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Review

Smoking cessation interventions for adults aged 50 or older: A systematic review and meta-analysis

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ABSTRACT

Background: The older population size has increased substantially, and a considerable proportion of older adults are cigarette smokers. Quitting smoking is associated with reduced health risk. This review is among the first to quantitatively assess the relative efficacy of types of cessation interventions for smokers aged ≥50 years.
Methods: We conducted searches of the Cochrane Library, Embase, MEDLINE, and PsycINFO to identify smoking cessation studies on adults aged ≥50 years. Twenty-nine randomized clinical trials met the inclusion criteria. Three main types of interventions were identified. We analyzed relative cessation rates or Risk Ratios (RRs) between the type of intervention groups and the control group by fixed- and random-effects meta-analyses at the study level. We conducted a weighted least squares meta-regression of cessation rates on trial and sample characteristics to determine sources of outcome heterogeneity.
Results: Fixed-effects analysis showed significant treatment effects for pharmacological (RR = 3.18, 95% CI: 1.89–5.36), non-pharmacological (RR = 1.80, 95% CI: 1.67–1.94), and multimodal interventions (RR = 1.61, 95% CI: 1.41–1.84) compared with control group. Estimations based on meta-regression suggested that pharmacological intervention (mean point prevalence abstinence rate (PPA) = 26.10%, CI: 15.20–37.00) resembled non-pharmacological (27.97%, CI: 24.00–31.94), and multimodal interventions (36.64%, CI: 31.66–41.62); and non-pharmacological and multimodal interventions had higher PPAs than the control group (18.80%, CI: 14.48–23.12), after adjusting for a number of trial and sample characteristics.
Conclusions: A small number of smoking cessation studies examined smokers aged ≥50 years. Additional research is recommended to determine smoking cessation efficacy for diverse older population groups (e.g., ethnic minorities).

Contents

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1. Introduction

The older population (aged 65 and older) in the United States is projected to double from 40.2 million in 2010 to 88.5 million in 2050, largely driven by the aging of the 'baby boomers' born between 1946 and 1964 (Vincent and Velkoff, 2010). In 2014, the youngest 'baby boomers' turned 50 years old. By 2030, all the 'baby boomers' will have become over 65 years old (Vincent and Velkoff, 2010).

Based on data from the 2012 National Health Interview Survey (NHIS), it was estimated that about 18.1% (42.1 million) of U.S. adults were current cigarette smokers, who reported smoking at least 100 cigarettes in their lifetime, and reported smoking every day or some days at the time of the interview (Agaku et al., 2014). The prevalence of current smoking was lower among older adults aged ≥65 years (8.9%) than those aged 18–24 (17.3%), 25–44 years (21.6%), or 45–64 years (19.5%).

Survey data show that older cigarette smokers are less likely than younger adults to be interested in quitting smoking, make quit attempts, and achieve smoking cessation (CDC, 2011). From the 2010 NHIS, 53.8% of current smokers aged ≥65 years indicated that they would like to quit smoking completely, as compared with 70.2% among those aged 18–64 years (CDC, 2011). Prevalence of current and former smokers who made a quit attempt in the year before the interview were 62.4%, 56.9%, 45.5%, and 43.5% for adults aged 18–24, 25–44, 45–64, and 65 years and over, respectively. Accordingly, past-year smoking cessation rate was lower among people aged 45–64 years (4.7%) and ≥65 years (5.3%) than people aged 18–24 (8.2%) and 25–44 years (7.1%). This has important clinical implications as older adults are more likely than young adults to have aging-related medical illnesses (e.g., heart or lung related conditions) that may be exacerbated by smoking (DHHS, 2014).

As a leading cause of premature morbidity and mortality in the U.S., smoking may impact almost all organs in the human body, and is linked to a multitude of cancers and other diseases (DHHS, 2014). Based on self-reported and spirometry data from the US National Health and Nutrition Examination Survey, it was estimated that adults aged 35 years or older had about 14 million (95% CI, 12.9–15.1 million) major medical conditions attributable to smoking in 2009 (Rostron et al., 2014).

There are important health benefits to quitting smoking at any age (DHHS, 2014; Doll et al., 2004). Findings from a study of 34,439 male British doctors indicate that smoking cessation at age 60, 50, 40, and 30 would increase life expectancy by 3, 6, 9, 10 years, respectively (Doll et al., 2004).

Whilst population-level data suggest that there is a lower smoking cessation rate among older smokers than younger groups (CDC, 2011), when interventions have included or deliberately targeted older adults, they tend to perform as well as younger smokers (Abdullah and Simon, 2006; Doolan and Froelicher, 2008). Previous reviews have suggested that older smokers respond to smoking cessation interventions at similar rate to younger smokers and that cessation brings health benefits (Abdullah and Simon, 2006; Doolan and Froelicher, 2008). Intervention studies reporting stratified results by age group found that the abstinence rate for senior smokers was comparable to or even higher than younger age groups (Dale et al., 2001; Doolan et al., 2008; McFall et al., 2010; Tashkin et al., 2011). A study employing comprehensive behavioral intervention indicated that the quitting rate for older smokers aged 62 years and over (52.0%) was significantly higher than that for smokers younger than 62 years old (38.1%) at the 12-month follow-up (Doolan et al., 2008). However, such studies only represent a small proportion of cessation interventions for adults in general, as most studies do not report outcomes for different age groups. In addition, the number of interventions targeting specifically at the elderly is small. It highlights a critical knowledge gap in the efficacy of interventions for older smokers (Zbikowski et al., 2012).

Previous reviews tried to fill the gap by summarizing findings on smoking cessation for older smokers. Pharmacological interventions seemed to be effective in smoking cessation for older smokers (Zbikowski et al., 2012). There were various non-pharmacological interventions such as physician-delivered interventions, behavioral interventions, and interventions through printed materials. Physician-delivered interventions achieved moderate quit rates (Pilowsky and Wu, 2014; Zbikowski et al., 2012). Cessation outcomes from counseling/behavioral interventions varied with intensities of interventions and length of follow-ups (Pilowsky and Wu, 2014; Zbikowski et al., 2012). More intensive interventions and multimodal interventions involving both medications and counseling often resulted in best outcomes (Zbikowski et al., 2012). However, none of the past reviews on adults aged ≥50 years employed meta-analysis/regression to quantitatively assess the relative effectiveness of different intervention strategies, and how intervention outcomes are associated with trial and sample characteristics (Abdullah and Simon, 2006; Doolan and Froelicher, 2008; Pilowsky and Wu, 2014; Zbikowski et al., 2012).

