

# Behavioral interventions for smoking cessation among adolescents: a rapid review and meta-analysis for the Korea Preventive Services Task Force

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## ABSTRACT

**Objectives:** The aim of this study was to evaluate the effectiveness of behavioral smoking cessation interventions among adolescents.

**Methods:** MEDLINE, CENTRAL, Embase, CINAHL, KoreaMed, and KMBase were searched from inception to June 2020. Systematic reviews (SRs) or meta-analyses of randomized controlled trials (RCTs) were initially searched to perform a rapid SR. After selecting the final SR, RCTs after the publication year of the selected SR were searched. The primary outcome was smoking status after at least 6 months of follow-up, and the secondary outcome was smoking status at 4 weeks. Two reviewers independently assessed the selected studies' quality using the Cochrane risk of bias tool. The meta-analysis utilized a Mantel-Haenszel fixed-effect model reporting the relative risk (RR) and 95% confidence interval (CI). The subgroup analysis utilized Cochrane's Q.

**Results:** Thirty-two RCTs (11,637 participants) from a single SR were meta-analyzed. After 6 months of follow-up, the intervention group had significantly higher abstinence rates (RR, 1.30; 95% CI, 1.20–1.41;  $I^2=26.46\%$ ). At 4 weeks of follow-up, the intervention group also had significantly higher abstinence rates (RR, 1.92; 95% CI, 1.49–2.47;  $I^2=0.00\%$ ). The subgroup analysis indicated a significant difference in the abstinence rate according to the study setting and the period between intervention completion and follow-up.

**Conclusion:** This review showed that adolescent behavioral smoking cessation intervention programs significantly increased abstinence rates compared to the usual care.

**Keywords:** Adolescent; Behavior therapy; Practice guideline; Smoking cessation; Systematic review

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## Introduction

Tobacco consumption is the leading cause of preventable death, including from causes such as malignancy, coronary heart disease, stroke, chronic pulmonary disease, and other chronic diseases; tobacco kills more than half of its regular consumers according to the United States (US) Surgeon General's report on smoking cessation in 2020 [1]. Tobacco product use is primarily started and established during adolescence. In the US, where nearly 9 out of 10 daily adult smokers had first tried smoking by age 18 [2]. A World Health Organization report on adolescent smoking in 177 countries between 2008 and 2018 showed that about 24 million adolescents aged 13 to 15 years (17 million males and 7 million females) were currently smoking worldwide [3]. This corresponds to an average prevalence of 6.5% (male, 9%; female, 4%) among youth. The current smoking rate among Korean youth (aged 13 to 18 years, smoked cigarettes on at least 1 of the last 30 days) is 6.7% as of 2019. The age of first smoking experience is 13.2 years and the smoking rate for male adolescents was 9.3%, 2.5 times higher than that for female adolescents (3.8%) [4]. Although the smoking rate of male adolescents decreased after 2011, it has remained stable for the last 3 years. The smoking rate of female adolescents declined until 2016, and then increased again in the last 3 years. This situation has further reinforced the urgent need for early interventions that can promote healthy behaviors among children and adolescents and thus reduce the risk of later-life poor health outcomes.

The anti-tobacco movement implements 2 strategies to further its aims: prevention and cessation of smoking. The prevention of smoking initiation is vital for tobacco use reduction; however, this review focuses on interventions that help adolescents quit smoking. Adolescents often view smoking as a tool for networking with friends and for expressing emotions [5]. This, along with nicotine dependence, makes it very difficult for adolescent smokers to quit smoking. Furthermore, various factors complicate adolescent smoking; these include external factors such as parental smoking, the price and availability of cigarettes, exposure to advertising and promotions, the social norms around smoking in society as a whole and in low-income socioeconomic strata, personal factors such as low self-esteem and adolescent rebelliousness, skill factors such as inability to refuse, and attitude factors such as curiosity and positive thoughts about cigarettes.

Therefore, a comprehensive approach considering all factors is necessary to reduce smoking behavior among adolescents. Rather than a single or independent method, a combination of smoking-related education, anti-smoking

campaigns, tobacco price increases, prohibitions on public smoking, and smoking cessation programs have been shown to have a stronger effect on adolescent smoking cessation [6].

