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Primary Care Interventions for Prevention and Cessation of Tobacco Use in Children and Adolescents: A Systematic Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Structured Abstract

Background: Interventions to discourage use of tobacco products among children and adolescents may help decrease tobacco-related illness. Tobacco products for this review include electronic nicotine delivery systems, often referred to as e-cigarettes.

Purpose: To systematically update the 2013 U.S. Preventive Services Task Force (USPSTF) review on primary care relevant interventions for tobacco use prevention and cessation in children and adolescents.

Data Sources: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PsycINFO, and EMBASE (September 1, 2012 to June 25, 2019) with surveillance through February 7, 2020.

Study Selection: We selected primary care relevant studies based on inclusion and exclusion criteria developed for each key question. We included randomized and nonrandomized controlled trials of children and adolescents up to 18 years of age for cessation and 25 years of age for prevention. Trials that compared behavioral or pharmacological interventions with a no or minimal smoking intervention control group (e.g., usual care, attention control, wait list) were included.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): Twenty-six trials met inclusion criteria. Behavioral interventions were associated with decreased likelihood of smoking initiation compared with control interventions (k=13, n=21,700; 7.4% vs. 9.2%; relative risk [RR] 0.82, 95% confidence interval [CI] 0.73 to 0.92). In trials restricted to smokers, behavioral interventions had no effect on smoking prevalence (k=9, n=2,516, 80.7% vs. 84.1% continued smoking, RR 0.97, 95% CI, 0.93 to 1.01). Behavioral interventions were more effective than control interventions at decreasing smoking prevalence in trials of smokers and nonsmokers (k=7, n=10,533; 16.8% vs. 20.1%; RR 0.91, 95% CI, 0.83 to 0.995). However, these results were sensitive to inclusion of two trials of very intensive interventions. Two trials of bupropion and one trial of nicotine replacement therapy found no significant benefits of medication on likelihood of smoking cessation. One trial each found no evidence for a beneficial intervention effect on health outcomes or on adult smoking.

Limitations: Few trials addressed the prevention or cessation of tobacco products other than cigarettes; no trials evaluated effects of interventions on e-cigarette use. Trials of pharmacotherapy were few and had small sample sizes.

Conclusions: Behavioral interventions can reduce the likelihood of smoking initiation in nonsmoking youth and young adults. Research is needed to identify effective behavioral interventions for youth who smoke or who use other tobacco products and to understand the effectiveness of pharmacotherapy on cessation. Due to the rapid escalation of e-cigarette use

among youth, both prevention and cessation trials that target and/or include e-cigarettes are imminently needed.

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Chapter 1. Introduction and Background

Purpose

In 2013, the U.S. Preventive Services Task Force (USPSTF) issued a recommendation that primary care clinicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use among school-aged children and adolescents.[1] This recommendation was based on a systematic review published in 2012 on the efficacy and harms of primary care interventions to prevent tobacco initiation and encourage tobacco cessation among children and adolescents.[2,3]

The current systematic review will be used by the USPSTF to update its 2013 recommendation. It includes studies conducted since the last review, including literature on preventing and reducing use of newer tobacco products, such as e-cigarettes. In addition, this review extends the inclusion criteria for prevention studies to young adults (defined as ages 19 to 25 years old). Trials of smoking cessation in young adults are covered in a separate USPSTF review on tobacco smoking cessation in adults.[4]

Condition Background

Tobacco can be consumed in many forms including cigarettes, pipes, cigars, cigarillos, little cigars, bidis (tobacco wrapped in tendu or temburni leaves), smokeless tobacco (including chew, snuff including snus, and dissolvable tobacco in the form of strips, sticks, or lozenges), and through a hookah or waterpipe. Electronic nicotine delivery systems (ENDS) are battery-operated devices that heat a solution usually containing nicotine (usually derived from tobacco) that the user inhales. Effective August 8, 2016 the U.S Food and Drug Administration (FDA) extended its regulatory authority to include ENDS (e.g., e-cigarettes, e-hookah, e-cigars, vape pens, advanced refillable personal vaporizers, and electronic pipes).[5] However, there is inadequate evidence to conclude that ENDS use increases smoking cessation.[6]

