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Smoking Cessation Interventions for Potential Use in the Lung Cancer Screening Setting: A Systematic Review and Meta-Analysis

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Abstract

Objectives: Current guidelines recommend delivery of smoking cessation interventions with lung cancer screening (LCS). Unfortunately, there are limited data to guide clinicians and policy-makers in choosing cessation interventions in this setting. Several trials are underway to fill this evidence gap, but results are not expected for several years.

Methods and Materials: We conducted a systematic review and meta-analysis of current literature on the efficacy of smoking cessation interventions among populations eligible for LCS. We searched PubMed, Medline, and PsycINFO for randomized controlled trials of smoking cessation interventions published from 2010-2017. Trials were eligible for inclusion if they sampled individuals likely to be eligible for LCS based on age and smoking history, had sample sizes >100, follow-up of 6- or 12-months, and were based in North America, Western Europe, Australia, or New Zealand.

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Conflicts of Interest:
None declared.

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This systematic review is registered with PROSPERO and is available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018110322.

Results: Three investigators independently screened 3,813 abstracts and identified 332 for full-text review. Of these, 85 trials were included and grouped into categories based on the primary intervention: electronic/web-based, in-person counseling, pharmacotherapy, and telephone counseling. At 6-month follow-up, electronic/web-based (odds ratio [OR] 1.14, 95% CI 1.03-1.25), in-person counseling (OR 1.46, 95% CI 1.25-1.70), and pharmacotherapy (OR 1.53, 95% CI 1.33-1.77) interventions significantly increased the odds of abstinence. Telephone counseling increased the odds but did not reach statistical significance (OR 1.21, 95% CI 0.98-1.50). At 12-months, in-person counseling (OR 1.28 95% CI 1.09-1.51) and pharmacotherapy (OR 1.46, 95% CI 1.17-1.84) remained efficacious, although the decrement in efficacy was of similar magnitude across all intervention categories.

Conclusions: Several categories of cessation interventions are promising for implementation in the LCS setting.

Review Registration (PROSPERO): CRD42018110322

Keywords

smoking cessation; lung cancer screening; meta-analysis

1. Introduction

The National Lung Screening Trial (NLST) and the NEderlands-Leuvens Longkanker Screenings ONdersoek (NELSON) trial provided evidence that lung cancer screening with low-dose computed tomography (LCS) detected cancers earlier than when clinically symptomatic, and reduced lung cancer mortality by 20%-26% (1, 2). Professional groups, including the U.S. Preventive Services Task Force (USPSTF) and the National Comprehensive Cancer Network (NCCN) recommend LCS for individuals with a high risk of lung cancer based on their age (55-80 and 55-74 years, for the USPSTF and NCCN, respectively), a 30 pack-year smoking history, and other risk factors (3, 4).

The potential benefits of screening may go beyond the early detection of lung cancers. Screening may provide a “teachable moment” for encouraging cessation from smoking for the estimated four million current US smokers eligible for LCS, approximately half of all eligible individuals (5, 6). Smoking cessation, in turn, reduces the risk of several cancer types and cardiopulmonary disease. However, merely undergoing LCS does not influence smoking behaviors (7). Consequently, the Centers for Medicare and Medicaid Services (CMS) mandates that smoking cessation assistance is provided to all current smokers undergoing LCS, but leaves decisions about the type of cessation interventions up to clinicians and screening sites (8).

Presently, there are nine trials in progress in the US that will provide valuable evidence on the efficacy of smoking cessation in the context of LCS (9). However, results are not expected until after 2021. While a number of smoking interventions have been found to be effective in general populations (10), there is a paucity of data on whether these approaches will be effective in older, persistent, heavy smokers eligible for LCS. Only a handful of randomized controlled trials have thus far considered the efficacy of smoking cessation in

the screening setting (11-15). Reviews have highlighted the lack of sufficient data needed to make decisions regarding cessation in this setting concluding a need for more data to identify optimal screening strategies for this population (16, 17).

Hence, clinicians and policy-makers now have a mandate to provide cessation to smokers who present for LCS but have limited evidence on the most effective interventions to offer (11-15, 18). To address this lack of information while clinical trials are ongoing, we conducted a systematic review and meta-analysis of recently published clinical trials of smoking cessation that primarily included populations similar to those eligible for LCS. We grouped trials into intervention categories that reflect current clinical guidelines and practice, including electronic/web-based, in-person counseling, pharmacotherapy with drugs currently approved by the Food and Drug Administration, and telephone counseling (9, 10, 19, 20). The results of this analysis are intended to inform current clinical practice at screening sites. As new studies are conducted, the results of this analysis will also support the framework for future research on the expected population effects, costs, and cost-effectiveness of smoking cessation interventions in the LCS setting.

2. Methods

The review follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Appendix A.1) (21) and is registered with PROSPERO: http://www.crd.york.ac.uk/PROSPERO/display_record.php?rD=CRD42018110322.

2.1 Data Sources and Searches

Searches were conducted with the help of a health sciences research librarian in PubMed, Medline (Ovid), and PsycINFO for articles published from January 1, 2010, to December 31, 2017. This period was selected to represent current cessation practice. General smoking cessation search terms were used in conjunction with geographic specifications and clinical trial terms (Appendix B.1). The search terms were kept as inclusive as possible to identify all potentially relevant studies. We also searched the bibliographies of selected trials and reviews to identify any articles missed by the database searches. Results of the search were exported into Microsoft Excel 2010 workbooks designed by a health sciences research librarian specifically for screening article eligibility for systematic reviews (22).

2.2 Study Selection

Eligibility criteria were determined *a priori*. To be eligible, randomized controlled trials published in English tested the efficacy of one or more of four categories of cigarette smoking cessation interventions on 7-day point prevalence at 6- or 12-months post-intervention, had sample sizes >100, were conducted in North America, Western Europe, Australia or New Zealand, so as to reflect populations that could be generalizable to the US; and published between January 1, 2010 to December 31, 2017. The intervention categories included: electronic/web-based, in-person counseling, pharmacotherapy, and telephone counseling. We selected these four categories based on clinical guidelines, expert opinion, and comparability to current ongoing trials in the screening setting (9, 10, 19). Trials that

tested multiple interventions or combinations of interventions were deemed eligible for inclusion. Importantly, trials had to include individuals between the ages of 55 and 80 with no signs or symptoms of lung cancer and with indications of heavy smoking (e.g., based on cigarettes per day, or pack-year smoking history) (3, 4, 8). We excluded studies that did not include individuals over 55 (defined as mean age of < two standard deviations below 55 in each study arm or trial-wide), or that focused on light smokers (defined as mean cigarettes per day of <10). Studies could include individuals who were light smokers or below the age of 55. As only a handful of trials reported pack-years, it was not feasible to screen studies using that measure. We excluded trials that focused exclusively on institutionalized populations such as prisoners, long-term care residents, and drug rehabilitation residents, individuals with known cancer or severe COPD, or people with mental illness. Pharmacotherapy interventions needed to use FDA approved drugs to be eligible (i.e., nicotine replacement therapy, bupropion, and varenicline) (20). Interventions that tested a drug not currently approved by the FDA were excluded, as these would not be available in current clinical practice.

Following the deletion of duplicate publications, all trial titles and abstracts were reviewed to determine potential eligibility. If the abstract lacked sufficient evidence to determine eligibility, it was included in the full-text review. Three authors independently screened a sample of papers to measure inter-rater reliability using Cohen's κ where a $\kappa = 0.8$ indicates good inter-rater agreement. Disagreements between reviewers regarding eligibility were resolved through discussion to achieve consensus. The remaining titles and abstracts were screened with each abstract screened separately by two authors. The results were reconciled and the final list of studies for full-text review was identified.

The full-text of selected publications was then reviewed to determine final eligibility and identify multiple reports from the same trial. Where multiple reports of the same intervention were found, we used the report with the greatest level of detail regarding the effects of the intervention on smoking cessation at 6 and 12-months. Two reviewers conducted full-text review independently and any uncertainty over inclusion was discussed and resolved among three authors.

2.3 Data Abstraction and Quality Assessment

A data abstraction template was developed in Microsoft Excel 2010. Two reviewers independently abstracted data; disagreements on data elements were resolved by consensus. A random sample was re-abstracted by a third author for quality control; any discrepancies were resolved and the process updated as needed. Each intervention was classified into a category (electronic/web-based, in-person counseling, pharmacotherapy, or telephone counseling). When more than one intervention was included, trials were classified based on their primary focus. In these multimodal trials, primary focus was determined by the trial report. For instance, Burns et al. conducted a two-arm trial in the NY State Quitline where participants in the intervention arm were randomized to receive 4 vs. 8 weeks of NRT. This study would be classified as a pharmacotherapy intervention as both the intervention and control arms received the quitline care, but only the intervention arm received NRT. As another example, Wetter et al. conducted a trial where smokers received and initial group

counseling session followed by computer-based treatment vs. no further treatment. The intervention arm in this trial would be considered a multimodality electronic/web-based intervention as the control did not receive the computer-based treatment. Where a primary intervention was not specified we selected the intervention component that had to be fulfilled in order to receive supplemental components. All supplemental intervention types were noted. Trials with multiple intervention arms of the same generic type were combined and compared to the study's specified control arm (23). When intervention arms were of different intervention types, they were not combined.

Data were abstracted for the self-reported and biochemically verified number of individuals in each arm who were abstinent based on 7-day point prevalence of cessation at 6 and 12-months and the total number in the arm; all data abstraction was based on intention-to-treat. We assumed that participants lost to follow-up were not successful in smoking cessation. Additionally, we abstracted data on sample size, retention rate, the proportion of eligible individuals who enrolled in the trial, age, smoking history (cigarettes per day, years smoking, and pack-years, if available), active vs. minimal/usual care control, motivation to quit, whether or not conflicts of interest were reported by the authors, and funding source. The response rate by intervention arm were not abstracted.

We assessed the methodological quality of trials using an established system (24, 25). Studies were given one point based on having each of the following criteria: 1) a description of the methodology of randomization; 2) randomization resulted in balanced groups; 3) a description of the methods of masking participant allocation; 4) use of double-blinding when feasible; 5) a description of the follow-up rates and reasons for withdrawal; and 6) reported all study outcomes. Trials could receive a total of six points. In this system, a score of two or less was considered poor quality, and scores of three and above were deemed of moderate to high quality (24). The Society for Research on Nicotine and Tobacco recommends that studies with a significant in-person component use biochemical verification (26). Therefore, studies in the in-person counseling groups only received the point for reporting outcomes if they presented biochemically verified results. Additionally, as double-blinding is not always feasible in certain intervention types (electronic/web-based, in-person counseling, or telephone counseling) these interventions were scored out of five points, where two or more points were deemed moderate to high quality (27). Factors such as response rate, or mode of recruitment were not considered as indicators of study quality.

2.4 Data Synthesis and Analysis

The primary analysis was based on self-reported or biochemically verified 7-day abstinence at 6-months in the intervention arm vs. the control arm; 12-month outcomes were a secondary endpoint. When available, biochemically verified cessation rates were used for analysis; otherwise, cessation outcomes were self-reported.