This review focused on smokers aged 50 and over for several reasons. First, there are few intervention studies exclusively focusing on smokers aged ≥65 years, but there are relatively more studies on those aged ≥50 years. Second, a tailored smoking cessation guide for smokers aged ≥50 years (Clear Horizons) was developed by the National Cancer Institute, and tested in multiple studies on older smokers (Orleans et al., 2000; Ossip-Klein et al., 1997; Rimer et al., 1994). Third, the Clinical Practice Guideline on treating tobacco use and dependence referred to studies on smokers aged ≥50 years as evidence for treating older smokers (Fiore et al., 2008). Fourth, past

reviews on smoking cessation for older smokers included adults aged ≥50 years (Abdullah and Simon, 2006; Doolan and Froelicher, 2008; Pilowsky and Wu, 2014; Zbikowski et al., 2012).

Randomized controlled trials (RCTs) provide the evidence to help evaluate causal inferences, and decrease allocation bias and other types of bias if well designed (Levin, 2007). Following Zbikowski et al. (2012), we searched for RCTs published on and after January 1, 1990. The aims of this study were to (1) synthesize results published between January 1, 1990 and January 28, 2015 from RCTs on smoking cessation interventions for smokers aged ≥50 years, (2) determine relative effectiveness of intervention types (pharmacological, non-pharmacological, and multimodal interventions), and (3) examine whether trial and sample features were associated with intervention outcomes (abstinence rates).

2. Methods

2.1. Eligibility criteria

We used the PRISMA to guide our literature review and analysis (Moher et al., 2009). We included RCTs of smoking cessation that report abstinence rates for adult smokers aged ≥50 years, published in English between January 1, 1990 and January 28, 2015. Three main inclusion criteria were: (1) reporting results from smoking cessation RCTs; (2) presenting smoking abstinence either in the form of proportions or the numbers of abstainers and sample sizes; (3) including adult smokers aged ≥50 years, or reporting abstinence rates by age groups that included those ≥50 years.

2.2. Information sources and search strategy

We conducted a systematic search of the Cochrane Library, Embase, MEDLINE, and PsycINFO for eligible studies published between January 1, 1990 and January 28, 2015. We evaluated review articles related to this area to identify additional studies for including in the meta-analysis (Abdullah and Simon, 2006; Doolan and Froelicher, 2008; Zbikowski et al., 2012). The following search terms were used for the four databases: "(nicotine OR tobacco OR cigarette OR smoking) AND (program OR intervention)". The results shown in Embase and MEDLINE were restricted to "randomized controlled trial", "middle aged, aged, very elderly", "human", and "English". The results in PsycINFO were restricted to "treatment outcome/clinical trial", "middle aged, aged, very old", "human", and "English", "peer reviewed journal". We restricted the results from the Cochrane Library to "trials" (other restrictions were not available), and screened the results manually for eligible studies.

2.3. Study identification and data extraction

Records identified through the four databases and review articles were initially screened for duplication, and then by titles, abstracts, and full-texts sequentially by the first author (D.C.). After removal of duplicates, we excluded irrelevant titles and abstracts based primarily on the three inclusion criteria. Full-text files of the remaining articles were retrieved and reviewed systematically. Studies meeting all three criteria were included in the outcome-level analysis. Studies without an inactive or minimal control group were excluded from the study-level analysis.

We recorded the trial outcome, selected trial features, and baseline characteristics of study participants in each randomized arm from the included studies in a pre-specified excel worksheet. Each arm was classified into one of the four categories: pharmacotherapy (e.g., nicotine patches/gums, bupropion), non-pharmacological interventions (e.g., physician/nurse counseling, group counseling, counselor-initiated calls, Clear Horizons Guide, computer tailored messages, quitline), and multimodal interventions (pharmacotherapy plus counselling/behavioral interventions), and inactive or minimal control. The sample size of available numbers of studies precludes further grouping of interventions. Categorization was based on treatment actions of each randomized arm instead of case-control divisions in a study. For example, as the comparison group, the standard treatment in Hall et al. (2009) incorporated 12 weeks of bupropion, 10 weeks of nicotine gum plus 5 group counseling sessions, and thus was defined as a multimodal treatment rather than a control group.

2.4. Analysis at the study level

We conducted conventional fixed- and random-effects meta-analyses of risk ratios (RR) at the study level, using Mantel-Haenszel and DerSimonian and Laird methods, respectively. To determine the effect sizes of the studies identified in this review, our analyses were based primarily on results from fixed-effects analysis. Results from random-effects analysis were provided to aid understanding of the estimates of a larger population of studies (Hedges and Vevea, 1998). Heterogeneity in effect sizes was examined by I^2 statistic, and values of 25–50%, 50–75%, and ≥75% are considered low, moderate, and high, respectively (Higgins et al., 2003; Higgins and Thompson, 2004).

Studies with both a treatment group and an inactive control (comparison) group with minimum intervention were included in this level of analysis. Trials that involved an active comparison group were excluded from the analysis, because they did not examine the same effect size as studies with inactive controls. Studies testing more than one type of treatment strategies provided more than one pair of outcomes. A funnel plot was subsequently obtained to examine potential bias of the meta-analyses (Egger et al., 1997). Both Egger's test and Harbord's modified test were used to test for small-study effects—a tendency of larger treatment effects in smaller studies (Harbord et al., 2009; Sterne et al., 2000).

The reporting quality of the included studies was assessed by the 25-item Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist (Moher et al., 2010). Twelve of the 25 items included two sub-items, so there was a total number of 37 items in the checklist. The quality of the evidence was rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al., 2011).

2.5. Weighted least squares (WLS) meta-regression at the outcome level

2.5.1. Study variables. The dependent variable of the meta-regression was abstinence rate from a trial arm. We used intention-to-treat (ITT) outcomes wherever possible. The majority of the studies reported 7-day or longer point prevalent abstinence from smoking, based on participants' self-report with/without biochemical verification. In the study-level analysis, we extracted cessation outcomes observed with highest dosage, longest follow-up time, and for the combined older age group. The unit of analysis for the WLS meta-regression was any abstinence rate reported in a trial. For example, a number of studies reported abstinence rates at different follow-up times (Doolan et al., 2008; Ferketich et al., 2012; Hall et al., 2009) or various age subgroups (Dale et al., 2001; McFall et al., 2010; Vetter and Ford, 1990), thus supplying more than one data point to the regression.