While smokers often attempt to stop smoking on their own, advice from health professionals has been shown to increase quit attempts by 30% and to increase smoking cessation medication use, which can nearly double or triple the successful cessation rate [7]. Unlike adults, adolescents are undergoing rapid physical and psychological changes, so they often require separate smoking cessation programs. Since adolescent smoking often leads to lifelong smoking, it is important to confirm adolescent smoking cessation programs' effectiveness in the context of adolescents' individual and social burdens. Numerous studies have discussed smoking cessation services for adults; thus, similar suitably modified services should be considered for adolescents. However, various differences in adolescents' smoking patterns, lifestyles, and service-related attitudes may challenge this assumption. One recurrent review-related issue in this regard is the paucity of high-quality research for answering this important question. The US Preventive Services Task Force (USPSTF) found insufficient evidence to recommend or advise against tobacco use treatment interventions for adolescents [8]. According to a 2016 meta-analysis, intervention participants were 34% more likely to report quitting smoking at the end of the intervention relative to the control group [9], but a 2019 Cochrane systematic review (SR) found limited evidence that behavioral support increases long-term smoking cessation among young people [10].

We aimed to conduct an up-to-date SR and meta-analysis of trials to answer the following questions: (1) Do adolescent-oriented behavioral-based smoking cessation interventions effectively achieve smoking cessation? (2) What, if any, adverse effects are associated with such interventions? (3) What elements characterize efficacious treatment interventions? The current SR provides an update to include studies conducted since the last review, if possible, in order to inform the Korea Preventive Service Task Force (KPSTF) about the need for an updated recommendation statement.

## Materials and Methods

In this study, a rapid SR was conducted using the KPSTF's rapid SR method to provide available evidence within a limited timeline [11]. The protocol for this SR was approved by the KPSTF.

## Search Strategy

The following databases were searched: international databases including MEDLINE (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL); and domestic databases including the KoreaMed and KMBase. The search terms included “child,” “adolescent,” “tobacco,” “smoking cessation,” “abstinence,” “behavior control,” and other relevant terms (Methods S1). In order to perform a rapid SR, SRs or meta-analyses of randomized controlled trials (RCTs) were initially searched. After the final SR was selected, RCTs after the last search date of the selected SR were searched.

## Inclusion and Exclusion Criteria

We included studies involving all types of non-pharmacological smoking cessation interventions. These included individual or group psychosocial and behavioral counseling; family, school, and community-based programs; tailored self-help materials; and technology-based programs. We included programs combining behavioral interventions and pharmacotherapy if it was possible to extract data for the behavioral intervention outcomes. Interventions involving control groups included no interventions, usual care, or brief information about quitting smoking. The study participants were adolescents aged under 20 years, who were smoking regularly during the interventions. Studies had to have at least 6 months follow-up from the intervention’s beginning until its outcome assessment. No limit was placed on the publication year, and the last search date was June 19, 2020. The search was limited to studies published in English and Korean. We excluded adolescents who were pregnant. We also excluded mass media campaigns and policy-level interventions.

## Outcome Measure

The primary outcome of interest was the abstinence rate at 6 months of follow-up or a longer period from randomization. For the trials that reported multiple follow-up times, we chose those that were closest to 6 months for the primary outcome. “Abstinence” was defined as non-smoking status determined based on biochemical tests or self-reports at least 6 months or more after the baseline. When both methods were used, biochemical tests were applied first. Such biochemical tests involved testing for the presence of smoking-related substances in breath, saliva, urine, and blood. The secondary outcome of interest was the abstinence rate at 4 weeks of follow-up in studies that reported those results.

## Data Collection and Processing

Two review authors independently screened the titles

and abstracts of citations for inclusion. They obtained the full texts of potentially eligible studies, which were then judged against specified inclusion criteria. If disagreements occurred, consensus was achieved through an agreement between the 2 researchers or a discussion with a third researcher. Once the final SR was selected, RCTs after the publication year of the SR were searched. One researcher extracted data using a data extraction template that had been designed in advance, and another researcher conducted independent cross-checking. Any discrepancies were resolved through discussions with a third researcher. The following information was extracted: study identification, publication year, country, study design, setting, number of participants, intervention type and delivery method, follow-up period, abstinence verification method, and the most stringent abstinence rate reported.