We estimated potential publication bias using contour-enhanced funnel plots where an asymmetric plot suggests the possibility that studies with null intervention effects were less likely to be published than those with significant results (28). Funnel plot asymmetry was assessed using a simple weighted linear regression proposed by Peters, *et al.* rather than Egger's test, since the latter does not perform well when examining effects in large numbers

of studies with moderate to high heterogeneity (28). A p-value $p<0.05$ for Peters' test is considered an indication of possible publication bias.

The DerSimonian and Laird random-effects method was used to determine odds ratios and 95% confidence intervals for each intervention category, where each study effect was weighted by its sample size and variance (29, 30). The random-effects model, which recognizes variance between and within studies, was employed because heterogeneity was expected based on differences in interventions and patient populations. A measure of heterogeneity (I^2) was also calculated. I^2 values of 50%−75% and ≥75% indicate moderate and high heterogeneity, respectively. For one study, there was no event in the control arm (i.e., no quitters). In this case, 0.5 was added to each cell (intervention and control) to avoid infinite odds (31).

Sensitivity analyses tested the effects on pooled cessation estimates at 6-months for intervention arms that included pharmacotherapy as a supplemental intervention vs. not; single-vs. multi-modality interventions, where the intervention arm included supplementary interventions beyond the primary intervention type (including pharmacotherapy); if the study was able to enroll >50% of eligible patients; and active vs. minimal or no intervention controls. Additionally, we analyzed the impact on effect sizes of omitting trials that were identified as being of poor quality, or were industry-sponsored, on outcomes at 6-months. Finally, we compared the pooled statistics of biochemically-verified-only results with self-report-only results at both 6- and 12-months.

All analyses were conducted in STATA 14.0 (StataCorp. 2015. College Station, TX.).

3. Results

Searches identified 3813 unique articles of potentially eligible trials. The full screening process and reasons for exclusion are outlined in the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 1). Through abstract and title review, 332 articles were identified as potentially eligible. Inter-rater reliability was high between the three reviewers (Cohen's κ 0.72-0.84). Following the full-text review, 85 trials were deemed eligible and data were abstracted.

The 85 trials in the final analytic sample included 74 that reported 6-month outcomes for 93,827 participants; and 40 that reported 12-month outcomes for 46,844 participants. The trials ranged in size from 103 to 16,430 participants and the majority were conducted in the US (Table 1). We identified 26 publications that used electronic or web-based intervention methods, 25 utilized in-person counseling, 25 utilized pharmacotherapy agents, and 14 utilized telephone counseling. Twenty-seven trials included more than one intervention arm; of these, 22 had intervention arms of similar types that were collapsed into one. Five trials had intervention arms that were categorized into separate primary intervention types (Table 1). Forty-five trials (52.9%) included biochemically verified smoking cessation outcomes. Fourteen trials did not report the number of eligible individuals who declined to participate, of those that did the majority (71.7%) enrolled >50% of eligible individuals. Results for studies with higher (50%+) vs. lower (<50%) participation were similar.

There were notable differences in the structure of interventions within the four categories (Table 1). Pharmacotherapy interventions included the use of nicotine replacement for a little as two weeks to up to a year; and included various combinations of NRT and bupropion or varenicline. In-person counseling interventions ranged from short (15 minute) one-time counseling sessions to multiple hour-long individual or group sessions. Both telephone and in-person counseling interventions may have included culturally tailored interventions. Electronic/web-based interventions included website based cessation programs, texting interventions, and email reminders. The majority of trial intervention arms (82.2%) were classified as multimodal interventions, and 53.3% included active controls.

3.1 Study Outcomes

All interventions showed increased odds of quitting smoking (vs control) based on 7-day point prevalence of smoking abstinence at 6-months, but the telephone counseling effect did not reach statistical significance (Figure 2 and Table 2). We found pooled odds ratios and 95% confidence intervals for electronic/web-based of 1.14 (1.03-1.25), in-person counseling 1.46 (1.25-1.70), and pharmacotherapy 1.53 (1.33-1.77) and telephone counseling 1.21 (0.98-1.50).

At 12 months, overall efficacy was lower across all intervention groups (Table 2 and Appendix B.2) and only pharmacotherapy (OR 1.46 95% CI 1.17-1.84) and in-person counseling (OR 1.28 95% CI 1.09-1.51) remained statistically significant.

3.2 Sensitivity Analyses

An examination of the role of pharmacotherapy as a supplemental intervention generally increased the odds of cessation, but results were not consistently statistically significant since most interventions included active controls (Table 2 and Appendix B.3.1). Multi-modality approaches had greater efficacy than single modality approaches (Table 2 and Appendix B.3.2), although single-modality pharmacotherapy interventions were more efficacious than other categories of multi-modality interventions; likely due to the use of placebo controls among the single-modality studies. Efficacy was higher for all intervention categories when compared to a minimal or no intervention control vs. an active control arm (Table 2 and Appendix B.3.3).

Results for biochemically verified abstinence did not differ appreciably from self-report at either 6- or 12-month outcomes (Table 2). The removal of poor quality studies, those that were unable to enroll >50% of eligible participants, and of studies that reported a conflict of interest had minimal impact on cessation outcomes at 6-months (Table 2).

3.3 Quality and Bias Assessment

Only nine of the 85 trials included were determined to be low quality (Appendix B.4). The contour-enhanced funnel plots suggest that there may be some publication bias for in-person counseling and pharmacotherapy at 6- and 12-months (Appendix B.5). Peters' test only found significant evidence of publication bias for the 6-month outcome of telephone counseling (Appendix B.6) suggesting among this group some trials may not have been published due to non-significant results. However, the interpretation of these results must

acknowledge the difficulty of regression based measures of publication bias to account for between study heterogeneity (32).

4. Discussion

This meta-analysis is the only large synthesis of data on the efficacy of multiple categories of current smoking cessation interventions with populations similar to those eligible for LCS. We found that most classes of smoking cessation interventions were effective in increasing abstinence at 6 months among patients eligible for LCS. Among these, the most efficacious were pharmacological interventions, followed by in-person counseling and web-based approaches. Telephone counseling did not reach statistical significance at the 95% level, although the direction of the association is promising. This non-significant result may, in part, be due to the smaller number of telephone counseling studies (n=9 at 6-months). Multimodal interventions appeared to be more efficacious than a single modality. Finally, the odds of 6-month cessation appear to persist to 12-months among pharmacotherapy and in-person counseling interventions suggesting that LCS sites should consider the implementation of these interventions.

Our study is unique in its focus on cessation in older age groups and those with a heavier smoking history, making the results relevant to the LCS setting. Our results are similar to those of preliminary reports of studies in the field that suggest a range of smoking cessation interventions will be effective for individuals eligible for LCS (11-18). The results of four prior reviews of smoking cessation interventions for older adults suggested, like our meta-analysis, that most currently recommended approaches to cessation might be effective among older smokers (17, 19, 33, 34). However, three reviews did not pool study effectiveness. Two of these reviews considered only studies conducted in the screening setting, but were limited by small numbers of observational and randomized controlled trials and a dearth of substantial high quality data inappropriate for meta-analyzing (16, 17). We found small effects, and our summary odds ratios had lower point estimates (but overlapping confidence intervals) than previous meta-analyses of smoking cessation in general populations (10, 35-38). In contrast to studies in the general population, telephone counseling was not statistically significantly associated at the 95% level with cessation in our sample of trials that included older and heavier smokers, although the point estimate suggests a positive association and the number of trials was the smallest among the intervention categories (10, 36).

Our finding of lower intervention efficacy in LCS populations compared to use of the same interventions when applied in the general populations could be due to a greater difficulty to quit among long-term, heavy smokers compared to other smokers. Alternatively, our estimates may be lower because we included trials with both active and minimal care control groups, whereas the previous reviews compared intervention groups to minimal intervention controls (10, 35, 36). Our sensitivity analysis removing studies with an active control resulted in more comparable, albeit still lower point estimates of efficacy, across all intervention categories (10, 27, 35, 36).

Our findings show that multimodal interventions are likely to be more efficacious than single-modality interventions, although the results were inconclusive due to smaller samples in sub-group analyses. The greater efficacy in the single-modality pharmacotherapy arms is likely due to the four studies in the single-modality sub-group being placebo-controlled trials compared to predominantly active control trials in the multi-modality group (Table 1). This will be an important area for future investigation, since, if effective, single modality approaches are likely to be less costly than multi-faceted interventions. Our results, like those of others (10, 36), suggest that supplemental pharmacotherapy will be beneficial as part of multi-modality approaches to improving the odds of cessation in the LCS setting. It is encouraging that our results support cessation at 12-months among pharmacotherapy and in-person counseling interventions. Since long-term abstinence is necessary for the realization of screening benefits on mortality, it will be critical to re-evaluate the long-term maintenance of abstinence as new research studies become available. The ongoing NCI-funded Smoking Cessation at Lung Examination (SCALE) Collaboration trials were designed to address these gaps and the results are expected after 2021 (9).

The results of our study must be considered in the current context of LCS. To date, fewer than 5% of eligible individuals have presented for lung cancer screening (39, 40). Individuals who present for LCS are likely different from those who are eligible and not referred or those who are referred, but do not attend. The characteristics of these individuals will likely impact their willingness to accept cessation and their ultimate success in quitting smoking. We are unaware of research that looks at the different characteristics of those who do and don’t present for screening. However, it is possible that due to the healthy adherer bias (41), individuals who present for lung cancer screening are more likely to quit on their own. This would likely reduce the efficacy of an intervention tested in this setting, as participants in both the intervention and control arms would be more likely to quit on their own. Additionally, studies examining smoking cessation in lung screening trials found cessation to be associated with screen-detected abnormalities which could further bias results towards the null (42). It is hoped that future research by the SCALE Trials will provide some insight into these interactions. This meta-analysis has several strengths, including the large pooled sample size, the rigor of the methods, quality of included studies, and focus on trials that included smokers eligible for LCS. There are also several limitations that should be noted in considering our results. Our subgroup analysis by enrollment rate suggests that the results of these studies are likely to be generalizable to the target populations of the studies. However, none of the studies in this meta-analysis solely included individuals eligible for LCS. All trials included some individuals that were younger and with a lighter smoking history than necessary to qualify for lung cancer screening, potentially over-estimating effects that may be seen among smokers eligible for LCS. The effects seen in cessation trials in the LCS setting could also vary based on implementation difficulties, measurement differences, or differences in settings and populations. More attention should be focused on smoking cessation interventions for the LCS population, given the opportunity that screening provides for bringing smokers into cessation services and the mandate from the Centers for Medicaid and Medicare Services to include cessation as part of effective screening programs (8). Second, the pooling of studies into generic categories limits the ability to look more in depth at individual interventions or combinations of individual

interventions, including the types or intensity of counseling, pharmacotherapy, and electronic interventions. Due to the limited number of studies in this setting, we were unable to compare results by specific types of pharmacotherapy or intervention intensity. Determining the most effective and feasible regimens in LCS is an important priority for future research.