The 13 independent variables contained 10 variables of trial characteristics, two variables of sample demographics, and an intercept. The key trial characteristics were three dummy variables representing intervention types, with control as the reference; and two dummy variables indicating the mode of delivery (i.e., printed materials/mailings and phone intervention), with face-to-face intervention as the reference group. Face-to-face discussion especially with doctors is the preferred mode of delivery, although other modes have been shown to improve patients' knowledge and compliance with interventions (Harris et al., 2002). Past meta-analyses suggested that non-treatment factors such as definitions of abstinence, follow-up length, sample and setting may all contribute to variations in abstinence rates (Hughes et al., 2003). Measurements of reported abstinence rates were categorized into point prevalence abstinence (reference group), prolonged abstinence and continuous abstinence. It is expected that point prevalence is higher than prolonged or continuous abstinence at a given follow-up time (Hughes et al., 2003). Biochemical verification was dichotomized, indicating whether self-reported smoking cessation status was verified by biochemical methods, such as examining the carbon monoxide (CO) level in exhaled air and cotinine level in saliva or urine. It has been reported that self-reported cessation rates were higher than biochemically verified rates in a given study (Noonan et al., 2013; Rigotti et al., 2014). Follow-up times reported in different units were converted to values in months, and they were further classified into three categories: up to 3 months (reference), 3 to 12 months (binary variable), and over 12 months (binary variable). Regarding the sample demographics, we controlled for age and gender composition, since national survey data show varied cessation rates by age group and gender (CDC, 2011). While mean age could be used to characterize each randomized group, due to missing information in many observations, the lower bound of an age group was employed. Specifically, the lower bound of an age group referred to the minimum age of the sample for studies on smokers aged ≥50 years, or the minimum age of an age group for studies reporting stratified results by age group. The last covariate in the regression was percentage of female subjects in the trial arm.

We also recorded the upper bound of the age group, mean age, percentage of white participants, average number of cigarettes consumed per day, mean duration of smoking in years, and mean pack-years in each group where available. However, they were not covariates in the regression because substantial missing information on these variables would decrease the sample size, leading to lower analysis power. To evaluate one additional covariate, more than 10 additional observations are needed (Baker et al., 2009). The ratio of independent variables to observations in this meta-regression (13–138) fell within the recommended range (lower than 1–10).

2.5.2. Model description. Publication bias was defined as "The result of the tendency of authors to submit, organizations to encourage, reviewers to approve, and editors to publish articles containing 'positive' findings (e.g., a gene-disease association), especially 'new' results, in contrast to findings or reports that do not report statistically significant or 'positive' results" (Porta, 2008). In the presence of publication selection bias, WLS meta-regression has been shown to outperform random-effects meta-regression, especially when large heterogeneity was present (Stanley and Doucouliagos, 2013). Specifically, simulation results indicated that WLS meta-regression yielded smaller bias and mean squared error

than random-effects meta-regression, regardless of publication bias (Stanley and Doucouliagos, 2013). Meta-analysts in medical research have long recognized the important role of weighted regression in adjusting for publication bias and heterogeneity (Moreno et al., 2009; Thompson and Sharp, 1999).

Following notations from Cameron and Trivedi (2010), we first specified a linear regression model with heteroskedastic independent errors as follows:

$$Y_i = x_i'\beta + \mu_i, \quad i = 1, 2, \ldots, N \tag{1}$$

where, Y_i represented abstinence rates, $\boldsymbol{x}_i$ was a vector of independent variables abovementioned, μ_i denoted an error term equaling to $\sigma(\boldsymbol{z}_i)\varepsilon_i$. It was assumed that $E(\varepsilon_i|\boldsymbol{x}_i, \boldsymbol{z}_i|)=0$, $E(\varepsilon_i\varepsilon_j|\boldsymbol{x}_i, \boldsymbol{z}_i, \boldsymbol{x}_j, \boldsymbol{z}_j)=0$ when $i \neq j$, and $E(\varepsilon_i^2|\boldsymbol{x}_i, \boldsymbol{z}_i) = 1$. The errors were heteroskedastic with variance $\sigma^2(\boldsymbol{z}_i)$, so Ordinary Least Squares (OLS) estimates were consistent but not efficient. Transforming model (1) by multiplying each term by $w_i = 1/\sigma(\boldsymbol{z}_i)$ would yield the following linear regression model with homoskedastic errors.

$$\frac{Y_i}{\sigma(\boldsymbol{z}_i)} = \left\{\frac{\boldsymbol{x}_i}{\sigma(\boldsymbol{z}_i)}\right\}'\beta + \varepsilon_i \tag{2}$$

Based on a robust estimate of the error variance, an OLS estimator for the transformed model yielded a WLS estimator, which was more efficient than OLS estimates for model (1).

In this study, the skedasticity function was specified as $\sigma^2(\boldsymbol{z}_i) = \exp(\boldsymbol{v}_i'\alpha)$, where $\boldsymbol{v}_i$ was a vector of factors including the log of sample size and trial location from each study that influenced the skedasticity function, and α represented the corresponding coefficients. Differences in study methodology might result in heteroskedastic errors. Large trials usually yield lower standard errors (higher precision) than small trials (Egger et al., 1997). A systematic review of controlled trials indicated that unusually high proportions of favorable treatment effects were found in trials conducted in certain countries (China, in particular) than other countries (e.g., England, U.S.; Vickers et al., 1998). The trial location in this study was a binary variable indicating whether the trial was conducted in the U.S.

Based on the estimated regression coefficients ($\hat{\beta}$), we calculated the average abstinence rates $\left(\frac{\sum_i \boldsymbol{x}_i'\beta}{N}\right)$ of different treatment categories by setting the treatment dummies at specified values, and other covariates at sample values. For instance, average point prevalence abstinence rate for multimodal treatment was calculated by setting the dummies for pharmacological, non-pharmacological, multimodal interventions, prolonged abstinence, and continuous abstinence, to 0, 0, 1, 0, 0, respectively, for all observations. All statistical analyses were carried out in STATA Version 13.1 (Cameron and Trivedi, 2010).

3. Results

Searches through databases and review articles located 7605 records (Fig. 1). After removing 2351 duplicated records or records before January 1, 1990, 3656 irrelevant titles, and 675 ineligible abstracts, 923 articles were retained for full-text review. Of them, 894 were eliminated for not fulfilling one of the criteria. Thus, 29 studies were included for outcome-level analysis. Eight studies without an inactive control or minimum intervention were excluded; 21 studies were retained for study-level meta-analysis.

3.1. Study-level results

3.1.1. Descriptive results. Of the 29 studies, 21 studies compared efficacies between interventions and inactive or minimal controls, yielding 25 comparisons in the study-level meta-analysis (See Table S1[1] for additional details). Two studies adopted pharmacological treatments alone; 16 employed non-pharmacological interventions; 8 used multimodal interventions. Two studies adopted both non-pharmacological and multimodal interventions; and one study employed both pharmacological and multimodal interventions. The majority of the trials were conducted in the U.S. ($n = 17$); the rest ($n = 12$) came from other countries with distinct demographic features. Sample sizes of the 29 studies ranged from 18 participants (Ferketich et al., 2012) to 7354 Medicare beneficiaries (Joyce et al., 2008). Eighteen of the 29 identified trials focused on middle and older smokers aged ≥50 years. Others included wider age ranges, but reported abstinence rates for older age subgroups. Seven studies indicated that their trials were blinded either on the participant or investigator side, and four reported no blinding. It was unclear whether blinding was implemented in other studies. Studies also differed in some inclusion criteria such as pre-existing diseases and smoking intensities.