## Quality Assessment

The Assessment of Multiple Systematic Reviews (AMSTAR) tool was used to assess the selected SR’s quality [12]. The AMSTAR tool contains 11 items for evaluating the methodological quality of SRs. A score of 0 to 3 is classified as low quality, a score of 4 to 7 as moderate quality, and a score of 8 to 11 as high quality. The quality of the selected RCTs was assessed using the Cochrane risk of bias (RoB) tool. The RoB tool assesses study quality by making judgments (high, low, unclear) in 7 domains: random sequence generation, allocation concealment, selective reporting, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and other sources of bias [13]. At least 2 researchers independently assessed the included studies’ quality and, in cases of disagreement, had discussions with a third researcher in order to reach an agreement.

## Statistical Analysis

The meta-analysis was performed using Stata/MP ver. 16.1 (StataCorp., College Station, TX, USA). The overall effect on smoking abstinence at 6 months (or longer) post-initiation of intervention was presented as a relative risk (RR) and 95% confidence interval (CI). Statistical heterogeneity (assessed using the Higgins  $I^2$  test) was low; therefore, a fixed-effect analysis using the Mantel-Haenszel model was applied [14]. Publication bias was tested using a funnel plot and the Egger linear regression test [15]. Subgroup analyses were performed based on the program’s theoretical basis, program intensity, the type of counseling, the place providing the program, and the period between intervention completion and follow-up outcome assessment.

## Results

### Search Results

Our search strategy yielded 1,550 studies. Following title and abstract screening, 144 full-text SRs were assessed for eligibility. We identified 1 high-quality 2017 SR from the Cochrane Library (AMSTAR score, 10 out of 11). Among the 41 primary studies from the selected SR, 31 studies satisfied our selection criteria. After searching RCTs published from 2017 (the publication year of the selected systematic literature review) onward, 1 study was selected. Finally, 32 studies were selected for meta-analysis. Although many studies had been conducted on smoking cessation among South Korean adolescents, none satisfied all the inclusion criteria.

Each study reported a different intervention period, method, and intensity for the smoking cessation program. The intervention duration was 1 to 12 months, and the intervention delivery methods were personal counseling, group counseling, customized texting, using smartphone applications, and telephone counseling. [Figure 1](#) depicts a flowchart of the literature selection process, and the characteristics included in the meta-analysis are detailed in the supplementary file.

### Effects of Smoking Cessation Interventions

[Table S1](#) details the characteristics of the 32 selected studies. The meta-analysis results showed that, at 6 months, the intervention group's abstinence rate was 30% higher than that of the control group (RR, 1.30; 95% CI, 1.20–1.41;  $I^2 = 26.46\%$ ) ([Table 1](#), [Figure 2](#)). When the funnel plot was evaluated, there was a weak suspicion of publication bias ([Figure S1](#)). In the Egger linear regression method test, the  $p$ -value of the publication bias test was 0.0967. Therefore, missing values were imputed using the trim-and-fill method [16]. The RR before correction was 1.26 (95% CI, 1.164–1.366), and even after correcting the missing values, the RR was 1.249 (95% CI, 1.154–1.353). Therefore, we concluded that publication bias would not seriously affect the results.

The intervention group had significantly more favorable secondary outcomes than the control group. Among 32 RCTs, 13 studies presented the 4-week follow-up abstinence rate, and the intervention group had a higher abstinence rate than the control group (RR, 1.92; 95% CI, 1.49–2.47;  $I^2 = 0.00\%$ ) ([Figure 3](#)). In the Egger linear regression method test, the  $p$ -value of the publication bias test was 0.4928; therefore, we concluded that there was no publication bias.

### Risk of Bias

All the selected studies were comparative RCTs, and bias

risk assessment was performed using the Cochrane RoB tool ([Figure S2](#)). One study mentioned that the participants selected the group that was to be assigned, so it was concluded that the RoB of random sequence generation would be high. For 6 studies, the RoB of allocation concealment was judged to be high because the assignment order was determined by the participants' enrollment order. Regarding participant and personnel blinding, since six studies mentioned that blinding was impossible, they were deemed to be highly biased. Thirteen studies stated that the evaluator could not be blinded, so it was concluded that the RoB of outcome assessment blinding was high. Six studies were determined to have a high RoB for incomplete outcome data because the difference in dropout rates between the intervention group and the control group was large.