5. Conclusion

The results of our meta-analysis provide important information to guide LCS sites, clinical practices, and health systems that are faced with having to make decisions about integrating smoking cessation interventions in their LCS practices ahead of definitive studies about cessation specific to screening populations. We found that multiple categories of cessation interventions are likely to be efficacious in a population similar to those undergoing LCS, but that screening sites looking for the most efficacious intervention could consider pharmacotherapy or in-person counseling since electronic/web-based and telephone counseling interventions either has non-significant effects at 6 months and/or failed to show effects on cessation at 12-months. With a wide range of possible effective interventions for screening sites to choose from, implementation will depend on feasibility, scalability, acceptability, cost, and specific characteristics of each environment and patient population. Results from ongoing clinical trials are expected to address several dimensions of implementation, efficacy, and cost (9). Until then, our results provide a useful framework for estimating the impact of different models of care for the integration of smoking cessation into the LCS setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

Appendix B.1:

Search Terms*

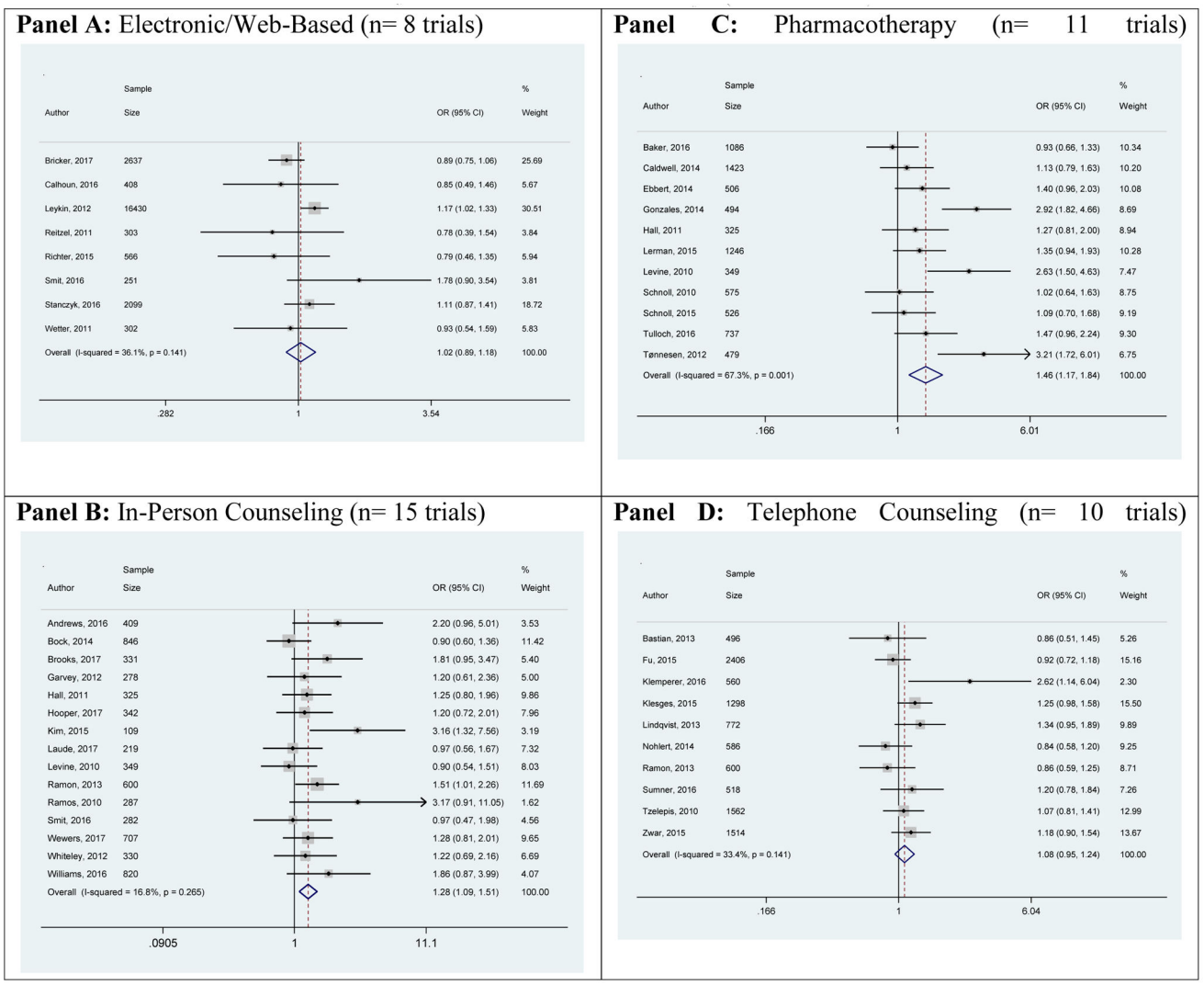
	Medline Search Strategy
1	smoking/ or pipe smoking/ or tobacco smoking/ or cigar smoking/ or cigarette smoking/ or vaping/
2	(cigar* or ecigarette* or smoking or tobacco or vaping).ti,ab,kw.
3	1 or 2
4	(abstinence or cessation or quit or quits or quitting or "stop smoking" or "stopped smoking").ti,ab,kw.
5	3 and 4
6	smoking cessation/ or smoking reduction/ or "tobacco use cessation"/ or "Tobacco Use Cessation Products"/
7	5 or 6
8	limit 7 to (english language and yr="2010 - 2017")
9	(8 and (adult/ or aged/ or middle aged/)) or (8 not (adolescent/ or young adult/ or child/ or infant/))
10	(9 and (north america/ or exp united states/ or exp australia/ or exp canada/ or exp europe/)) or (9 not (exp africa/ or exp asia/ or exp south america/))
11	("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or (randomi?ed adj7 (studies or study or trial or trials)).ti,ab,kw. or (controlled adj3 trial*).ti,ab,kw. or (clinical adj2 trial*).ti,ab,kw. or ((single or doubl* or tripl* or treb*) and (blind* or mask*)).ti,ab,kw. or ("4 arm" or "four arm").ti,ab,kw.
12	10 and 11

	PsycINFO Search Strategy
1	tobacco smoking/
2	(cigar* or smoking or tobacco).ti,ab,id.
3	1 or 2
4	(abstinence or cessation or quit or quits or quitting or "stop smoking" or "stopped smoking").ti,ab,id.
5	3 and 4
6	smoking cessation/
7	5 or 6
8	clinical trials/ or "treatment outcome clinical trial".md. or ((randomi?ed adj7 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*)) or (controlled adj3 trial*) or (clinical adj2 trial*)).ti,ab,id.
9	7 and 8
10	(aged 65 yrs older or middle age 40 64 yrs).ag.
11	(adolescence 13 17 yrs or school age 6 12 yrs or thirties 30 39 yrs).ag.
12	(9 and 10) or (9 not 11)
13	limit 12 to (all journals and english language and yr="2010 - 2017")

	PubMed Search Strategy
1	smoking[mesh:noexp] OR pipe smoking[mesh:noexp] OR tobacco smoking[mesh:noexp] OR cigar smoking[mesh:noexp] OR cigarette smoking[mesh:noexp] OR vaping[mesh:noexp]
2	(cigar*[tiab] OR ecigarette*[tiab] OR smoking [tiab] OR tobacco [tiab] OR vaping [tiab])
3	#1 OR #2

	Medline Search Strategy
4	(abstinence[tiab] OR cessation[tiab] OR quit[tiab] OR quits[tiab] OR quitting[tiab] OR "stop smoking"[tiab] OR "stopped smoking"[tiab])
5	#3 AND #4
6	smoking cessation[mesh:noexp] OR smoking reduction[mesh:noexp] OR "tobacco use cessation"[mesh:noexp] OR "Tobacco Use Cessation Products"[mesh:noexp]
7	#5 OR #6
8	#7 AND english[1a] AND 2010:2017[dp]
9	(#8 AND (adult[mesh:noexp] OR aged[mesh:noexp] OR middle aged[mesh:noexp])) OR (#8 NOT (adolescent[mesh:noexp] OR young adult[mesh:noexp] OR child[mesh:noexp] OR infant[mesh:noexp]))
10	(#9 AND (north america[mesh:noexp] OR united states[mesh] OR australia[mesh] OR canada[mesh] OR europe[mesh])) OR (#9 NOT (africa[mesh] OR asia[mesh] OR south america[mesh]))
11	Clinical Trial [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii" [pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial" [pt] OR "multicenter study" [pt] OR "randomized controlled trial" [pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials" [MeSH Terms:noexp] OR "multicenter studies as topic" [MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab] OR study[tiab] OR studies[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind* [TIAB] OR mask* [TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])
12	#10 AND #11
	PubMed Search Strategy
1	smoking[mesh:noexp] OR pipe smoking [mesh:noexp] OR tobacco smoking[mesh:noexp] OR cigar smoking[mesh:noexp] OR cigarette smoking[mesh:noexp] OR vaping[mesh:noexp]
2	(cigar* [tiab] OR ecigarette*[tiab] OR smoking[tiab] OR tobacco[tiab] OR vaping[tiab])
3	#1 OR #2
4	(abstinence[tiab] OR cessation [tiab] OR quit[tiab] OR quits[tiab] OR quitting [tiab] OR "stop smoking"[tiab] OR "stopped smoking"[tiab])
5	#3 AND #4
6	smoking cessation[mesh:noexp] OR smoking reduction[mesh:noexp] OR "tobacco use cessation" [mesh:noexp] OR "Tobacco Use Cessation Products"[mesh:noexp]
7	#5 OR #6
8	#7 AND english[1a] AND 2010:2017[dp]
9	(#8 AND (adult[mesh:noexp] OR aged[mesh:noexp] OR middle aged[mesh:noexp])) OR (#8 NOT (adolescent[mesh:noexp] OR young adult[mesh:noexp] OR child[mesh:noexp] OR infant[mesh:noexp]))
10	(#9 AND (north america[mesh:noexp] OR united states[mesh] OR australia[mesh] OR canada[mesh] OR europe[mesh])) OR (#9 NOT (africa[mesh] OR asia[mesh] OR south america[mesh]))
11	Clinical Trial [PT:NoExp] OR "clinical trial, phase i" [pt] OR "clinical trial, phase ii" [pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study" [pt] OR "randomized controlled trial" [pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials" [MeSH Terms:noexp] OR "multicenter studies as topic” [MeSH Terms:noexp] OR “Double-Blind Method”[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab] OR study[tiab] OR studies[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])
12	#10 AND #11

*On the advice of a research librarian, search terms were kept as broad as possible to find all potentially relevant smoking cessation studies. Studies were then eliminated during abstract and full-text review based on the a priori inclusion criteria (Figure 1).



