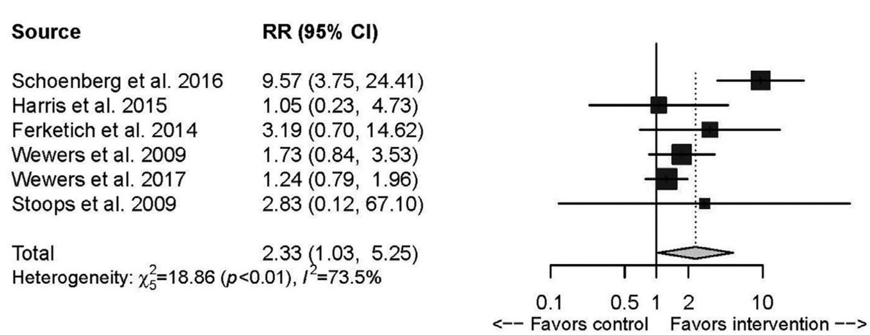

Figure 3. Results of random effects meta-analysis of smoking-cessation intervention effects on smoking abstinence (RRs).

of various types of interventions was observed on smoking abstinence, across multiple populations.

Six trials, with a total of 1,845 participants, reported data in sufficient detail for a meta-analysis to be performed. The estimated pooled RR of 2.33 indicated that smoking-cessation programs in this rural and socioeconomically disadvantaged population are an effective tool to achieve abstinence. This reflects a number needed to treat of 9. In other words, to achieve abstinence in one participant, 9 individuals need to participate in a smoking-cessation program.

These findings are in agreement with previous systematic reviews on the efficacy of smoking-cessation programs that focused on the general adult population. For example, internet-based interventions, such as those used in 3 trials included in this review (Harris et al.,[13] Reynolds and colleagues,[25] and Stoops et al.[15]), have been shown to be moderately more effective than nonactive controls.[29] Similarly, individual behavioral counseling, as employed in 3 trials included in this review (Cropsey and colleagues,[26] Wewers et al.,[14] and Wewers and colleagues[24]) has been shown to be useful in helping smokers quit.[30] Finally, nicotine-replacement therapy, which was employed in 3 trials (Wewers et al.,[14] Cropsey and colleagues,[26] and Schoenberg et al.[16]), has been found to increase quit rates by 50%−60%, regardless of setting.[31]

Appalachia has one of the highest smoking prevalence rates[5] and simultaneously one of the worst health outcomes in the U.S., resulting in a mean gap in life expectancy of 2.4 years compared with the national average.[6] Indeed, smoking-related illnesses account for more than half of the life expectancy gap between Appalachia and the rest of the U.S.[6] Reducing smoking prevalence should remain as a critical component of efforts to reduce health disparities in this vulnerable population.

Limitations

There are several limitations to this systematic review that merit discussion. First, there was substantial heterogeneity on several levels among the included studies. Despite the narrow inclusion by geography, the populations studied were diverse and varied widely (e.g., some studies were adults only and others were adolescents only; others included only pregnant women, or only people living with HIV). Another important source of heterogeneity arose from varying definitions and ascertainment of smoking status and abstinence (e.g., some studies biochemically validated smoking status, and others were entirely self-reported). More consistency in ascertaining and defining individuals' smoking status would improve the validity of the estimates and one's ability to make inferences about them. Furthermore, the nature of the smoking-cessation interventions varied substantially, ranging from web-based interventions with economic incentives for traditional counseling to screening, brief intervention, and referral for treatment, telephone counseling, and nicotine-replacement therapy. Heterogeneity also stemmed from differing control interventions, ranging from usual care to active control interventions such as telephone counseling services (i.e., "quitlines"). The fact that most of the trials included an active control arm rather than usual care or a sham intervention likely underestimates the effect of the smoking-cessation programs on abstinence rates.

Second, the number of studies included in this systematic review was rather low. As a consequence of the narrow geographic inclusion criterion, a substantial number of studies had to be excluded, as they pooled data across several states and did not report outcomes in sufficient regional granularity. However, as Appalachia is uniquely disadvantaged in economic and social terms that greatly influence health behaviors, a regional focus is justified. For future reviews, a larger number of studies, ideally with a greater number of participants, would help clarify and increase the certainty of the potential size of the effect estimate of smoking-cessation interventions on smoking abstinence in this area. Because of the small number of studies included in the meta-analysis, each study had a substantial effect on the pooled parameter estimate, as illustrated by the results of the leave-one-out sensitivity analysis. Omitting any 1 of 4 studies (Schoenberg and colleagues,[16] Ferketich et al.,[27] Wewers and colleagues,[14] or Stoops et al.[15]) from the meta-analysis resulted in a pooled RR of smoking cessation that was not statistically significant (Appendix Figure 6).

A third limitation originated from the difficulty in pooling the results of cluster randomized trials with individually randomized trials, particularly when the ICCs and average cluster sizes were reported inadequately. This uncertainty was addressed by performing sensitivity analyses with a range of potential ICCs derived from the literature for similar outcomes, which left the pooled estimate largely unchanged. If there had been a larger number of studies that satisfied the exclusion criteria for this systematic review, pooled effect estimates could have been estimated separately for cluster and individually randomized trials or the data could have been subgrouped by the unit of randomization to better address concerns about heterogeneity among the studies included in the meta-analysis.[32]

Fourth, most of the studies included in this review reported outcomes over a limited follow-up period ranging from 6 to 17 weeks. Only 2 trials (Wewers and colleagues[14] and Wewers et al.[24]) followed participants for 12 months. Thus, short-term follow-up restricts any predictions about the long-term efficacy of anti-smoking interventions in Appalachian smokers. However, given substantial relapse rates, smoking cessation must be a long-term commitment to substantially impact cardiovascular disease and cancer prevalence rates.[33,34]

Fifth, the trials included in this review addressed combustible tobacco only. Given the elevated rates of smokeless tobacco use (particularly among men) in rural areas[35] and the high co-use of other forms of tobacco,[36] up to 12% of nicotine users might not be included in the studies identified in this review. However, the broad term of "tobacco" employed in the search should have captured any randomized trials studying smokeless tobacco and its various products (such as chewing tobacco, dry snuff, and moist snuff [snus]). Future cessation trials should therefore aim to include smokeless tobacco users.

Finally, although the funnel plot appears symmetric, thus indicating minimal to no publication bias, this finding should be interpreted with caution given the low number of included studies. It is possible that a larger number of studies might reveal evidence for publication bias, affecting the ability to interpret the external generalizability of this review.

These limitations highlight the need for more rigorous research to identify successful smoking-cessation interventions for the Appalachian population. Notably, standardized definitions of smoking status, routine ascertainment of nicotine dependence and concurrent use of other tobacco products, and standardized control arms ("quitlines") might reduce the heterogeneity of future studies and facilitate inferences about the best interventions available.

CONCLUSIONS

The pooled estimate of the meta-analysis showed significant effectiveness of smoking-cessation interventions in rural Appalachia, and this qualitative systematic review supported this finding. This estimate is in line with previous systematic reviews in general adult populations, which emphasize the important potential of these interventions to improve population health. Particularly in disadvantaged populations, such as in Appalachia, successful smoking-cessation programs hold the promise to decrease health disparities. However, taken together with the low number of studies included in this meta-analysis, as well as the substantial heterogeneity and high risk of bias among these studies, the evidence of the effectiveness of smoking-cessation interventions in Appalachia appears to be limited and must be interpreted with caution.

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SUPPLEMENTAL MATERIAL

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