There are multiple types of ENDS: electronic cigarettes (i.e., e-cigarettes or e-cigs) that look like cigarettes and are disposable or partly disposable, vape pens that are rechargeable (most have a universal serial bus [USB] charger) and have customizable looks and tips, Modified Vape Devices (Mods) or box-style mods that allow even greater customization (e.g., wattage, temperature control) and are generally larger and more powerful than the previous two ENDS types, and lastly, small and discreet devices, such as JUULS or Suorin, that look like USB sticks or highlighters and deliver the e-fluid through an insertable pod that is not intended to be refillable. Combustible cigarette cartridges or pods sold in the United States can only contain tobacco or menthol flavors. However, little cigars, or cigarillos, like e-fluid, also come in flavors such as cherry, grape, watermelon, rum, mango, and guava, and are appealing to youth. Although the FDA now is prioritizing enforcement against companies that continue to sell unauthorized e-cigarette cartridges in flavors that appeal to children, other e-fluid flavors that are not cartridge-based including fruit, candy, dessert, and cereal remain available.[7]

In this review, the term "tobacco and nicotine use" indicates the use of any tobacco product including e-cigarettes and the term "smoking" refers to the use of combustible tobacco products (primarily cigarettes in this review). The term e-cigarette refers to all ENDS.

Prevalence and Burden of Disease/Illness

Tobacco use, not including exposure to second-hand smoke, is the leading cause of preventable death in the United States. An estimated 437,000 premature deaths occur annually among current or former smokers that are attributable to tobacco use, including 82 percent of 158,530 lung cancer deaths and 24 percent of 412,590 heart disease deaths in the United States from 2005 to 2009.[8] Tobacco's toll is not only physical, but also economic, as smoking costs the United States approximately $132.5 to 175.9 billion each year in direct medical costs and $156 billion from productivity losses.[8] While cigarette smoking is still the predominant form of tobacco use in the United States among adults, e-cigarette use has seen a huge increase among adolescents and is now more common among youth than cigarette smoking.[9] Although the short-term health risks of e-cigarette use may be less than those of cigarettes, the long-term effects of these products on morbidity and mortality are not yet clear.[10] The 2014 Surgeon General's Report on smoking concluded that exposure to nicotine during adolescence may have lasting adverse consequences for the still-developing adolescent brain.[8] These consequences may include long-lasting effects on brain function including cognition.[11,12] Additionally, one observational study found an adjusted odds ratio (AOR) for myocardial infarction of 1.79 (95% CI, 1.20 to 2.66) in adults who used e-cigarettes daily and 2.72 (95% CI, 2.29 to 3.24) in those who used cigarettes daily.[13]

It is estimated that approximately 1,600 children smoke their first cigarette every day,[14] and that about 5.6 million adolescents alive today will die prematurely due to a smoking-related illness.[15] Even though the legal age to purchase tobacco products is now 21 years of age,[16] over 85 percent of adults who have ever smoked daily smoked their first cigarette by the age of 18; and 98 percent initiated tobacco use by the age of 26.[8] The Centers for Disease Control and Prevention's (CDC's) National Youth Tobacco Survey (NYTS) of middle and high school students found that prevalence of current tobacco and cigarette use, defined as use in the past 30 days, declined between 2011 and 2017. Use of any tobacco product decreased from 24.2 percent to 19.6 percent among high school students[9] during that time period but increased to 27.1 percent in 2018[17] and to 31.2% in 2019.[9] Use of any tobacco product declined from 7.5 percent in 2011 to 5.6 percent among middle school students but increased to 7.2 percent in 2018 and to 12.5 percent in 2019.[9] This reversal in prevalence of tobacco product use among both middle and high schooler students is alarming. Since 2014, e-cigarettes have been the most commonly used tobacco product among both middle and high school students.[9,17] Not only is the proportion of students using e-cigarettes increasing, but cigar use is also increasing among high schoolers (7.6% smoking cigars, cigarillos, or little cigars vs. 5.8% smoking cigarettes) and is now as frequent as cigarette use among those in middle school (2.3%).[9,17] The proportion of students using more than one type of tobacco product is also increasing. In 2017, 9.2 percent of high school and 2.4 percent of middle school students reported using two or more tobacco products in the past 30 days.[18] In 2019, those percentages were 10.8 and 4.0, respectively.[9] Use of more than one tobacco product is associated with increased reporting of dependence symptoms.[19] The prevalence of current use of all tobacco products by school level (i.e., middle school vs. high school) is presented in **Table 1**.