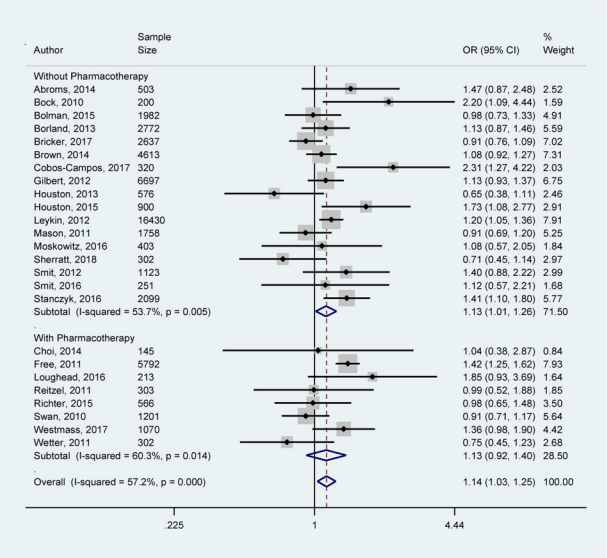
Appendix B.2: Odds of Smoking Cessation From Random-Effects Meta-Analysis of Trials with Smokers Potentially Eligible for Lung Screening Based on 7-day Point Prevalence of Abstinence at 12-Months by Primary Intervention Type (n= 40 Trials)*

Forest plots display weighted odds ratios and 95% confidence intervals of included trials. Trial weights are generated from a random effects analysis. Squares around point estimates indicate study weight relative to the lowest weighted study for each meta-analysis. The vertical dashed line represents the pooled odds ratio with the diamond representing the 95% confidence interval.

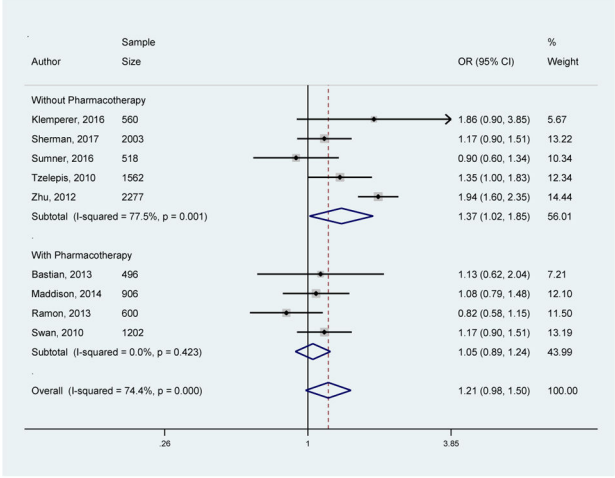
* Some trials included more than one intervention of a differing generic type so that the sum of the sample of all intervention types is greater than the total number of trials included.

B.3.1 With or Without Pharmacotherapy

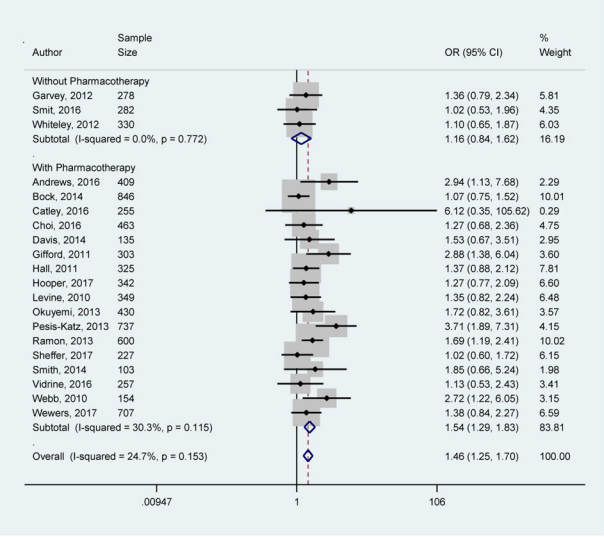
Panel A: Electronic/Web-Based (n= 25 trials)



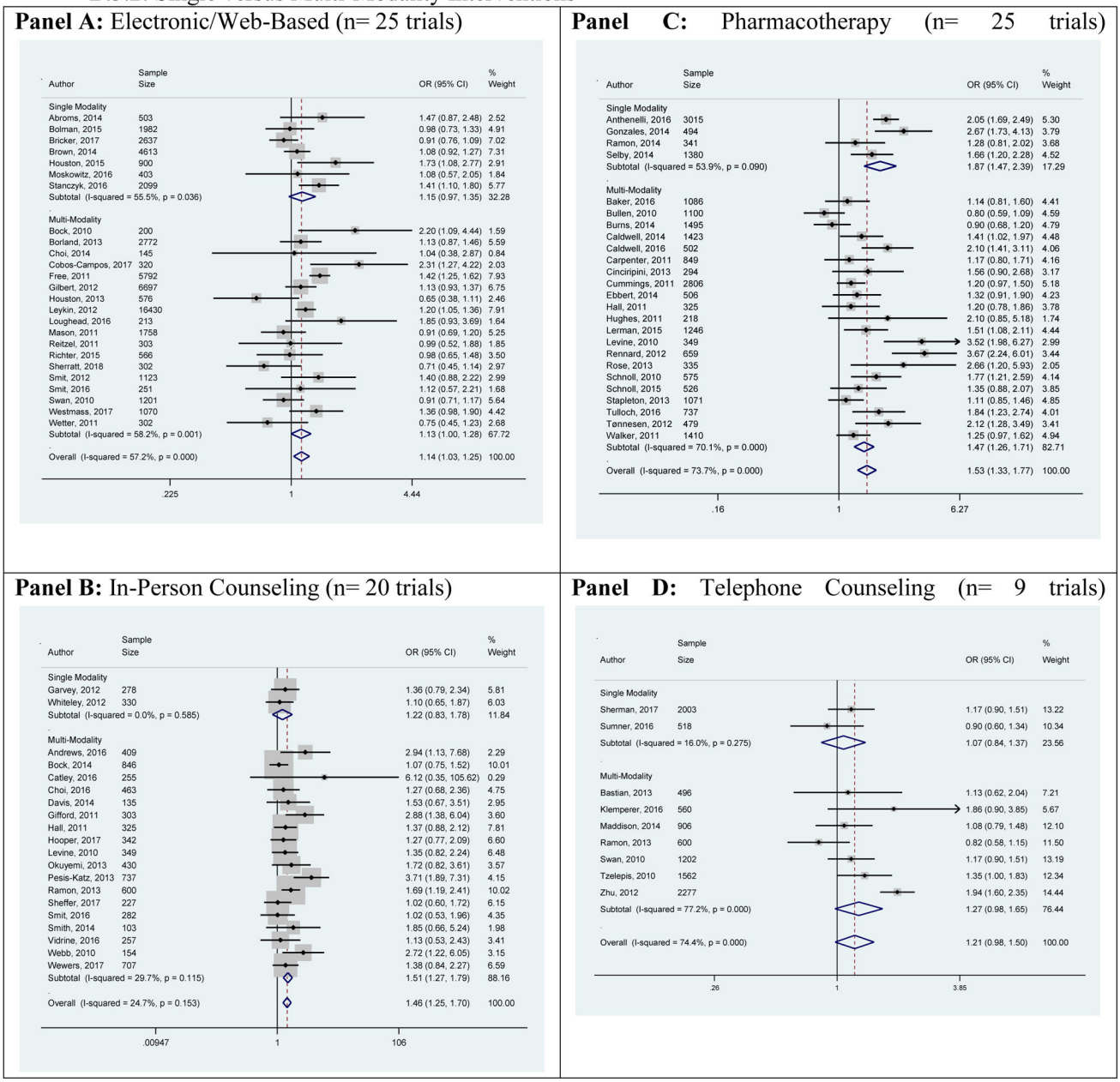
Panel C: Telephone Counseling (n= 9 trials)



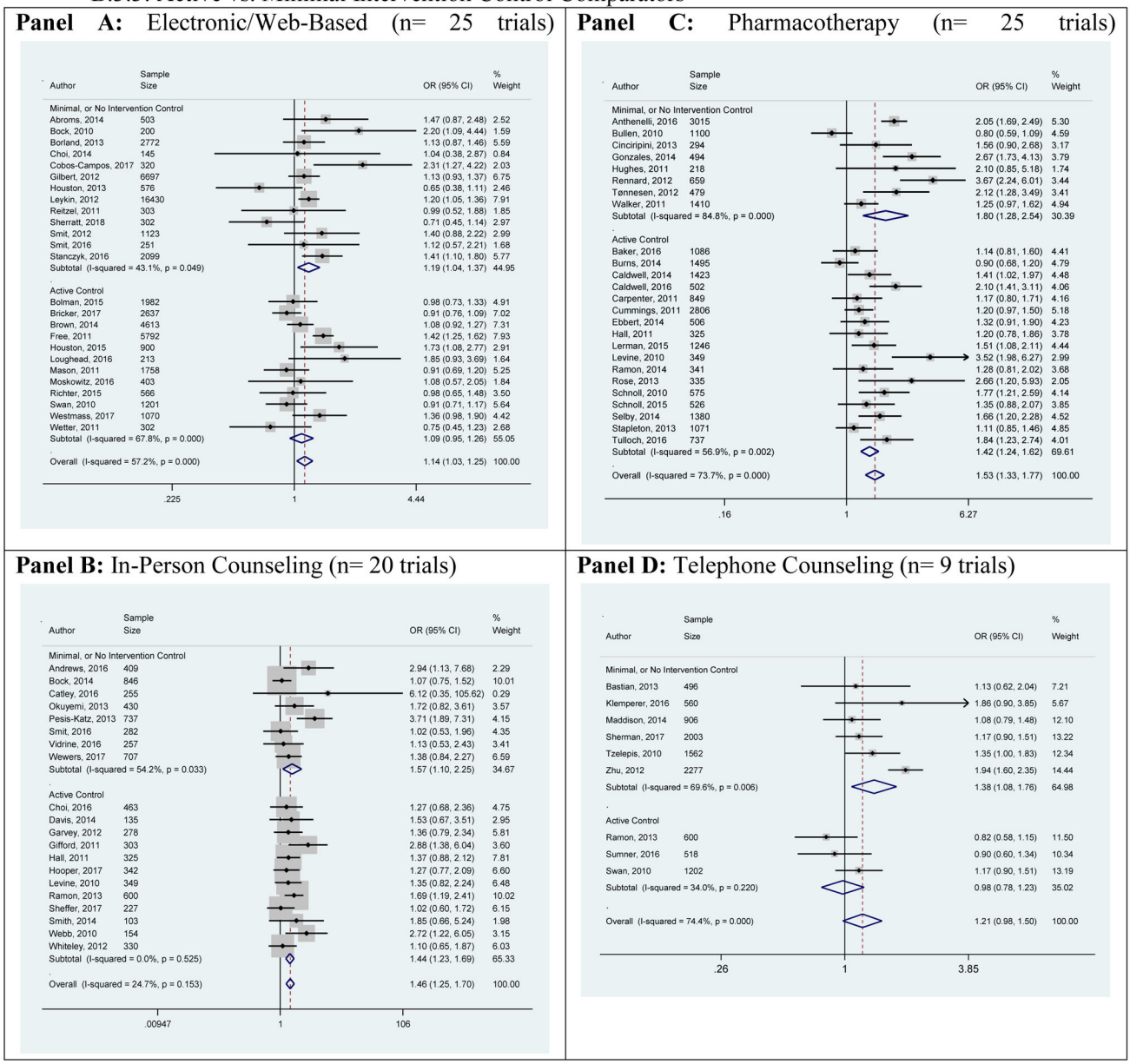
Panel B: In-Person Counseling (n= 20 trials)



B.3.2: Single versus Multi-Modality Interventions



B.3.3: Active vs. Minimal Intervention Control Comparators



Appendix B.3: Sensitivity Analyses Examining Change in Odds of Smoking Cessation From Random-Effects Meta-Analysis of Trials with Smokers Potentially Eligible for Lung Screening Based on 7-day Point Prevalence of Abstinence at 6-Months by Primary Intervention Type (n= 74 Trials)*

Forest plots display weighted odds ratios and 95% confidence intervals of included trials. Trial weights are generated from a random effects analysis. Squares around point estimates indicate study weight relative to the lowest weighted study for each meta-analysis. The vertical dashed line represents the pooled odds ratio with the diamond representing the 95% confidence interval.