The 29 studies on average reported 20 items (range: 6–28) out of the 37 items in the CONSORT 2010 checklist. The numbers and percentages of reporting for individual items varied (Table S2[2]). Three of the items were reported in all the studies (items 2b, 5, and 6a); twelve of the items were reported in over 25 of the studies (1b, 1a, 3a, 4a, 12a, 12b, 13a, 15, 16, 18, 22, and 25). Some of the items were poorly reported with fewer than 5 reports out of 29 studies, including allocation concealment mechanism (9), implementation (10), blinding (11a, 11b), presentation of both absolute and relative effect sizes for binary outcomes (17b), harms (19) and protocol (24). Four items largely concerning changes to the trial design and outcome after commencement, and interim analysis and stopping rules were not mentioned in any of the studies (3b, 6b, 7b, and 14b).

By the GRADE criteria, the quality of evidence was high for studies on pharmacological and multimodal interventions (Table S3[3]). There were only two studies on pharmacological interventions alone, and they generated a relatively large pooled effect (strong association), with a wide confidence interval (moderate imprecision). The quality of evidence for studies of non-pharmacological interventions was low with serious risks of bias and inconsistency.

3.1.2. Estimates from meta-analysis. Stratified meta-analysis results by treatment type are presented in Fig. 2. Fixed-effects models indicated that pharmacological (Relative Cessation Rate or Risk Ratio [RR] = 3.18, 95% confidence intervals [CI]: 1.89–5.36), non-pharmacological (RR = 1.80, 95% CI: 1.67–1.94), and multimodal interventions (RR = 1.61, 95% CI: 1.41–1.84) were associated with higher cessation rates than control groups. There was high heterogeneity among studies testing the effects of non-pharmacological interventions ($I^2 = 92.6\%$); there was no evidence of heterogeneity among pharmacological ($I^2 = 0.0\%$) and multimodal trials ($I^2 = 0.0\%$).

Random-effects analyses tended to give lower pooled treatment effects in all models and conservative estimates of treatment effects (wider confidence intervals) than fixed-effects models when there was substantial heterogeneity. The treatment effects of non-pharmacological interventions were lower with wider confidence intervals (RR = 1.52, 95% CI: 1.10–2.09).

The funnel plot with contours of statistical significance indicated missing observations on the left-hand side of the plot, suggesting a lack of studies reporting non-significant and significantly lower cessation rates in intervention groups (Fig. 3). If it was assumed that studies were selected based on two-sided p-values, then publication bias was likely to be one of the factors for funnel asymmetry (Palmer et al., 2008). However, there was no significant evidence of small-study effects by Egger's test ($p = 0.781$) and Harbord's modified test ($p = 0.357$).

3.2. Outcome-level analysis

3.2.1. Descriptive results. Among 138 observations drawn from the 29 studies, the average abstinence rate was 26.31% (Table 1). Mean cessation rates from pharmacological, non-pharmacological, multimodal interventions, and control arms were 29.69% ($n = 11$),

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org/10.1016/j.drugalcdep.2015.06.004

[2] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org/10.1016/j.drugalcdep.2015.06.004

[3] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org/10.1016/j.drugalcdep.2015.06.004

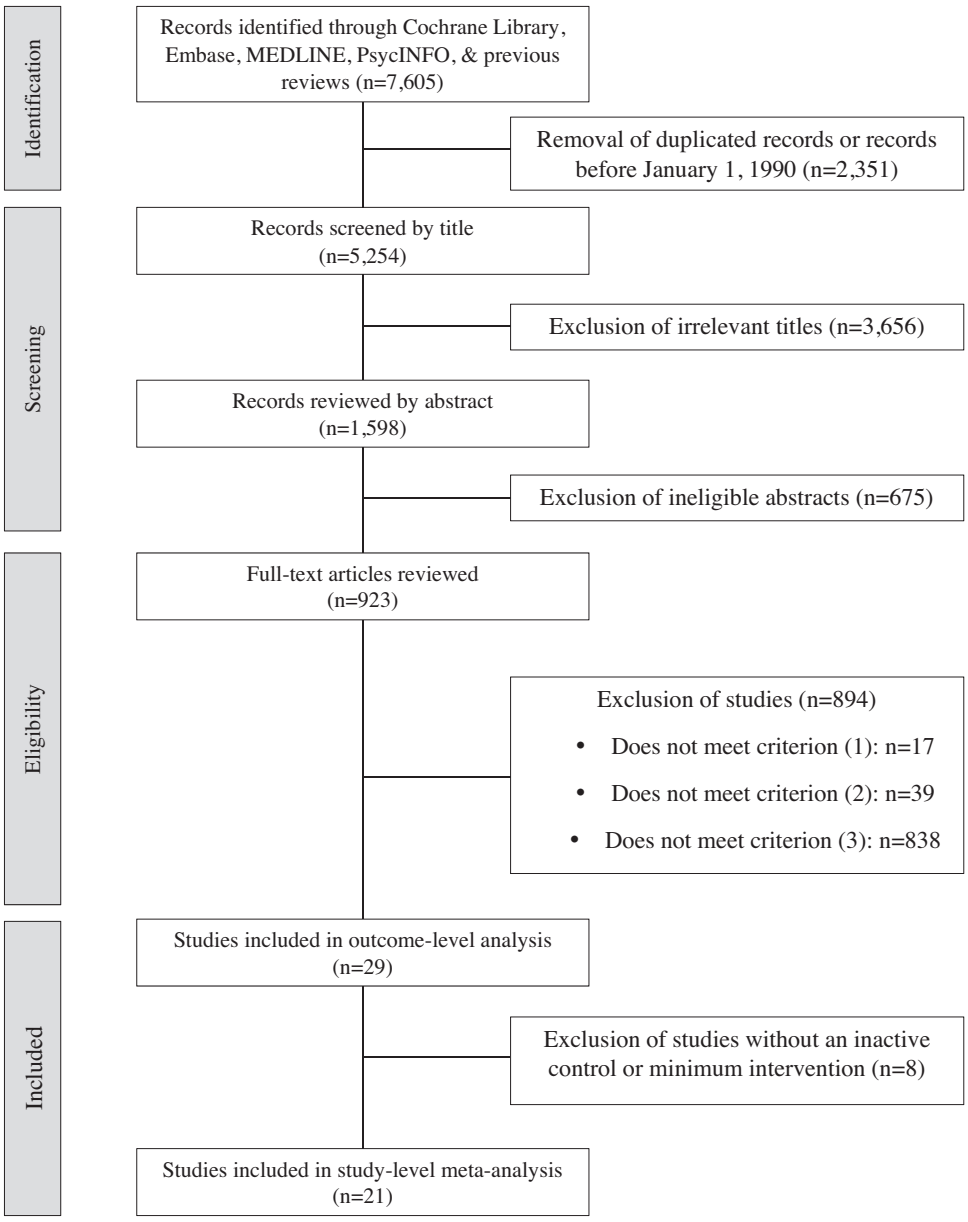

Fig. 1. Flow chart of article identification.