### Subgroup Analyses

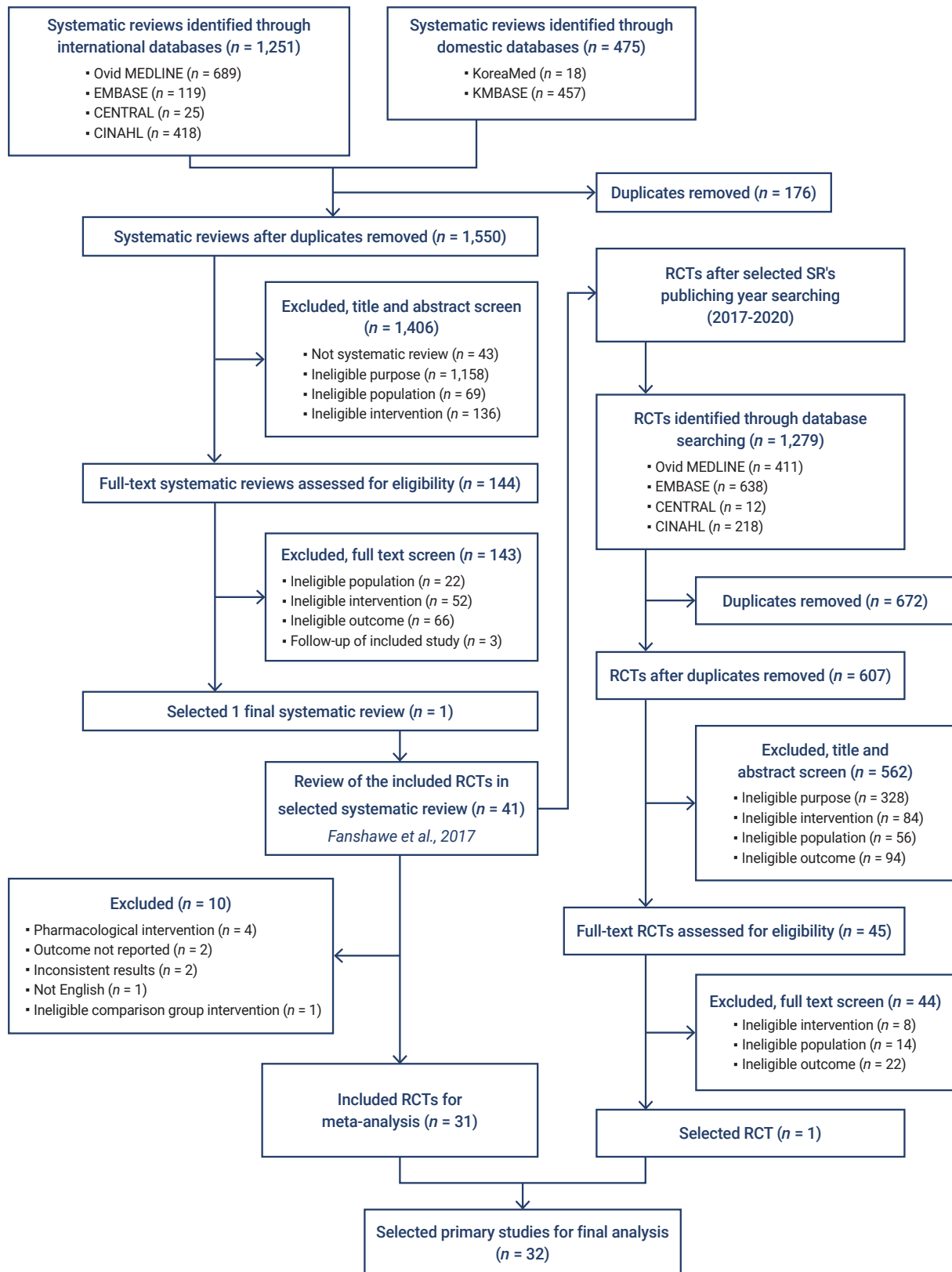
A subgroup analysis showed that programs implemented at a medical institution had significantly higher abstinence rates than those implemented elsewhere ( $p = 0.03$ ). Furthermore, the subgroup with less than 1 month between the intervention completion (including booster sessions) and the follow-up had significantly higher abstinence rates than the subgroup where more than 1 month had elapsed ( $p = 0.03$ ).

Beyond this, there was no other significant difference in the abstinence rate between subgroups based on the country of the study ( $p = 0.53$ ), theoretical basis ( $p = 0.53$ ), intensity ( $p = 0.09$ ), type of counseling ( $p = 0.82$ ), biochemical confirmation or self-report ( $p = 0.15$ ), simplicity or complexity ( $p = 0.49$ ), and whether the interventions included face-to-face interactions ( $p = 0.27$ ). The following variables were not statistically significant: program location (school vs. non-school), follow-up time (6–8 months vs. 12–14 months), and the period between the intervention completion time and the follow-up time (less than 2 months vs. more than 2 months).