* Some trials included more than one intervention of a differing generic type so that the sum of the sample of all intervention types is greater than the total number of trials included.

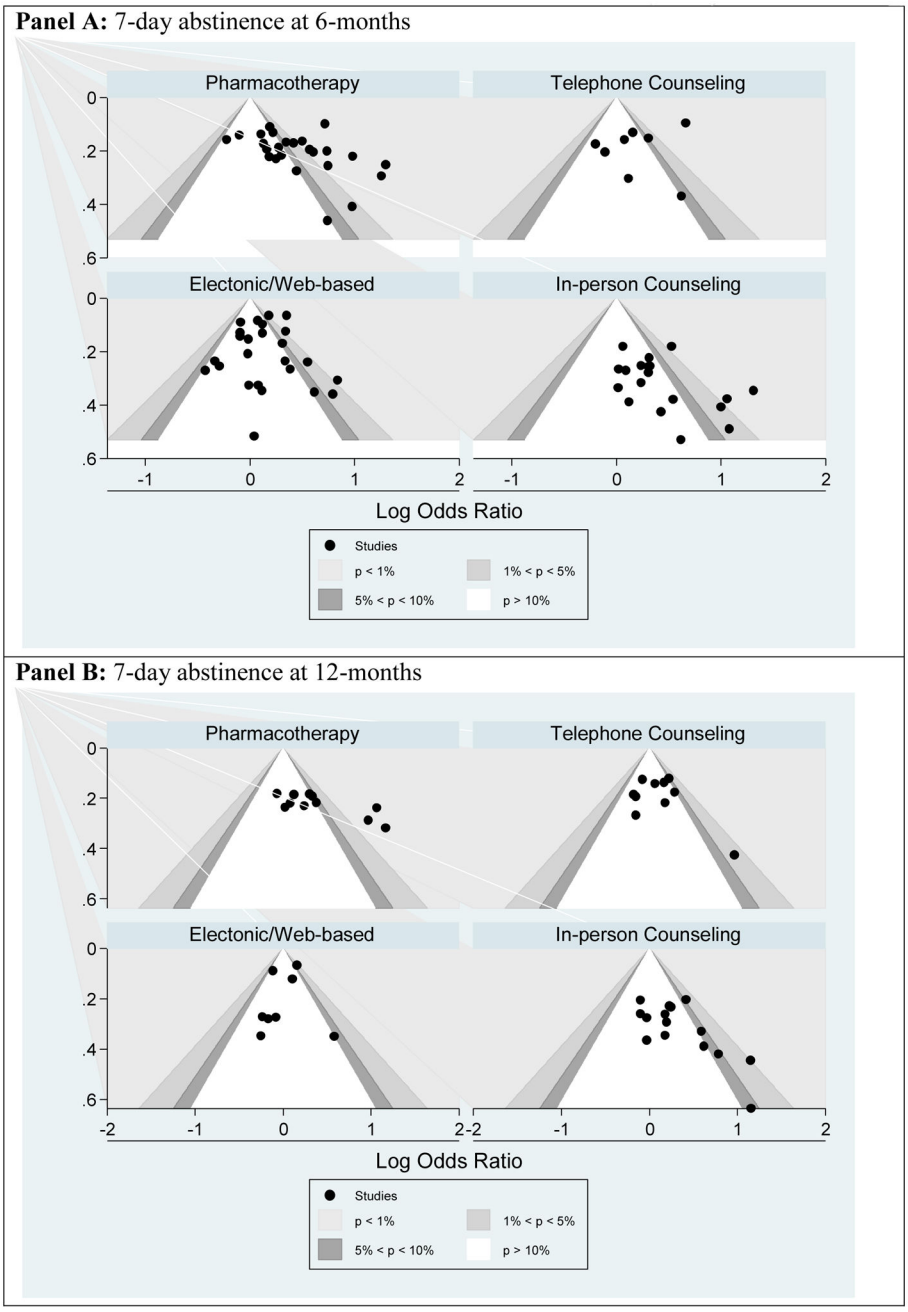
Appendix B.4:

Study Quality Assessment

Author, Year	Randomized (1/0)	Similar Patient Characteristics (1/0)	Double Blind (1/0)	Masking (1/0)	Withdrawal (1/0)	Selective Reporting (1/0)	Total
Electronic/Web-Based							
Abroms, 2014	1	1	NA	0	1	1	4
Bock, 2010	1	0	0	0	0	1	2
Bolman, 2015	1	1	NA	1	1	1	5
Borland, 2013	1	0	NA	1	1	1	4
Bricker, 2017	1	1	NA	1	1	1	5
Brown, 2014	1	1	NA	1	1	1	5
Calhoun, 2016	1	1	NA	0	1	0	3
Choi, 2014	0	0	NA	1	1	1	3
Cobos-Campos, 2017	1	0	NA	0	1	1	3
Free, 2011	1	1	NA	1	1	1	5
Gilbert, 2013	1	0	NA	0	1	1	3
Houston, 2013	1	0	NA	1	0	1	3
Houston, 2015	1	1	NA	1	0	1	4
Leykin, 2012	1	1	NA	0	1	1	4
Loughead, 2016	1	1	NA	0	1	1	4
Mason, 2012	1	1	NA	1	1	1	5
Moskowitz, 2016	1	0	NA	1	1	1	4
Reitzel, 2011	0	1	NA	0	0	1	2
Richter, 2015	1	1	NA	0	1	1	4
Sheratt, 2018	1	0	NA	1	0	1	3
Smit, 2012	1	1	NA	0	1	1	4
Stanczyk, 2016	1	0	NA	1	1	1	4
Westmass, 2018	1	1	NA	0	0	1	3
Wetter, 2011	1	1	NA	0	1	1	4
In-Person Counseling							
Andrews, 2016	0	1	NA	1	1	1	4
Bock, 2014	1	0	NA	0	1	0	2
Brooks, 2017	1	0	NA	0	1	1	3
Catley, 2016	1	1	NA	1	1	1	5
Choi, 2016	1	1	NA	0	1	1	4
Davis, 2014	0	0	NA	1	1	1	3
Garvey, 2012	1	1	NA	0	0	0	2
Gifford, 2011	1	1	NA	0	1	0	3
Hooper, 2017	0	1	NA	0	1	1	3

Author, Year	Randomized (1/0)	Similar Patient Characteristics (1/0)	Double Blind (1/0)	Masking (1/0)	Withdrawal (1/0)	Selective Reporting (1/0)	Total
Kim, 2015	1	0	NA	1	1	1	4
Laude, 2017	1	0	NA	0	1	1	3
Okuyemi, 2013	1	1	NA	0	1	1	4
Pesis-Katz, 2011	0	1	NA	0	0	0	1
Ramos, 2010	1	0	NA	1	1	1	4
Sheffer, 2017	1	0	NA	1	0	1	3
Smith, 2014	0	0	NA	0	1	1	2
Vidrine, 2016	1	1	NA	0	1	1	4
Webb, 2010	1	1	NA	0	1	1	4
Wewers, 2017	0	1	1	1	1	1	5
Whiteley, 2012	0	1	NA	1	1	1	4
Williams, 2016	0	0	NA	0	0	0	0
Pharmacotherapy							
Anthenelli, 2016	1	1	1	1	1	1	6
Baker, 2016	1	0	0	0	1	1	3
Bullen, 2010	1	0	NA	1	1	1	4
Burns, 2014	0	1	0	0	1	1	3
Caldwell, 2016	1	1	1	1	0	0	4
Caldwell, 2014	1	1	1	1	1	1	6
Carpenter, 2011	1	1	NA	0	0	1	3
Cinciripini, 2013	1	1	1	1	1	1	6
Cummings, 2011	0	1	NA	1	1	1	4
Ebbert, 2014	1	1	1	1	1	1	6
Gonzales, 2014	1	1	1	1	0	1	5
Hughes, 2011	1	1	1	1	1	1	6
Lerman, 2015	1	1	1	1	1	1	6
Ramon, 2014	1	1	0	1	1	1	5
Rennard, 2012	1	1	1	1	1	1	6
Rose, 2013	0	1	1	1	0	1	4
Schnoll, 2015	1	1	0	0	1	1	4
Schnoll, 2010	1	1	1	1	1	1	6
Selby, 2014	1	0	NA	0	0	1	2
Stapleton, 2013	1	0	0	0	1	1	3
Tønnesen, 2012	1	1	1	1	0	1	5
Tulloch, 2016	1	1	0	0	1	1	4
Walker, 2011	1	0	NA	1	1	1	4
Telephone Counseling							
Bastian, 2013	0	1	NA	0	1	0	2

Author, Year	Randomized (1/0)	Similar Patient Characteristics (1/0)	Double Blind (1/0)	Masking (1/0)	Withdrawal (1/0)	Selective Reporting (1/0)	Total
Fu, 2015	0	1	NA	1	1	1	4
Klemperer, 2017	1	1	NA	1	1	0	4
Klesges, 2015	1	1	NA	1	1	1	5
Lindqvist, 2013	1	1	NA	0	1	1	4
Maddison, 2014	0	1	NA	1	1	1	4
Nohlert, 2014	0	0	NA	0	1	1	2
Sherman, 2018	1	0	NA	0	1	1	3
Sumner, 2016	1	1	NA	0	1	1	4
Tzelepis, 2010	1	0	NA	1	1	1	4
Zhu, 2012	1	1	NA	0	1	1	4
Zwar, 2015	0	1	NA	1	1	1	4
Multiple Interventions							
Hall, 2011	1	1	0	1	1	1	5
Levine, 2010	0	1	1	0	1	1	4
Ramon, 2013	1	1	NA	0	1	1	4
Smit, 2016	1	1	NA	0	1	1	4
Swan, 2010	1	1	NA	0	1	1	4



Appendix B.5: Contour-Enhanced Funnel Plots to Assess Publication Bias of Smoking Cessation Interventions from a Random Effects Meta-Analysis by Intervention Type

Funnel plots compare the effect estimate of a study to some measure of its precision. Larger more powerful studies are placed at the top and smaller less powerful studies are at the bottom. Contour-enhanced funnel plots add areas of statistical significance to aid in the identification of areas of significance or non-significance from which studies appear to be missing.