23.72% ($n = 46$), 36.67% ($n = 45$), and 15.64% ($n = 36$), respectively. Most of the outcomes were point prevalence abstinences (78.26%), biomedically verified (63.77%), delivered face-to-face (71.01%), and conducted in the United States (73.91%). One-way ANOVA indicated that the mean cessation rates, lower and upper bound of age range, mean smoking duration, and pack-years differed significantly among the four categories. Chi-square test or Fisher's exact test (if one or more of the cells has an expected frequency of five or less) for binary variables suggested that there were statistically significant relationships between biomedical verification, delivery of intervention, follow-up length, and location with treatment (control) categories.

3.2.2. WLS meta-regression. The study-level analyses cannot examine the sources of heterogeneity, and random-effects meta-regression is not the best solution in the presence of publication bias and large heterogeneity. Therefore, we conducted WLS meta-regressions to explore whether abstinence rates differ by intervention strategies and whether the heterogeneity in effect sizes were related to design and sample characteristics.

Results from the WLS meta-regression are shown in Table 2. Sample size and the location variable, US, were not associated with error variance. At the 5% significance level, non-pharmacological and multimodal interventions yielded higher abstinence rates than control groups, after adjusting for heteroskedastic errors related to the trial location and sample size, and controlling for other covariates. However, the coefficient for pharmacotherapy was not statistically significant. Prolonged abstinence rates were lower than point prevalence abstinence rates. Cessation rates with biochemical confirmation were higher than unverified rates. Intervention delivered over the phone had lower abstinence rates than face-to-face intervention. Having 3–12 months of follow-up was marginally associated with decreased cessation rates compared with having $\leq$3 months of follow-up. A 1 year increase in the lower bound of the age range was associated with 0.42 percentage point increase in abstinence rate. A 1 percentage point increase in the percentage

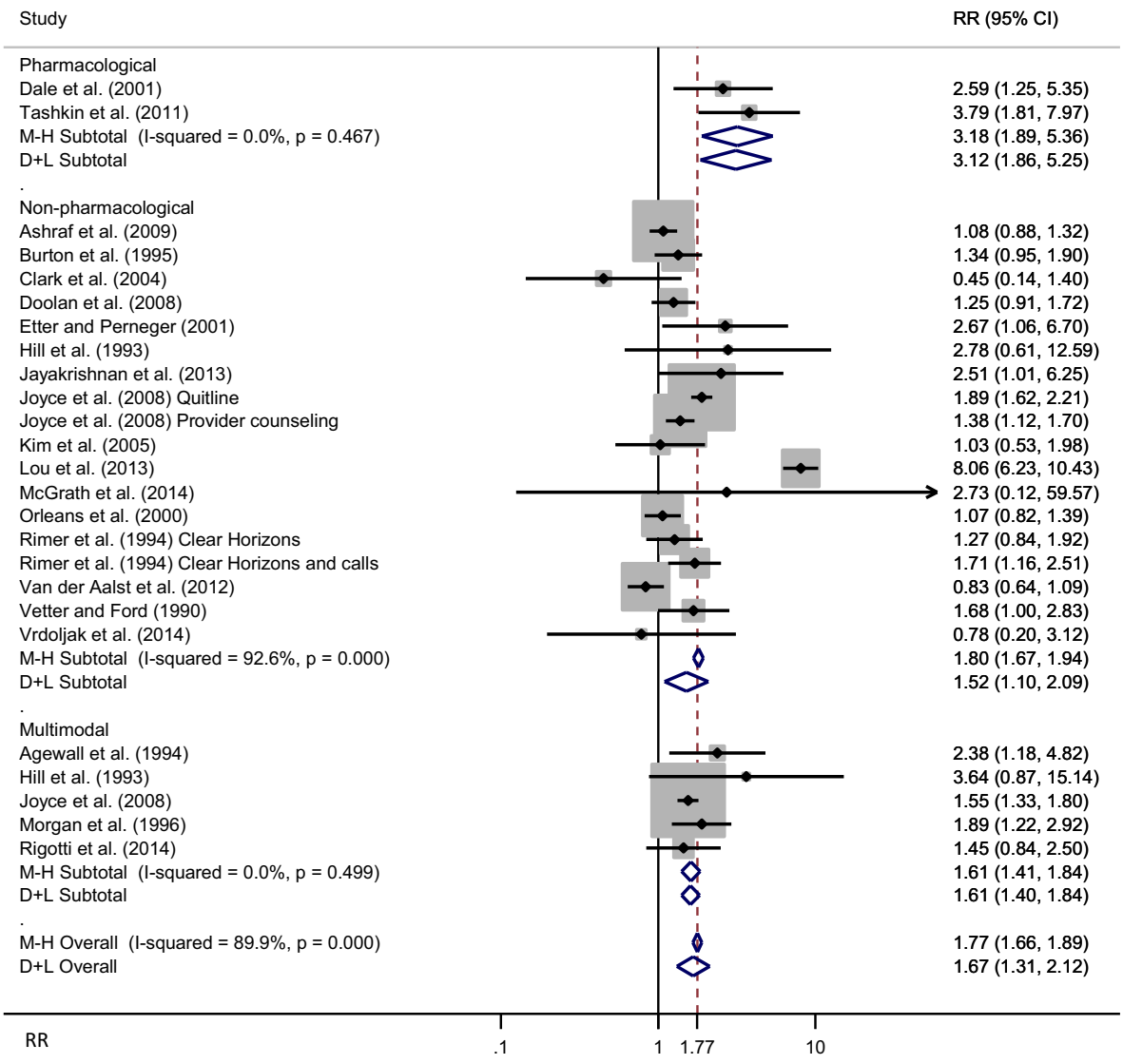

Fig. 2. Forest plot showing a fixed-effects meta-analysis of smoking cessation interventions on abstinence stratified by treatment category, along with overall random effects
Note: RR stands for risk ratio, which could be interpreted as relative cessation rates. 25 RRs were obtained from 21 studies.

of female participants was associated with a 0.14 percentage point increase in abstinence rate.