These findings are consistent with those of the National Youth Risk Behavior Survey.[20] Overall, the prevalence of current tobacco use was higher among male (23.4%) than female (15.6%) students, and among those identifying as gay, lesbian, or bisexual (27.2%) than those identifying as heterosexual (19.2%). The prevalence of tobacco use was higher among white high school students (22.4%) compared with Hispanic (16.6%) and black high school students (14.9%). Current use of an e-cigarette was 13.2 percent among high school students, with higher proportions of males reporting use (15.9%) than females (10.5%). Frequent use was reported by 3.3 percent of high school students and 2.4 percent reported daily use.

Etiology and Natural History

There are five stages for the process of smoking onset and established daily smoking: 1) not susceptible to smoking; 2) susceptible or preparing to smoke; 3) initiation or experimentation (trying the first cigarette); 4) becoming a smoker or irregular smoking; and 5) established or regular smoking (e.g., smoking every day or almost every day).[21,22] More research is needed on the natural history of e-cigarette use; however, the most commonly cited reasons for use of e-cigarettes among youth (and young adults) were curiosity, flavoring, and low perceived harm relative to regular tobacco products.[23]

Although children as young as age 10 years may be susceptible to smoking, it can take up to 2 years to progress from early experimentation to addiction.[20,24] While this is the path for most adolescent smokers, some children and adolescents progress rapidly to nicotine dependence, underscoring the need to prevent initial smoking uptake.[25] Of all high school students who smoke, 45.5 percent have tried to stop smoking in the past year.[26] However, most will fail and 75 percent will go on to smoke into adulthood.[27] In fact, of adolescents aged 15 to 18 years who are daily smokers, only 12 percent were former smokers by ages 22 to 25 years.[27] There is evidence that adolescent e-cigarette users also experience nicotine dependence[28] and that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults.[10] While the most serious health outcomes associated with adolescent tobacco use typically appear during adulthood, there are immediate adverse health effects among child and adolescent smokers, including increased negative respiratory effects such as impaired lung growth, early onset of lung function decline, respiratory and asthma-related symptoms (e.g., coughing and wheezing), and early abdominal aortic atherosclerosis.[8,27] Concerns regarding adolescent and young adult use of e-cigarettes include nicotine addiction, harm to the developing brain, progression to combustible tobacco use, nicotine toxicity, inhalation of toxins or carcinogens, and explosions and fires caused by the device.[23] Use of e-cigarettes can also cause serious harm such as lung injury and death, depending on the substances comprising the e-fluid.[29]

The relationship between e-cigarettes use in children and adolescents and the use of other tobacco products is discussed further in this report as a contextual question.

Risk Factors

Risk factors for combustible cigarette smoking identified in the 2018 Monitoring the Future cohort of about 44,500 students in the 8th, 10th, and 12th grade in 392 schools in the United States