Appendix B.6:

Results of Peters et al.'s Regression Test for Publication Bias of Smoking Cessation Interventions from a Random Effects Meta-Analysis by Intervention Type at 6- and 12-Months

Intervention Category	6-Month p-Value	12-Month p-Value
Electronic/Web-Based	0.871	0.552
In-Person Counseling	0.866	0.325
Pharmacotherapy	0.212	0.122
Telephone Counseling	0.048	0.992

Abbreviations:

CMS	Centers for Medicare and Medicaid Services
FDA	Food and Drug Administration
LCS	lung cancer screening with low-dose computed tomography
NCCN	National Comprehensive Cancer Network
NELSON	Nederlands-Leuvens Longkanker Screenings ONdersoek trial
NLST	National Lung Screening Trial
OR	Odds Ratio
SCALE	Smoking Cessation at Lung Examination trials
USPSTF	United States Preventive Services Task Force
95% CI	95% Confidence Interval

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Highlights:

- Many efficacious interventions exist that could be implemented by screening sites.
- Cessation estimates are lower than the general population.
- Multi-modality interventions appear to be most efficacious.
- Cessation persists at 12-months in two intervention categories.

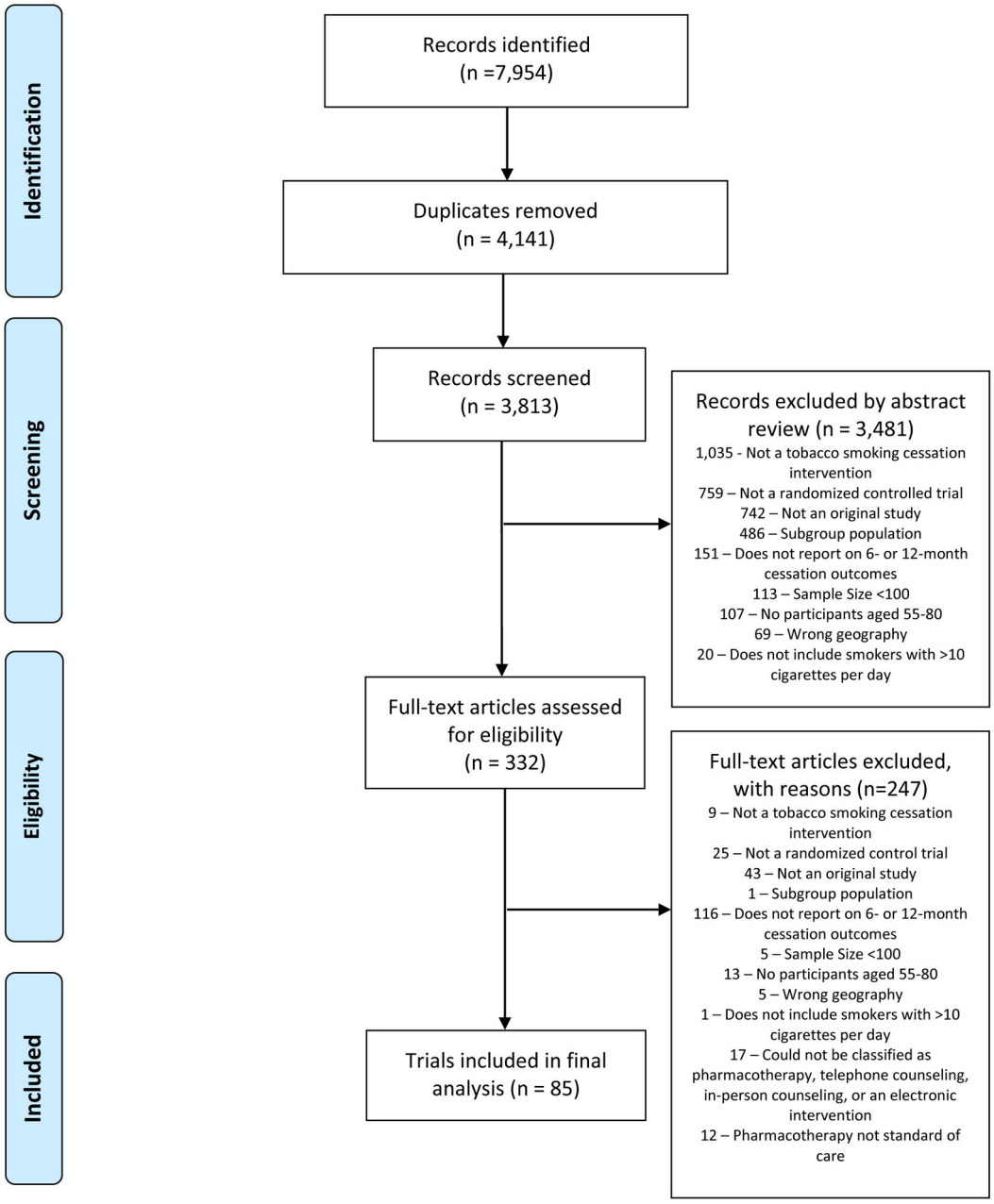

Figure 1: Selection of Trials Published from 2010 to 2018 to Estimate the Efficacy of Smoking Cessation in Lung Screening-eligible Populations

The PRISMA diagram depicts the flow of studies through the phases of the systematic review from study identification to data analysis. A priori reasons for exclusion are presented at each stage.

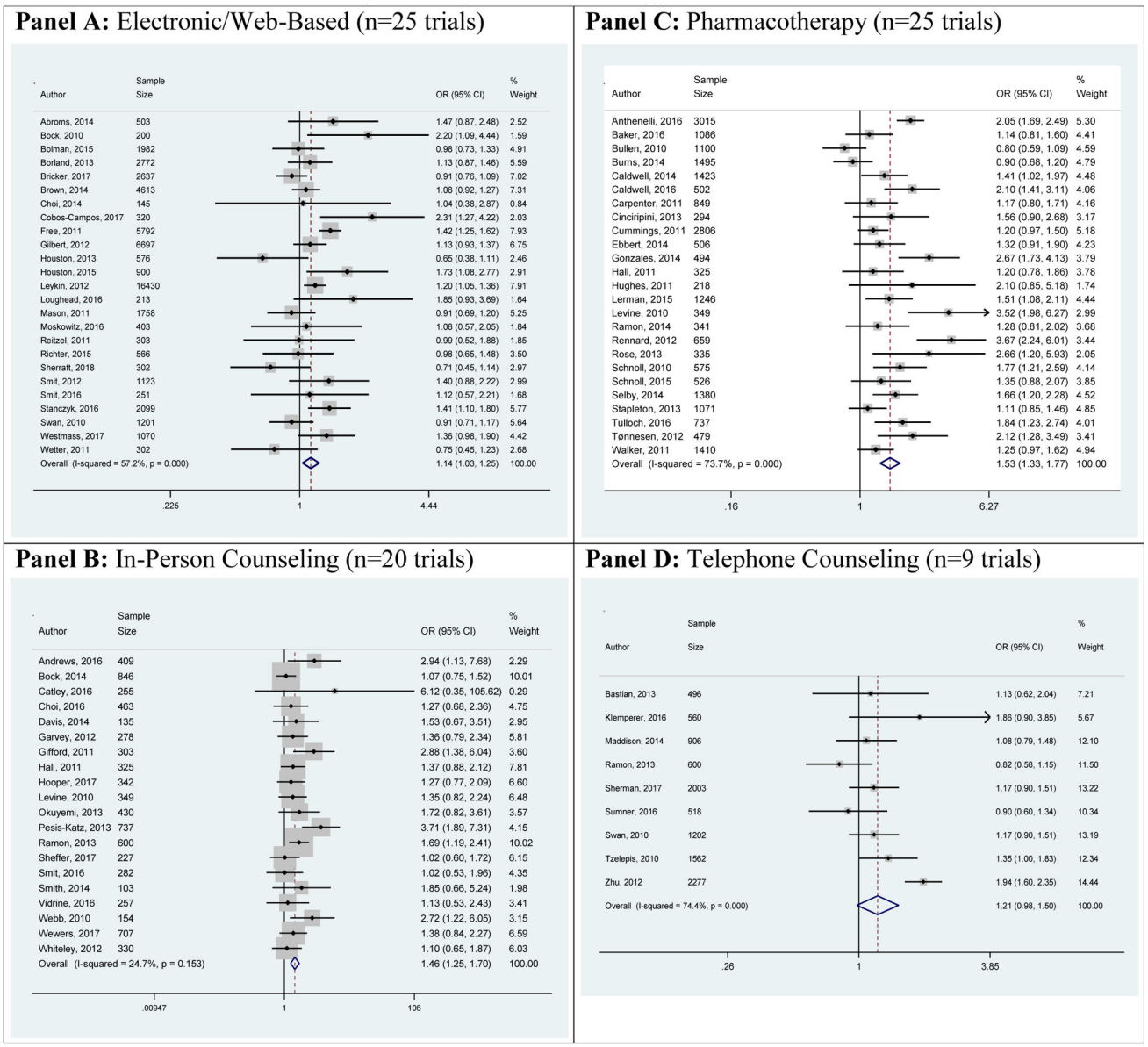

Figure 2: Odds of Smoking Cessation From Random-Effects Meta-Analysis of Trials with Smokers Potentially Eligible for Lung Screening Based on 7-day Point Prevalence of Abstinence at 6-Months by Primary Intervention Type (n= 74 Trials)*

Forest plots display weighted odds ratios and 95% confidence intervals of included trials. Trial weights are generated from a random effects analysis. Squares around point estimates indicate study weight relative to the lowest weighted study for each meta-analysis. The vertical dashed line represents the pooled odds ratio with the diamond representing the 95% confidence interval.

* Some trials included more than one intervention of a differing generic type so that the sum of the sample of all intervention types is greater than the total number of trials included.

Table 1:

Characteristics of Trials Included in Meta-Analysis of Smoking Cessation Efficacy by Category of Intervention.