Based on estimated coefficients from the meta-regression, we calculated the average point prevalence abstinence rates by treatment groups (including the control group), adjusting for other covariates in the regression. Pharmacological intervention (mean point prevalence abstinence rate = 26.10%, CI: 15.20–37.00) resembled non-pharmacological (27.97%, CI: 24.00–31.94), and multimodal interventions (36.64%, CI: 31.66–41.62); and non-pharmacological and multimodal interventions had higher abstinence rates than the control group (18.80%, CI: 14.48–23.12). The estimated point prevalence abstinence rates were further stratified by both intervention category and follow-up length (Fig. 4).

4. Discussion

4.1. Main findings

This study identified 29 RCTs of smoking cessation interventions for smokers aged 50 and older, compared to 13 studies identified in a recent review (Zbikowski et al., 2012). Results based on the CONSORT checklist suggested that the reporting quality of these studies was moderate. Using GRADE criteria, the quality of evidence was high for studies on pharmacological and multimodal interventions, and low for studies of non-pharmacological interventions. This study is among the first to quantitatively review relative effect sizes of different treatment modalities for older smokers. By employing both study-level and outcome-level analyses, it identified various trial and sample characteristics related to heterogeneous abstinence rates.

First, descriptive statistics at the outcome-level showed that mean cessation rates differed significantly among pharmacological, non-pharmacological multimodal interventions, and control groups. Second, fixed-effects meta-analyses at the study level indicated that there were significant treatment effects in pharmacological, non-pharmacological and multimodal interventions. Random-effects analyses generated lower pooled effect sizes in all types of interventions and wider confidence intervals in non-pharmacological interventions than fixed-effects analyses. Third, WLS meta-regression results at the outcome level similarly showed that non-pharmacological and multimodal interventions had significantly higher abstinence rates than the inactive control or minimum intervention group. We also found that use of biochemical verification (vs. non-verification), lower bound of age range,

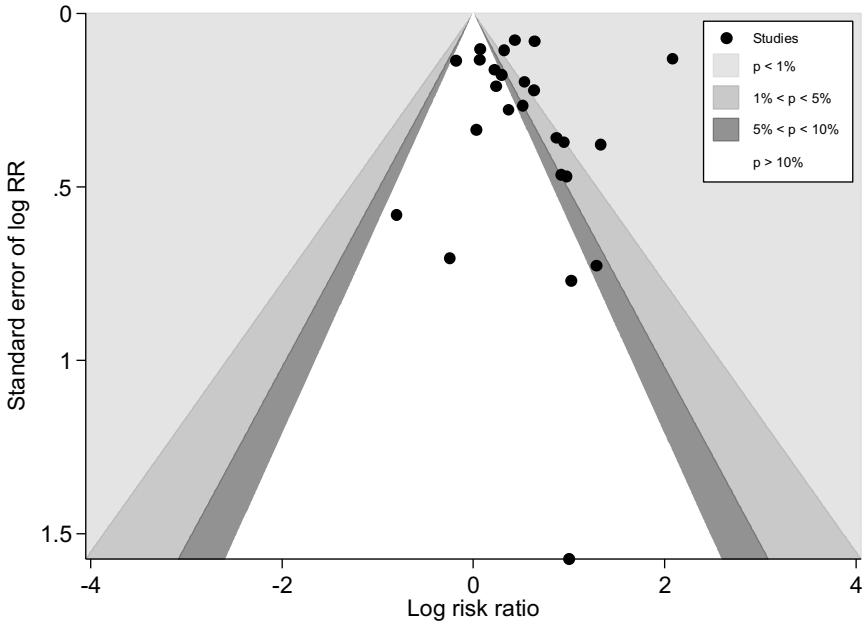

Fig. 3. Funnel plot with contours of statistical significance.

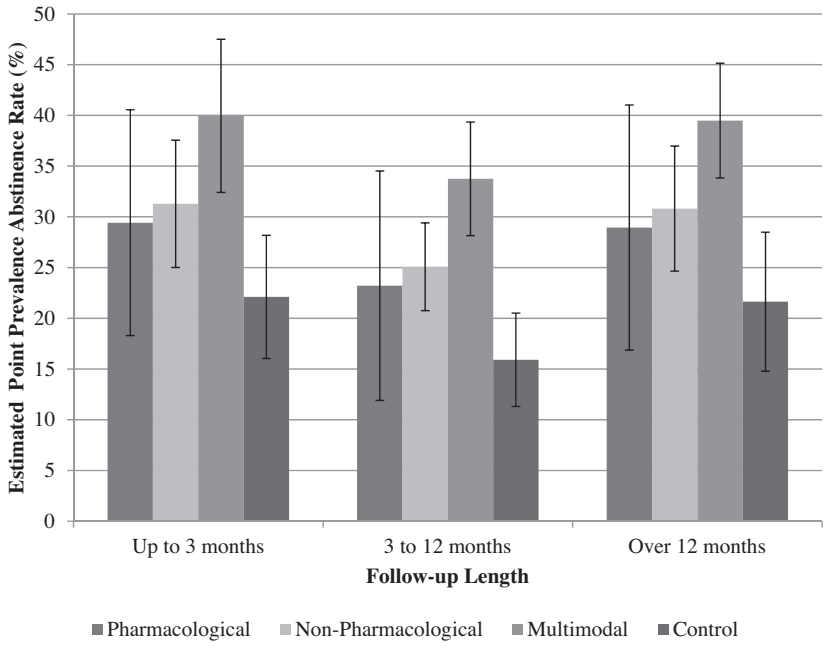

Fig. 4. Estimated mean abstinence rate by treatment group and follow-up length.

and percentages of female subjects were positively associated with cessation rates, whereas use of phone intervention (vs. face-to-face intervention), prolonged abstinence (vs. point prevalence), follow-up at 3-12 months (vs. follow-up at 3 months or less) was negatively related to abstinence rates.

Our findings are consistent with prior studies on adult smokers in general, showing that multimodal interventions usually produce the highest abstinence rates (APA, 2006; Zbikowski et al., 2012). Pharmacotherapy and behavioral interventions have been considered two complimentary modalities to improve smoking cessation synergistically, so a combined approach is often recommended by clinical practice guidelines (Stead and Lancaster, 2012). Pharmacotherapy alone is an effective treatment for smoking cessation, but it may not be as effective as the combined approach, partly because patients' compliance with medication could be improved by various behavioral interventions such as motivational interviewing, family-assisted approaches, or cognitive behavioral therapies (Carroll et al., 2004).