were being male, white, not college-bound, from a rural area, and having parents with lower levels of education.[30] Prospective data from two studies conducted in the United Kingdom were compared, the British Cohort Study, which enrolled children in 1970 and the Millenium Cohort Study, which enrolled children in 2001. When the children were 10 to 11 years of age 14.3 percent had smoked in the British cohort, while in the Millenium cohort conducted 31 years later only 2.4 percent of children had smoked.[31] The decline in children smoking was attributed to increases in maternal education, fewer parents smoking, and fewer childhood friends smoking in the Millenium sample. The children most likely to have smoked by 11 years old in both cohorts were those whose mothers had less education, both parents smoked heavily, and the child had at least one friend who smoked. According to the Department of Health and Human Services, other risk factors associated with tobacco use include being an older adolescent, being male, being white, lacking college plans, having parents who did not attend college, and experiencing highly stressful events (e.g., incarcerated parent, victim of abuse).[32] Adolescent perceptions of risk of cigarette smoking has increased while the perception of risk associated with e-cigarette use remains very low (only 20% see regular e-cigarette use as a "great risk").[32]

Evidence also suggests that multiple factors influence a child's or adolescent's continuation of smoking and the probability they will become nicotine dependent. Among smokers, pleasant initial sensitivity to tobacco use, parental nicotine dependence, adolescent nicotine dependence, and extensiveness of smoking at the initial interview were the strongest predictors of adolescent nicotine dependence 2 years later.[33] Other risk factors for continued smoking include behavioral factors such as alcohol use and being with friends who smoke, smoking in early adolescence, and concerns about weight gain with quitting.[32] Genetics may also play a role.[32]

Prevention and Cessation Interventions

Interventions to address tobacco use in youth and young adults include behavioral interventions that discourage use of tobacco products, either to prevent initiation of use in those not using (prevention), to encourage quitting the use of tobacco products in those who currently use (cessation), or discourage use of tobacco products in both users and nonusers (combined prevention and cessation). Primary care relevant interventions are those that could be conducted by health care personnel in a primary care setting or that could be referred from primary care (e.g., behavioral counseling). In addition to directly targeting the child or young adult, interventions could target the parent or caregiver (e.g., to stop smoking, to increase communication and support for the child).

The use of pharmacologic adjuncts as an aid in cessation for adolescent smokers is also of interest, given the positive effects of these therapies in adults.[6,34-36] However, there are currently no medications approved for tobacco cessation in adolescents and children. The FDA instructs adolescents to see their doctors if they are interested in nicotine replacement therapy (NRT).[37] However, there is currently no data on physician prescribing practices of any pharmacotherapy in children and adolescents for decreasing or stopping the use of tobacco products. Because the safety and effectiveness of these drugs in pediatric patients have not been established, bupropion hydrochloride (known as Zyban®), an aminoketone antidepressant, and varenicline tartrate (known as Chantix®) are not FDA approved for smoking cessation for people younger than age 18 years.

Current Clinical Practice

Many children and adolescents are not asked about the use of tobacco products when they visit their doctor. In a study based on data from the 2013 National Survey on Drug Use and Health, less than half of adolescents who visited a health care provider in the past 12 months reported being asked about tobacco use.[38] Of those that reported past 30-day use, only 26.3 percent were screened and advised to quit. Adolescents who were screened by their physician were predominantly female (56.6%), white (60.1%), older (83.0%), and covered by private health insurance (63.8%). Hispanic adolescents were significantly less likely to receive advice to quit from their physician compared with non-Hispanic white adolescents.

In a study using NYTS data, the overall prevalence of tobacco screening was 32.2 percent in 2011, 37.9 percent in 2013, and 36.6 percent in 2015 among children and adolescents in grades 6 through 12 who visited a physician within the past year.[39] The largest relative change from 2011 to 2015 was among females and blacks, with no significant increase among males, younger students aged 9 to 14 years, and e-cigarette users. Older students were more likely than younger students to be asked about tobacco use and students identifying as a racial or ethnic minority were less likely than non-Hispanic whites to be asked. Current cigarette only users, e-cigarette only users, and dual users were more likely to be asked about tobacco use than noncurrent users. Despite increased screening for tobacco use, the study found low and declining rates of advice to avoid or quit tobacco use among this population. The overall prevalence of being advised not to use tobacco decreased from 31.4 percent in 2011 to 30.1 percent in 2013 and 26.9 percent in 2015 with a relative decrease of 14.3 percent. Males and older students were more likely to be advised not to use tobacco, whereas Hispanics were less likely than whites to be so advised. Current cigarette-only users and dual users of cigarettes and e-cigarettes had higher odds of being encouraged not to use tobacco than noncurrent users. No significant difference was found between e-cigarette only users and those who reported no current tobacco use.