Authors	Year	Intervention Description	Multi-Modal Intervention	Biochemical Verification	Outcome	Sample Size	Mean Age (SD)*	Mean Cigarettes per Day (SD)*	Response Rate at 6-months
Electronic/Web-Based									
Abroms et al. (43)	2014	Text messaging vs. website control	Yes	Yes	6-months	503	35.7 (10.7)	17.29 (8.03)	76%
Bock et al.(44)	2010	Computer driven individually tailored intervention vs. computer driven individually tailored intervention with NRT	Yes	Yes	6-months	300	~45.5 (10.8)	~18.2 (9.1)	80%
Bolman et al. (45)	2015	Computer tailored cessation messages with action plan vs. computer tailored cessation messages	No	No	6-months	1982	38.8 (11.4)	NR	23%
Borland et al. (46)	2013	Personalized internet-delivered advice program vs. text messaging program	Yes	No	6-months	3530	42.1 (NR)	16.9 (NR)	86%
Bricker et al. (47)	2017	Website based behavioural cessation program vs. standard cessation website	No	No	6- and 12-months	2637	46.2 (13.4)	NR −33% smoke >20 CPD	88%
Brown et al. (48)	2014	Interactive website vs. control website	No	No	6-months	4613	39.5 (13)	18.7 (8.9)	72%
Calhoun et al. (49)	2016	Internet-based tele-health intervention vs. clinic referral	Yes	No	12-months	413	42.9 (13.9)	15.2 (8.7)	NR
Choi et al.(50)	2014	Interactive website with nurse counseling by phone vs. state quitline	Yes	No	6-months	145	42 (9.5)	20.9 (9.9)	73%
Cobos-Campos et al. (51)	2017	Texting intervention + brief counseling vs. brief counseling alone	Yes	Yes	6-months	320	45 (9.1)	NR −94.6% >5 CPD	46%
Free et al.(52)	2011	Text message cessation program vs. non-cessation related text message program	Yes	No	6-months	5800	~36.8 (11)	NR	96%
Gilbert et al. (53)	2013	Computer tailored cessation advice and progress report vs. non-tailored information	Yes	No	6-months	6911	44.6 (12.2)	17.8 (9.4)	75%
Houston et al. (54)	2013	Cessation website and brief advice vs. usual care	Yes	No	6-months	576	NR −43.2 % aged 45+	NR	98%
Houston et al. (55)	2015	Enhanced cessation website with counselor messenger vs. enhanced cessation website vs. control website	No	No	6-months	900	NR −33 % aged 55+	NR – 73% smoke >10 CPD	51%

Authors	Year	Intervention Description	Multi-Modal Intervention	Biochemical Verification	Outcome	Sample Size	Mean Age (SD)*	Mean Cigarettes per Day (SD)*	Response Rate at 6-months
Leykin et al. (56)	2012	Four internet-based smoking cessation interventions of increasing intensity	Yes	No	6- and 12-months	16430	~36.5 (14.5)	−19.5 (10.1)	25%
Loughead et al.(57)	2016	Web-based relaxation guide and 8-weeks NRT vs. Web-based relaxation and cognitive conditioning with 8-weeks NRT	Yes	Yes	6-months	213	43.3 (12.5)	16.1 (5.7)	83%
Mason et al. (58)	2012	Computer tailored cessation advice and progress report vs. non-tailored content	Yes	No	6-months	1758	37.8 (11.3)	18.2 (8.7)	NR
Moskowitz et al.(59)	2016	Internet-based program vs. virtual support and reinforcement	Yes	No	6-months	403	40.7 (10.6)	13.1 (6.8)	50%
Reitzel et al. (60)	2011	Computer delivered treatment vs. standard treatment; plus pharmacotherapy	Yes	Yes	6- and 12-months	303	41.4 (10.1)	22.5 (10.4)	NR
Richter et al. (61)	2015	4 computer-based telemedicine sessions in primary care setting vs. 4 sessions of telephone counseling	Yes	No	6- and 12-months	566	47.4 (12.9)	19.7 (10.3)	86%
Sherratt et al. (62)	2018	Computer-based lung cancer risk projection and brief counseling and personalized pamphlet vs. generic smoking risk pamphlet	Yes	No	6-months	302	~42 (NR)	~20 (NR)	62%
Smit et al.(63)	2012	Fully automated web-based smoking cessation program vs. no intervention	Yes	No	6-months	1129	~48.4 (12.2)	20.6 (12.4)	26%
Stanczyk et al. (64)	2016	Text messaging vs. video messaging vs. brief message control	No	No	6- and 12-months	2099	45.7 (12.8)	18.8 (8.6)	58%
Westmass et al.(65)	2018	Three varying level of intensity of emailed cessation advice	Yes	No	6-months	1070	40.3 (11.8)	17.4 (7.9)	60%
Wetter et al. (66)	2011	Initial group counseling followed by computer delivered treatment vs. no further treatment	Yes	Yes	6- and 12-months	302	~44 (11.2)	~20.5 (8)	98%
In-person Counseling									
Andrews et al. (67)	2016	Community health worker and group support sessions vs. written materials	Yes	Yes	6- and 12-months	409	~41.1 (14.1)	~12.6 (7.5)	93%
Bock et al.(68)	2014	Motivational enhancement treatment, physician advice, and NRT vs. standard care	Yes	Yes	6- and 12-months	846	39.6 (11.4)	NR	50%

Authors	Year	Intervention Description	Multi-Modal Intervention	Biochemical Verification	Outcome	Sample Size	Mean Age (SD)*	Mean Cigarettes per Day (SD)*	Response Rate at 6-months
Brooks et al. (69)	2017	Multiple visits by Tobacco Treatment Advocate vs. single visit	Yes	Yes	12-months	331	NR −68 % aged 40+	NR 43.2% smoke >10 CPD	76%†
Catley et al. (70)	2016	4 sessions of motivational interviewing vs. 4 sessions of health education vs. brief advice	Yes	Yes	6-months	255	45.8 (10.9)	17.1 (8.9)	89%
Choi et al.(71)	2016	Culturally tailored counseling program vs. untailored counseling program	Yes	Yes	6-months	463	44.3 (NR)	15.4 (NR)	54%
Davis et al. (72)	2014	Mindfulness counseling program vs. American Lung Association matched program	Yes	Yes	6-months	135	44.5 (12.7)	17.7 (8.6)	44%
Garvey et al. (73)	2012	Front-loaded counseling vs. weekly counseling	No	No	6- and 12-months	278	46.9 (11.5)	17.9 (7.9)	90%
Gifford et al. (74)	2011	Bupropion with acceptance and relationship focused behavioural intervention vs. bupropion alone	Yes	Yes	6-months	303	~45.8 (12.8)	~24.0 (8.6)	70%
Hooper et al. (55)	2017	8 group sessions of culturally tailored cognitive behavioral therapy vs. 8 standard cognitive behavioural therapy sessions; both with NRT	Yes	Yes	6- and 12-months	342	49.5 (NR)	18.0 (10.8)	87%
Kim et al.(75)	2015	Culturally tailored counseling vs. standard counseling; plus NRT	Yes	Yes	12-months	109	49.7 (9.3)	17.1 (5.8)	73%
Laude et al. (76)	2017	In-person cognitive behavioral therapy for 26 weeks vs. 48 weeks	Yes	Yes	12-months	219	~42.1 (12.1)	~16.7 (5.9)	93%
Okuyemi et al. (77)	2013	NRT and motivational interviewing vs. NRT and brief advice	Yes	Yes	6-months	430	44.4 (9.9)	19.3 (13.7)	75%
Pesis-Katz et al.(78)	2011	Four sessions with health counselors vs. smoking cessation pamphlets and information on local treatment programs	Yes	Yes	6-months	737	~45.8 (12)	~20.2 (10)	70%
Ramos et al. (79)	2010	Individual counseling vs. group counseling vs. minimal intervention	Yes	Yes	12-months	287	~45 (10.9)	~20 (NR)	50%
Sheffer et al. (80)	2017	6 standard cognitive behavioral therapy sessions vs. 6 socioeconomic status adapted cognitive behavioral therapy session	Yes	Yes	6-months	227	48.2 (9)	13.8 (7.4)	88%
Smith et al. (81)	2014	Culturally tailored in-person counseling for American Indian/Alaska Native vs. non-tailored	Yes	Yes	6-months	103	39.8 (13.1)	14.4 (7.9)	95%

Authors	Year	Intervention Description	Multi-Modal Intervention	Biochemical Verification	Outcome	Sample Size	Mean Age (SD)*	Mean Cigarettes per Day (SD)*	Response Rate at 6-months
		counseling; plus varenicline							
Vidrine et al. (82)	2016	Mindfulness-based counseling program vs. cognitive behavioral therapy vs. brief counseling session	Yes	Yes	6-months	485	48.7 (11.9)	19.9 (10.1)	56%
Webb et al. (83)	2010	Group cognitive behavioral therapy vs. group general health education; plus NRT	Yes	No	6-months	154	44 (NR)	13 (NR)	70%
Wewers et al. (84)	2017	In-person counselling from community health worker vs. quitline	Yes	Yes	6- and 12-months	707	NR −30.7 % aged 55+	~22.3 (11.7)	85%†
Whiteley et al. (85)	2012	Cognitive behavioral therapy + exercise vs. cognitive behavioral therapy + contact control	No	Yes	6- and 12-months	330	43.52 (9.96)	17.48 (7.16)	81%
Williams et al. (86)	2016	In-person counseling 8 session + medication vs. 8 sessions alone vs. 6 sessions	Yes	No	12-months	820	47.39 (NR)	18.87 (NR)	25%
Pharmacotherapy									
Anthenelli et al.(87)	2016	Varenicline vs. bupropion vs. nrt patch vs. placebo	No	Yes	6-months	4028	~46.1 (12.8)	~20.8 (8.2)	78%
Baker *et al*(88)	2016	Varenicline vs. NRT Patch with Lozenge vs. NRT patch	Yes	Yes	6- and 12-months	1086	48.1 (11.6)	17.0 (8.3)	84%†
Bullen et al. (89)	2010	Pre-cessation NRT in quitline vs. quitline usual care	Yes	Yes	6-months	1100	39.6 (13.1)	19 (8.7)	74%
Burns et al. (90)	2014	4 vs. 8 weeks of NRT in state quitline	Yes	No	6-months	1495	NR −15.3% aged 55+	~19.8 (NR)	58%
Caldwell and Crane(91)	2016	NRT inhaler vs. placebo inhaler both with NRT patch 5 weeks	Yes	No	6-months	502	~45.2 (11.2)	~19 (6.7)	62%
Caldwell et al. (92)	2014	Nicotine spray vs. placebo both with NRT patch	Yes	Yes	6- and 12-months	1423	~45.6 (11.4)	~20 (7.3)	20%
Carpenter et al.(93)	2011	NRT sampling and practice quit attempt vs. practice quit attempt alone	Yes	No	6-months	849	~50.5 (11.8)	~18.6 (8.8)	87%
Cinciripini et al.(94)	2013	12-weeks of Varenicline, Bupropion, or Placebo plus intensive counseling	Yes	Yes	6-months	294	44.3 (10.43)	19.7 (9.36)	73%
Cummings et al.(95)	2011	Callers to quitline randomized to 2, 4, or 6 weeks of NRT patch	Yes	No	6-months	2806	NR ~27.9% aged 55+	NR 67.8% smoke >20 CPD	60%
Ebbert et al. (96)	2014	12 weeks of varenicline/ bupro pion combination vs. 12 weeks varenicline/ placebo	Yes	Yes	6- and 12-months	506	~42.2 (12.2)	~19.5 (7.3)	60%