Our results suggested that face-to-face interventions generated higher cessation rates than interventions by phone after controlling for a number of other trial and sample characteristics. This is in line with findings that face-to-face discussions with health professionals such as physicians and nurses are the preferred means of information delivery for patients (Harris et al., 2002; James et al., 1999).

We also found that studies using biochemical verification showed higher cessation rates than those without, which was seemingly contradictory to evidence that self-reported cessation

Table 1
Summary statistics by intervention category.

	Whole sample				Pharmacological		Non-pharmacological		Multimodal		Control	
	N	Mean (SD) or %	Min	Max	*N*	Mean (SD) or %	*N*	Mean (SD) or %	N	Mean (SD) or %	*N*	Mean (SD) or %
Abstinence rate (%)	138	26.31(17.46)***	0	66	11	29.69(20.94)	46	23.72(14.33)	45	36.67(17.43)	36	15.64(12.41)
Point prevalence abstinence (1 = Yes, 0 = No)	138	78.26%	0	1	11	54.55%	46	82.61%	45	84.44%	36	72.22%
Prolonged abstinence (1 = Yes, 0 = No)	138	18.84%†	0	1	11	45.45%	46	13.04%	45	15.56%	36	22.22%
Continuous abstinence (1 = Yes, 0 = No)	138	2.90%	0	1	11	0.00%	46	4.35%	45	0.00%	36	5.56%
Biomedical verification (1 = Yes, 0 = No)	138	63.77%***	0	1	11	100.00%	46	41.30%	45	82.22%	36	58.33%
Face-to-face intervention (1 = Yes, 0 = No)	138	71.01%***	0	1	11	100.00%	46	50.00%	45	95.56%	36	58.33%
Printed materials/mailings (1 = Yes, 0 = No)	138	21.74%***	0	1	11	0.00%	46	30.43%	45	2.22%	36	41.67%
Phone intervention (1 = Yes, 0 = No)	138	7.25%**	0	1	11	0.00%	46	19.57%	45	2.22%	36	0.00%
Follow-up (Up to 3 months) (1 = Yes, 0 = No)	138	23.19%*	0	1	11	63.64%	46	21.74%	45	17.78%	36	19.44%
Follow-up (3 to 12 months) (1 = Yes, 0 = No)	138	50.72%*	0	1	11	9.09%	46	58.70%	45	51.11%	36	52.78%
Follow-up (Over 12 months) (1 = Yes, 0 = No)	138	26.09%	0	1	11	27.27%	46	19.57%	45	31.11%	36	27.78%
US (1 = Yes, 0 = No)	138	73.91%**	0	1	11	81.82%	46	69.57%	45	91.11%	36	55.56%
Sample size	138	269.93(481.43)	4	2605	11	71.82(57.50)	46	313.52(421.97)	45	206.76(526.09)	36	353.75(549.76)
Lower bound of age range	138	54.82(6.74)***	50	80	11	56.73(6.05)	46	56.54(7.37)	45	51.53(3.64)	36	56.14(7.76)
Upper bound of age range	37	69.41(6.99)***	56	79	5	61.20(3.90)	12	73.50(3.58)	8	62.50(6.65)	12	73.33(3.60)
Mean age	72	59.44(7.73)	9.5	72.3	0	0.00(0.00)	23	61.70(5.24)	30	57.48(2.15)	19	59.78(13.48)
Female (%)	138	47.49(25.34)	0	100	11	37.60(20.87)	46	54.52(23.73)	45	44.96(22.27)	36	44.72(30.48)
White (%)	96	76.57(28.61)	0	100	11	83.11(16.79)	28	77.09(37.08)	36	78.14(9.57)	21	69.77(40.65)
Mean No. of cigarettes per day	93	22.89(4.35)†	14.6	32.8	9	25.11(2.82)	28	24.06(4.19)	39	21.74(4.37)	17	22.41(4.61)
Mean smoking duration (Year)	74	39.01(3.72)***	30.4	46	5	37.22(2.90)	21	42.11(3.09)	36	36.90(2.89)	12	40.67(2.73)
Mean pack-years	72	44.25(8.94)***	23.9	58.1	3	37.56(0.00)	22	51.09(7.98)	36	40.38(7.41)	11	45.06(8.36)

Note: "*N*" denoted number of observations. 138 observations were obtained from 29 studies. For binary variables, we presented the percentages of observations equal to 1 in the table. Significance levels were obtained by conducting one-way ANOVA for continuous variables, and Chi-square test or Fisher's exact test (if one or more of the cells has an expected frequency of five or less) for binary variables across treatment categories.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
† $p < 0.1$.

rates were overestimated (Noonan et al., 2013; Rigotti et al., 2014). For instance, one study investigating the validity of self-reported cessation by a biochemical test found that 15 out of 72 self-reported quitters did not pass the urine cotinine test, resulting in an over-reporting rate of 21% (Noonan et al., 2013). However, the meta-regression analysis compared results from studies with vs. those without using biochemical verification (instead of comparing unverified and verified results from the same study); thus, the results should be interpreted differently.

This review suggests an association between a trial's follow-up times and cessation rates. Some studies showed lower cessation rates at longer follow-up times (Ferketich et al., 2012; Tashkin et al., 2011) or fluctuations but a generally downward trend over time (Hall et al., 2009; Hill et al., 1993). Potential reasons for this pattern may be related to relapse in the post-treatment period (Tashkin et al., 2011) or a decline in compliance to intervention over time (Costello et al., 2011). On the other hand, two studies using self-help materials (i.e., Clear Horizons Guide tailored to older smokers) generated comparatively high cessation rates at longer follow-up times (Ossip-Klein et al., 1997; Rimer et al., 1994). Rimer et al. (1994) concluded that "referring to the Clear Horizons Guide repeatedly over time" would increase the time of exposure to intervention. In such a situation, follow-up time may be suggestive of some levels of treatment exposure. In this analysis, follow-up times were based on study time points reported by each study. The regression results showing higher cessation rates in the short-term category (≤3 months of follow-up) were specific to the studies included in the analysis and generally agreed with findings from most studies except for the two studies on self-help manuals.

The positive association between lower bound of age range and cessation rates indicates that increased age may be associated with higher cessation rates among middle and older aged smokers. This is consistent with evidence from interventions stratified by age groups (Dale et al., 2001; Doolan et al., 2008; McFall et al., 2010; Tashkin et al., 2011). The gender differences in cessation rates are in line with observational findings from surveys in that a lower

Table 2
Results from weighted least square meta-regression with abstinence rates as the dependent variable.