## Discussion

We evaluated the effectiveness of behavioral smoking cessation interventions for adolescents. This review presented objective evidence that behavioral smoking cessation interventions targeting adolescent smokers significantly increased their abstinence rate compared to the abstinence rate of a control group that received usual care or brief advice or was exposed to self-help materials. Therefore, non-pharmacological smoking cessation interventions for adolescents could aid in the management of adolescent behavioral smoking within the community.

Our results showed that the abstinence rate at 6 months



**Figure 1.** Flowchart of the selection of studies included in the meta-analysis. CENTRAL, Cochrane Central Register of Controlled Trial; CINAHL, Cumulative Index to Nursing and Allied Health Literature; RCTs, randomized controlled trials; SR, systematic review.

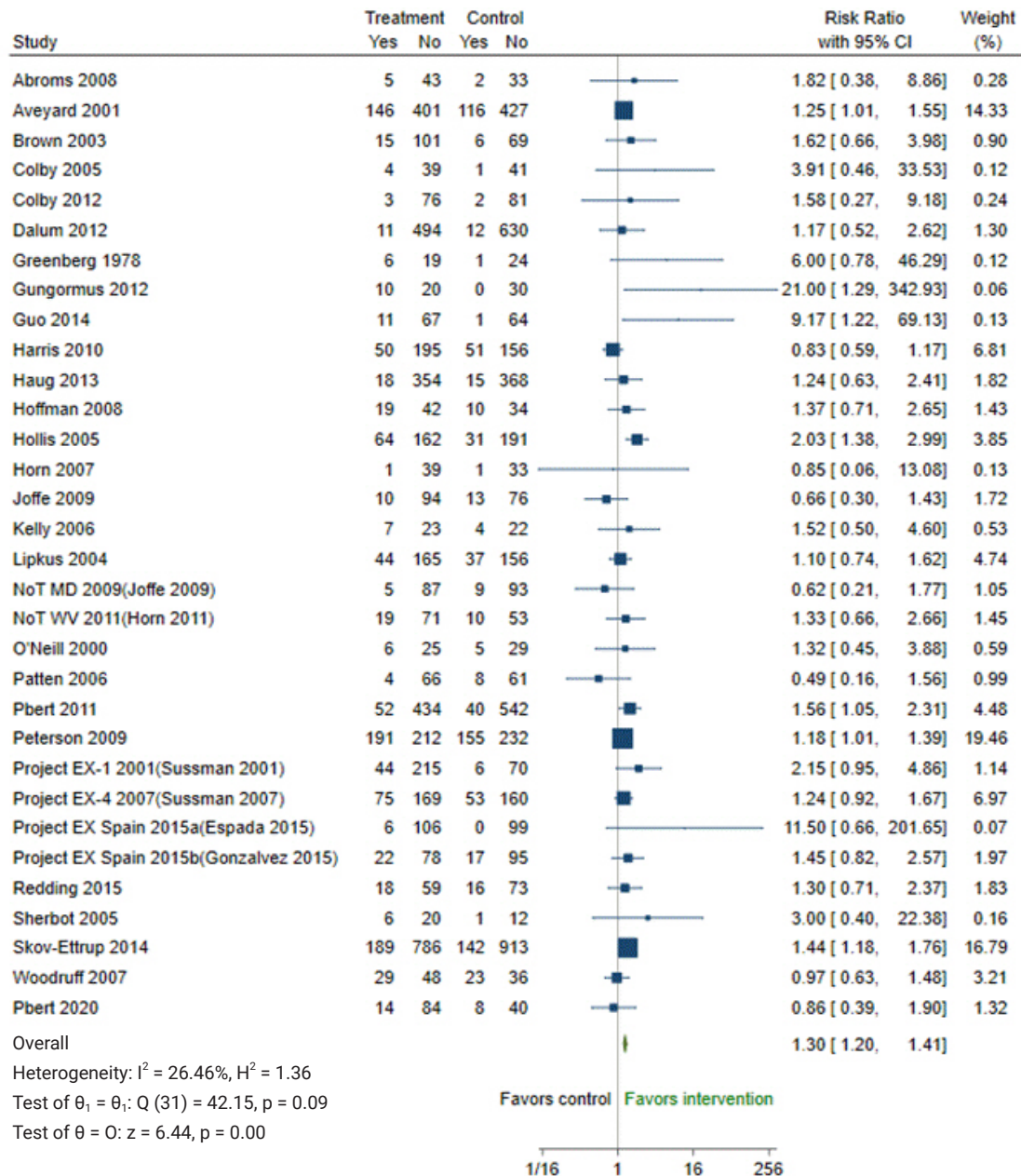
**Table 1.** Results of the subgroup analysis