Authors	Year	Intervention Description	Multi-Modal Intervention	Biochemical Verification	Outcome	Sample Size	Mean Age (SD)*	Mean Cigarettes per Day (SD)*	Response Rate at 6-months
Gonzales et al. (97)	2014	Varenicline vs. Placebo	No	Yes	6- and 12-months	498	47.5 (NR)	20 (NR)	63%†
Hughes et al. (98)	2011	Varenicline vs. placebo; plus behavioral counseling	Yes	Yes	6-months	218	~45 (13)	~19 (9)	70%
Lerman et al. (99)	2015	Verenicline + patch vs. patch + placebo vs. Placebo	Yes	Yes	6- and 12-months	1246	45 (12)	17.5 (5.9)	71%
Ramon et al. (l00)	2014	Varenicline + patch vs. Varenicline + placebo	No	No	6-months	341	~44.1 (14.8)	~29.2 (NR)	71%
Rennard et al. (101)	2012	Varenicline vs. placebo	Yes	No	6-months	650	~43.9 (12.5)	~21.3 (NR)	NR
Rose and Behm(102)	2013	NRT patch vs. bupropion + NRT patch vs. varenicline	Yes	Yes	6-months	335	~46.0 (10.8)	~21.9 (8.8)	58%
Schnoll et al. (103)	2015	8 vs. 24 vs. 54 weeks NRT patch	Yes	Yes	6- and 12-months	525	46.4 (12.1)	17.1 (8.4)	65%
Schnoll et al. (104)	2010	Nicotine patch vs. nicotine lozenge	Yes	Yes	6- and 12-months	568	~44.7 (12.7)	~20.6 (8.9)	76%
Selby et al. (105)	2014	NRT, Bupropion, or Varenicline prescription with vs. without payment card	No	Yes	6-months	1380	~46.5 (12.3)	~22.2 (9.5)	65%
Stapleton et al. (106)	2013	NRT vs. bupropion vs. bupropion plus NRT; plus behavioral support	Yes	Yes	6-months	1071	~41.2 (12.1)	~20.3 (9.7)	62%
Tønnesen et al. (107)	2012	NRT mouth spray vs. placebo mouth spray	Yes	Yes	6- and 12-months	470	~47 (10.9)	~22.7 (8.8)	50%
Tulloch et al. (108)	2016	10 weeks NRT patch vs. 10 weeks patch + gum or inhaler vs. 12 varenicline; all receive counseling	Yes	Yes	6- and 12-months	737	48.6 (10.8)	23.2 (10.8)	69%
Walker et al. (109)	2011	Quitline with nicotine sampling vs. standard quitline care	Yes	Yes	6-months	1410	~40.5 (13.4)	~20 (9.6)	81%
Telephone Counseling									
Bastian et al. (110)	2013	Counselor initiated counseling calls vs. tailored self-directed materials	Yes	No	6- and 12-months	496	~46 (12)	~20 (11)	100%
Fu et al.(111)	2015	Proactive telephone counseling vs. usual care	Yes	No	12-months	2406	NR −46.1% aged 35-64	13.6 (9.2)	74%
Klemperer et al.(112)	2017	Telephone-based motivational interviewing vs. Telephone based cigarette reduction vs. Brief telephone counseling	Yes	No	6- and 12-months	560	51 (11)	20 (8.4)	63%

Authors	Year	Intervention Description	Multi-Modal Intervention	Biochemical Verification	Outcome	Sample Size	Mean Age (SD)*	Mean Cigarettes per Day (SD)*	Response Rate at 6-months
Klesges et al. (113)	2015	Proactive quitline with 8-weeks NRT vs. reactive quitline with 2-weeks NRT	Yes	No	12-months	1298	39.5 (13.7)	17.8 (8.5)	80%
Linqvist et al. (114)	2013	Motivational interviewing vs. standard treatment in a quitline setting	Yes	No	12-months	772	~48 (14.2)	NR	62%
Maddison et al.(115)	2014	Telephone based exercise program vs. Quitline	Yes	No	6-months	906	37.5 (12.2)	19.6 (9.3)	92%
Nohlert et al. (116)	2014	Proactive vs. reactive calls in a national quitline.	No	No	12-months	586	NR -56% aged 50+	NR - 39% smoke >15 CPD	59%†
Sherman et al. (117)	2018	Proactive vs. reactive telephones counseling	No	No	6-months	2003	~53.7 (10.8)	~17.7 (9.9)	79%
Sumner et al. (118)	2016	Directive vs. non-directive telephone counseling	No	No	6- and 12-months	518	~47 (NR)	~11 (NR)	56%
Tzelepis et al. (119)	2010	Proactive telephone cold-calls vs. mailed written materials	Yes	No	6- and 12-months	1562	~45.4 (12.7)	~19.9 (9.6)	82%
Zhu et al.(120)	2012	Culturally tailored multilingual telephone counseling vs. self-help materials	Yes	Yes	6-months	2277	NR –52% aged 45+	NR –54.9% smoke >14 CPD	90%
Zwar et al. (121)	2015	Nurse advice + quitline vs. quitline vs. usual care	Yes	No	12-months	2390	~43.5 (14.3)	~17.4 (10.7)	83%
Multiple Categories									
Hall et al.(122)	2011	Combination of extended behavioural therapy, pharmacotherapy and placebo	Yes	Yes	6- and 12-months	406	40.7 (9.8)	19 (7.4)	95%
Levine et al. (123)	2010	Weight concern related smoking cessation vs. standard cessation counseling; both with/ without placebo or bupropion	Yes	Yes	6- and 12-months	349	42.0 (10.1)	20.7 (8.4)	53%
Ramon et al. (124)	2013	Individual counselling, combined telephone and individual counselling, or telephone counselling.	Yes	No	6- and 12-months	600	47.4 (12.1)	~26.7 (12.9)	71%†
Smit et al. (125)	2016	Web-based computer tailoring and nurse counseling vs. computer tailoring alone vs. usual care	Yes	No	6- and 12-months	414	48.0 (11.9)	NR	38%
Swan et al. (126)	2010	Web-based counseling vs. telephone-based counseling vs. combined web and telephone; plus varenicline	Yes	Yes	6-months	1202	47.3 (NR)	19.7 (NR)	74%

*Studies that did not report the information are marked as not reported (NR). Mean age and standard deviation (SD), as well as mean cigarettes per day (CPD) and SD for the entire trial sample, was not reported in all studies. For those studies that only reported mean age and CPD by arm, the values for the intervention arm are provided and marked with a tilde. For those studies that only reported median the median is reported and marked

with a tilde and SD is marked as not reported. For those studies that only included age and CPD categories the categories that are most similar to the age and CPD levels of interest for this analysis are reported.

[†]Studies report response rate at 12-months.

Table 2:

Odds of Smoking Cessation from Random-Effects Meta-Analysis of Trials with Smokers Potentially Eligible for Lung Screening Based on 7-day Point Prevalence of Abstinence at 6-Months and 12-Months by Primary Intervention Type

	Electronic/Web-Based			In-Person Counseling			Pharmacotherapy			Telephone Counseling		
	n	OR (95% CI)	I^2 (%)*	n	OR (95% CI)	I^2 (%)*	n	OR (95% CI)	I^2 (%)*	n	OR (95% CI)	I^2 (%)*
Overall at 6-Months	25	1.14 (1.03-1.25)	57.2	20	1.46 (1.25-1.70)	24.7	25	1.53 (1.33-1.77)	73.7	9	1.21 (0.98-1.50)	74.4
Without Pharmacotherapy	17	1.13 (1.01-1.26)	53.7	3	1.16 (0.84-1.62)	0.0	NA	NA	NA	5	1.37 (1.02-1.85)	77.5
With Pharmacotherapy	8	1.13 (0.92-1.40)	60.3	17	1.54 (1.29-1.83)	30.3	NA	NA	NA	4	1.05 (0.89-1.24)	0.0
Single Modality	7	1.15 (0.97-1.35)	55.5	2	1.22 (0.83-1.78)	0.0	4	1.87 (1.47-2.39)	53.9	2	1.07 (0.84-1.37)	16.0
Multi-Modality	18	1.13 (1.00-1.28)	58.2	18	1.51 (1.27-1.79)	29.7	21	1.47 (1.26-1.71)	70.1	7	1.27 (0.98-1.65)	72.2
Minimal or No Intervention Control	13	1.19 (1.04-1.37)	43.1	8	1.57 (1.10-2.25)	54.2	8	1.80 (1.28-2.54)	84.8	6	1.38 (1.08-1.78)	69.9
Active Control	12	1.09 (0.95-1.26)	67.8	12	1.44 (1.23-1.69)	0.0	17	1.42 (1.24-1.62)	56.9	3	0.98 (0.78-1.23)	34.0
Biochemically Verified Results	7	1.31 (0.93-1.83)	65.6	16	1.44 (1.20-1.73)	31.4	19	1.55 (1.33-1.81)	69.0	2	1.52 (0.92-2.49)	89.6
Self-Reported Results	20	1.16 (1.05-1.29)	62.3	9	1.75 (1.40-2.17)	22.0	12	1.51 (1.23-1.86)	78.5	7	1.10 (0.94-1.30)	24.9
High Quality	22	1.11 (1.01-1.23)	57.8	16	1.44 (1.24-1.67)	0.0	24	1.53 (1.32-1.77)	74.6	8	1.22 (0.97-1.53)	77.4
Low Quality	3	1.56 (1.02-2.38)	34.3	4	1.68 (0.96-2.96)	72.0	1	1.66 (1.20-2.28)	.†	1	1.13 (0.62-2.04)	.†
No Conflict of Interest Reported	22	1.14 (1.02-1.28)	62.0	18	1.50 (1.27-1.78)	27.7	16	1.34 (1.19-1.51)	46.8	9	1.21 (0.98-1.50)	74.4
Conflict of Interest Reported	3	1.17 (1.04-1.32)	0.0	2	1.22 (0.82-1.82)	0.0	9	2.01 (1.46-2.77)	82.1	NA‡	NA‡	NA‡
Studies With >50% Enrollment	14	1.16 (1.02-1.31)	64.3	11	1.48 (1.19-1.84)	36.0	13	1.50 (1.25-1.80)	70.4	8	1.22 (0.97-1.53)	77.4
Studies With <50% Enrollment	4	1.35 (0.96-1.92)	58.3	5	1.35 (1.05-1.74)	0.0	8	1.43 (1.16-1.77)	58.7	1	1.13 (0.62-2.04)	.†
Overall at 12-Months	8	1.02 (0.89-1.18)	36.1	15	1.28 (1.09-1.51)	16.8	11	1.46 (1.17-1.84)	67.3	10	1.08 (0.95-1.24)	33.4
Biochemically Verified Results	3	0.84 (0.60-1.67)	0.0	12	1.31 (1.10-1.56)	24.3	11	1.46 (1.17-1.84)	67.3	1	0.86 (0.59-1.25)	.†
Self-Reported Results	5	1.06 (0.90-1.26)	54.6	5	1.32 (1.04-1.67)	0.0	1	1.32 (0.93-1.86)	.†	10	1.08 (0.95-1.24)	34.1

*The I^2 statistic is a measure of heterogeneity that describes the percentage of variation across studies not due to chance.

†The I^2 cannot be calculated for a single intervention in a given group.

‡No telephone counseling interventions reported a conflict of interest.