Variable name	Coefficient β	Standard error	P value
Control (reference)			
Pharmacological	7.30	5.90	0.218
Non-pharmacological	9.17	2.87	0.002
Multimodal	17.84	3.46	<0.001
Face-to-face intervention (reference)			
Printed materials/mailings	−3.69	3.75	0.327
Phone intervention	−8.43	3.69	0.024
Point prevalence abstinence (reference)			
Prolonged abstinence	−10.95	4.02	0.007
Continuous abstinence	0.61	5.07	0.904
Biomedical verification	12.90	3.65	0.001
Follow-up (Up to 3 months) (reference)			
Follow-up (3 to 12 months)	−6.21	3.00	0.041
Follow-up (Over 12 months)	−0.47	4.03	0.907
Lower bound of age range	0.42	0.21	0.047
Female percentage	0.14	0.07	0.046
Intercept	−14.60	11.96	0.224
Error variance equation	Coefficient α		
Log of sample size	−0.02	0.09	0.796
US	−0.17	0.25	0.494
Intercept	5.37	0.51	<0.001

$R^2 = 0.45$, $F(12, 138) = 9.19$, $P < 0.001$.

proportion of male smokers than female smokers quitted smoking (CDC, 2011). However, previous studies were mixed regarding gender differences in the efficacy of nicotine replacement therapy (NRT). While an earlier review did not find gender difference in quitting rate (Munafò et al., 2004), two prior reviews showed that women were less likely than men to quit when using NRT (Cepeda-Benito et al., 2004; Perkins and Scott, 2008). Biological, psychological, and social factors may be related to gender differences in cessation outcome (Torchalla et al., 2011). Women have special genetic variations that may reduce the benefit of NRT, have higher nicotine and cotinine metabolism levels due to hormone changes in the body or more weight concerns, and they are more likely than men to develop negative mood and depression during a quit attempt (Torchalla et al., 2011). On the other hand, there was evidence that, compared to men, female smokers were more likely to adopt treatment in a quit attempt, especially behavioral and multimodal treatment (Shiffman et al., 2008).

Methodologically, this study not only analyzed the effect sizes of smoking cessation RCTs by fixed- and random-effects models at the study level, but also used WLS meta-regression to explore the sources of heterogeneity at the outcome level. The lack of non-significant and unfavorable results for cessation interventions in the funnel plot suggested possible publication bias, though we did not find any small-study effects in studies included for the meta-analysis. WLS meta-regression performed well in the presence of publication bias and substantial heterogeneity. We adjusted for possible heteroskedatic errors associated with trial locations and sample sizes in the meta-regression, but their effects were not significant.

4.2. Limitations

First, sample size at the study level was small, reflecting a pattern that smoking cessation interventions among older adults have been understudied. Indeed, only a small portion of trials have focused on older adults specifically or reported cessation outcomes stratified by age groups. Older smokers are at high risk of morbidity and mortality, so cessation interventions targeted at the elderly deserve research. The number of observations in the pharmacotherapy only group was quite small, which resulted in a wider confidence interval than other categories. The estimation for this category should be interpreted with caution.

Second, there are a number of sources for funnel plot asymmetry. Only 29 studies published in English were included in the analyses. That is, published studies are more likely to report significant results than unpublished ones, and studies published in languages other than English may have different preferences. Although we used WLS meta-regression to reduce the estimation bias in response to potential publication bias, not every source of funnel plot asymmetry was explored by the analyses. For example, studies reporting "negative" results are less likely to be cited, which has decreased their probability of being located during the literature search process (Egger et al., 1997).

Third, covariates in the meta-regression were not exhaustive. Survey data have shown that whites (compared to ethnic minorities) and heavier smokers were more likely to undertake treatment (Shiffman et al., 2008), so racial composition and pre-treatment smoking intensity were both good candidates for the model. However, univariate regression did not show that percentage of white participants and mean pack-years in the trial arm were significant predictors of abstinence rates (results not shown). In addition, there was missing information for these two variables in a large proportion of the observations, so they were not included in the final model. Mean age was substituted by the lower bound of the age group for the same reason. Overall, this highlights an important issue in the quality of trial reporting, and it calls for a need to improve reporting for older smokers' racial/ethnic backgrounds and smoking history.

Other unmeasured factors related to outcome heterogeneity are not accounted for. Regardless of treatment types, more intensive treatment tends to show better outcome; but it is difficult to find a variable that measures treatment intensity consistently across studies of various intervention strategies. Not all the studies reported ITT results (almost half of the observations in the outcome level analysis), which might increase reported abstinence rates and bias. It should be emphasized that different categorization of treatment methods might yield different results. Finally, our results are also limited by the number of databases searched and by not searching non-academically published articles. We restricted our review to studies published in English between January 1, 1990 and January 28, 2015. The search results were screened systematically by a single researcher (the first author). A multilingual and larger research team may identify more relevant studies and increase the reliability of search results.

4.3. Conclusions and recommendations

Overall, this meta-analysis adds quantitative evidence to the field regarding smoking cessation interventions for older smokers. Regardless of the type of method being used, study-level analyses show that there are significant treatment effects in pharmacological, non-pharmacological, and multimodal interventions, in relation to the control group. Similarly, outcome-level regression results indicate that all the intervention types have higher cessation rates than the control group except for pharmacotherapy. The regression results suggest that cessation rates vary with a number of trial and sample characteristics.

The overall results are based on the available information reported by identified studies, and they should be considered as preliminary estimates and interpreted within the context of study limitations, including a small sample size of available studies for analysis. One important reason for focusing on smokers aged 50 and over is the lack of studies on older smokers aged 65 and over. This review reveals a need for more controlled trials on smoking cessation for both middle-aged and older smokers to better understand how and whether combining pharmacotherapy with behavioral

interventions improve abstinence rates for different gender and racial/ethnic groups. This review also suggests that multimodal interventions delivered face-to-face, with rigorous methodology (e.g., with biochemical verification of cessation), and strict implementation are preferred designs.

Given a high proportion of white population in extant studies, future studies should reach a more diverse population by recruiting more minorities. There was a low probability of adopting treatment among less-educated, low-income, and minority smokers (Shiffman et al., 2008).

The lack of information on sequence generation, allocation concealment, and blinding increased the risk of bias in studies using non-pharmacological interventions. Missing information on trial and sample characteristics, such as mean age and smoking intensity of each randomized arm, has limited the number of covariates in the meta-regression. As such, we urge researchers to report randomization methods, key demographics, smoking history and patterns more thoroughly, which will facilitate the process of evaluation and improve the quality of estimates in future meta-analyses.

Non-pharmacological interventions yielded highly heterogeneous outcomes across studies. Additional research is needed to identify the sources of serious inconsistency in this type of intervention particularly.

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Contributors

Danhong Chen contributed to study designs, conducted literature searches and data analyses, and drafted the manuscripts. Li-Tzy Wu contributed to study designs and analyses, drafted the manuscripts, and supervised the work.

Conflict of interest

No conflict declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2015.06.004

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