Subgroup	Population (RCT)	Relative risk (95% CI)	I <sup>2</sup> (%) (heterogeneity)	Subgroup difference (p-value)
Overall effect	11,637 (32)	1.30 (1.20–1.41)	26.46	-
Study country				0.53
North America	8,367 (21)	1.28 (1.17–1.41)	31.55	
Europe and others	3,270 (11)	1.36 (1.16–1.60)	26.46	
Program location 1				0.38
School	7,658 (21)	1.27 (1.15–1.40)	26.68	
Others	3,979 (11)	1.37 (1.19–1.57)	26.03	
Program location 2				0.03
Including a medical institution	935 (6)	1.78 (1.33–2.40)	0	
Non-medical institution	10,702 (26)	1.27 (1.16–1.38)	27.23	
Theoretical basis				0.53
Stages of change model	3,283 (6)	1.31 (1.09–1.57)	0	
Motivational interviewing	1,511 (9)	1.11 (0.88–1.40)	9.56	
Social cognitive theory	4,006 (9)	1.32 (1.12–1.54)	33.97	
Complex theoretical model	2,837 (8)	1.35 (1.20–1.53)	51.72	
Program intensity				0.09
Low	2,300 (6)	1.50 (1.17–1.92)	15.53	
Middle	7,284 (16)	1.25 (1.14–1.38)	21.78	
High	2,053 (10)	1.39 (1.13–1.71)	40.02	
Counseling type				0.82
Private	1,997 (6)	1.21 (0.95–1.54)	42.34	
Group	7,730 (17)	1.32 (1.08–1.63)	28.03	
Other	1,910 (9)	1.31 (1.20–1.44)	27.07	
Program simplicity or complexity				0.49
Simple program	8,736 (23)	1.32 (1.20–1.46)	29.79	
Complex program	2,901 (9)	1.25 (1.08–1.44)	18.09	
Smoking status assessment method				0.15
Biochemical method	4,834 (15)	1.19 (1.03–1.38)	34.42	
Self-report	6,643 (17)	1.36 (1.23–1.49)	16.34	
Face-to-face or non-face-to-face				0.27
Face-to-face	5,170 (18)	1.31 (1.13–1.53)	30.68	
Face-to-face and non-face-to-face	2,140 (6)	1.46 (1.22–1.74)	40.16	
Non-face-to-face	4,327 (8)	1.23 (1.10–1.38)	5.2	
Period between intervention completion and follow-up 1				0.03
Less than 1 mo	1,161 (7)	1.75 (1.32–2.31)	36.61	
More than 1 mo	10,476 (25)	1.26 (1.16–1.37)	16.56	
Period between intervention completion and follow-up 2				0.90
Less than 2 mo	2,356 (9)	1.31 (1.15–1.50)	44.01	
More than 2 mo	9,284 (23)	1.30 (1.17–1.43)	21.17	

CI, confidence interval; I<sup>2</sup>, the Higgins I<sup>2</sup> test statistic; RCT, randomized controlled trial.

or more of follow-up was 30% higher in the behavioral intervention group than in the control group; furthermore, there was no difference based on the various types of behavioral smoking cessation interventions. The SR of Fanshawe et al. [10], our final SR choice, found evidence of an intervention effect for group counseling (RR, 1.35; 95% CI, 1.03–1.77) but not for individual counseling (RR, 1.07; 95% CI, 0.83–1.39), mixed methods (RR, 1.26; 95% CI,

0.95–1.66), or computer or messaging interventions (pooled RR between 0.79 and 1.18). The results may have differed because we did not include 10 out of the 41 studies that the previous SR had included (4 pharmacologic intervention; 2 outcomes not reported; 2 inconsistent results; 1 not English; 1 ineligible comparison group intervention). However, the subgroup that included medical institutions in the study setting had a higher abstinence rate than the non-medical

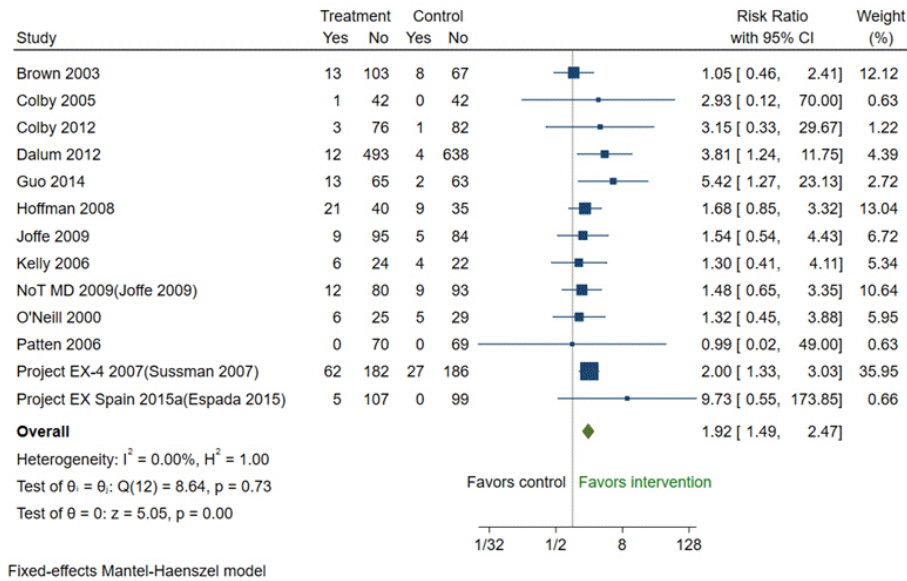


Fixed-effect Mantel-Haenszel model

**Figure 2.** Summary of meta-analysis findings for the primary outcome (at 6 months of follow-up). CI, confidence interval;  $I^2$ , Higgins  $I^2$  test statistic.

setting subgroup (1.78 vs. 1.27,  $p = 0.03$ ). One of the studies that included medical institutions was that of Hollis et al. [17]. The intervention began with a doctor providing some brief cessation-related advice to adolescents who visited the clinic. After this, adolescents who wished to quit smoking were guided to receive personalized computer-based cessation programs and motivational interviews. As such, the subgroup involving medical institutions in its

interventions had statistically significantly higher abstinence rates than the others. Six studies included in the meta-analysis had study settings involving medical institutions. The recruitment of participants in these studies was carried out in the emergency room, a psychiatric hospital, a hospital-based pediatrics and family medicine outpatient department, or a pediatrician's office. None of the studies compared the abstinence rate after cessation intervention in adolescent



**Figure 3.** Summary of meta-analysis findings for the secondary outcome (at 4 weeks of follow-up). CI, confidence interval;  $I^2$ , Higgins  $I^2$  test statistic.

smokers by medical characteristics. Therefore, only limited evidence was obtained regarding whether the effect of smoking cessation was caused by the agency providing the intervention or the smokers' characteristics themselves. The USPSTF recommends that primary care clinicians should provide interventions, including education or brief counseling, to prevent tobacco use initiation among children and adolescents [18]. The USPSTF concluded that the current evidence is insufficient for assessing the balance between benefits and harms from primary care-feasible tobacco cessation interventions among children and adolescents; however, our findings showed that adolescent behavioral smoking cessation interventions could be more effective if the intervention efficiently utilized medical institutions within communities. Therefore, it is desirable to mobilize all available resources, including schools, parents, medical institutions, and local communities, when designing smoking cessation programs for adolescents; furthermore, it is important to include medical institutions in the program whenever possible.

The subgroup with less than 1 month between intervention completion and follow-up had a significantly higher abstinence rate than the subgroup with more than 1 month (RR, 1.75 vs. 1.26;  $p = 0.03$ ). However, when we investigated the difference according to whether studies had more than 2 months between intervention completion and follow-up, there was no significant difference between the subgroups ( $p = 0.90$ ). The finding of the subgroup analysis regarding whether the gap between the intervention

completion and the follow-up was less than 1 month may indicate that adolescent behavioral smoking cessation interventions were effective. Most smokers repeat failures and successes until they completely quit smoking—often with an average of 6 or more attempts [19]. Adolescents are no exception to this trend, so even if they successfully quit smoking, they are more likely to smoke again because of certain adolescent characteristics including peer pressure, emotional instability, and ambivalence [20]. Therefore, further interventions for preventing relapses should also be considered within 1 month after the completion of a smoking cessation intervention.

This review's results are, for the most part, consistent with other recommendations related to behavioral interventions among adolescents, though those results are somewhat different from ours. In a 2008 US Guideline, the use of counseling was shown to approximately double the long-term abstinence rate when compared to usual care or no treatment [7]. However, according to the 2013 USPSTF recommendation, a pooled meta-analysis of 7 trials found a small but statistically insignificant effect at 6-month to 12-month follow-ups favoring the intervention [8]. In an SR by Peirson et al. [9], a meta-analysis showed that intervention participants were 34% more likely than controls to report that they quit smoking at the end of the intervention. The Canadian Task Force on Preventive Health care also recommended offering brief information and advice during primary care visits to treat adolescent tobacco smoking [19], and the European Network for Smoking and



Tobacco Prevention concluded that counseling was an effective smoking cessation method for teenagers [21]. A recent 2020 USPSTF recommendation concluded that the current evidence is insufficient for assessing the balance, in terms of benefits and harms, from primary care-feasible interventions for tobacco use cessation among school-aged children and adolescents [22].

This study had several limitations. First, the included RCTs were not of excellent quality. For interventions involving behavioral therapy, rather than pharmacological therapy, it was difficult to conceal participation in the study; this led to a high RoB in the blinding of the participants and personnel. Furthermore, the outcome measures were more biased when the participant's self-reports, rather than biochemical methods, were used to verify smoking status. Therefore, the level of evidence was evaluated as being moderate, because the included studies in the analysis were suspected of having some bias. Second, the included studies' smoking cessation programs were heterogeneous. Although a subgroup analysis was performed based on various program characteristics, there were limitations in the synthesis the effects. Third, while some programs used a single method, many programs used combinations of 2 or more methods, including individual counseling, technology use, group counseling, and additional telephone counseling. Therefore, confirming the effect of each factor was difficult, which made it difficult for us to present individual methods' effects.

Most of the studies included in the meta-analysis were conducted in the US and Europe. Although there were many studies examining smoking cessation among South Korean adolescents, none satisfied all the inclusion criteria. However, if the RCT on the Project EX group counseling program for South Korean adolescents conducted by Yu et al. [23] had at least 6 months of follow-up, it would have been included in the analysis. It is noted that adequate research has not been conducted to identify the effectiveness of smoking cessation programs targeting adolescents in the South Korean context. We suggest that it is necessary to conduct well-designed RCTs in South Korea to confirm the effectiveness of adolescent smoking cessation programs.

The results of several studies, and published protocols that are currently in progress, were not reported; thus, these could not be included in the evidence evaluation. Smoking cessation interventions for adolescents, especially research examining technology use, are currently being planned and conducted worldwide, and more literature is expected to be published in the next few years. Therefore, when ongoing studies' results are reported, and sufficient evidence is

secured, it is important to conduct additional evidence evaluation that includes those studies.

## Conclusion

The SR of 32 RCTs, which aimed to evaluate the clinical effects of behavioral smoking cessation interventions for adolescents, showed that such interventions significantly increased the abstinence rate compared to the control group. To develop an effective adolescent smoking cessation program, it is important to efficiently use all available resources such as schools, parents, medical institutions, communities, and technologies. Furthermore, it is necessary to conduct well-designed RCTs to confirm the long-term effects of smoking cessation programs and technology-based programs, especially including Korean adolescents.

## Supplementary Material

**Methods S1.** Search strategies; **Table S1.** Characteristics of the included studies; **Figure S1.** Funnel plot of the studies; **Figure S2.** Results of risk of bias among the included studies. Supplementary data are available at <https://doi.org/10.24171/j.phrp.2021.0018>.

## Notes

### Ethics Approval

Not applicable.

### Conflicts of Interest

The authors have no conflicts of interest to declare.

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### Availability of Data

All data generated or analyzed during this study are included in this published article. For other data, these may be requested through the corresponding author.

### Authors' Contributions

Conceptualization: all authors; Data curation: YC, CML; Formal analysis: YC, CML; Investigation: all authors; Methodology: all authors; Project administration: BC; Resources: all authors; Software: all authors; Supervision: BC; Validation: all authors; Visualization: all authors; Writing-original draft: YC, CML; Writing-review & editing: all authors.

### Additional Contributions

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