Recommendations of Other Groups

In 2015, the American Academy of Pediatrics (AAP) published a policy statement on clinical practice policy to protect children from tobacco, nicotine, and tobacco smoke.[40] The AAP recommends that pediatricians counsel parents and caregivers who use tobacco about the importance of and strategies for stopping tobacco product use, provide referral for additional tobacco dependence treatment resources and consider recommending or prescribing tobacco dependence treatment medication for parents and caregivers who smoke (Recommendation strength: Strong). Further, it was recommended that pediatricians provide brief counseling to all children and adolescents to prevent tobacco use initiation, and that all teenagers be screened for tobacco and nicotine use (Recommendation strength: Strong). For adolescents who want to stop using tobacco, it was recommended that tobacco dependence treatment and/or referral be offered (Recommendation strength: Strong), and that tobacco dependence pharmacotherapy can be considered for moderate to severely tobacco-dependent adolescents (Recommendation strength: Option). E-cigarettes were not recommended as a treatment for tobacco dependence (Recommendation strength: Strong).

A separate AAP policy statement was also published on e-cigarette use.[41] The policy statement included recommendations that pediatricians screen children and adolescents, parents, and caregivers for e-cigarette use, and provide prevention counseling for children and adolescents. Further, AAP recommended that parents, caregivers, and adolescents who use e-cigarette should be offered or referred for tobacco cessation counseling and FDA-approved tobacco dependence pharmacotherapies appropriate to their level of addiction and readiness to change and, again, that e-cigarette was not recommended as a treatment for tobacco dependence.

In a 2014 position paper, the American Academy of Family Physicians encouraged screening of children and adolescents for tobacco and nicotine use.[42] For all patients, family physicians are encouraged to use the five A's: Ask, Assess, Advise, Assist, and Arrange. Recommended interventions included referral; provision of self-help materials; provision of brief, intermediate, or intensive counseling (motivational interviewing); pharmacotherapy; NRT; group visits; or combinations of interventions.[42]

Previous USPSTF Recommendation

In 2013, the USPSTF updated its 2003 recommendation from an I (insufficient evidence) statement to a B recommendation that primary care clinicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use among school-aged children and adolescents.[1] This was based on moderate certainty that primary care-relevant behavioral interventions can prevent tobacco use in children and adolescents with moderate net benefit.

Chapter 2. Methods

Key Questions and Analytic Framework

The Pacific Northwest Evidence-based Practice Center (EPC) and the USPSTF worked together to determine the scope, key questions, and analytic framework for this review using established methods.[43] **Figure 1** outlines the analytic framework.

Key Questions

1. Do primary care interventions to prevent tobacco and nicotine use or improve tobacco and nicotine cessation rates in children and adolescents improve health outcomes (i.e., respiratory, dental, cardiovascular, and oral health) and reduce the likelihood of tobacco or nicotine use in adulthood?
2. Do primary care interventions prevent tobacco and nicotine use or improve tobacco and nicotine cessation rates in children and adolescents?
3. What adverse effects are associated with primary care interventions to prevent tobacco and nicotine use or improve tobacco and nicotine cessation rates in children and adolescents?

Contextual Questions

One Contextual Question was also requested by the USPSTF to help inform the report. Contextual Questions are not reviewed using systematic review methodology.

1. What is the relationship between use of e-cigarette and use of other tobacco products?

Search Strategies

A research librarian searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, Ovid MEDLINE, PsycINFO, and EMBASE (through June 25, 2019) for relevant English-language studies, systematic reviews, and meta-analyses. Searches included studies published in September 2012 to the present to update tobacco use, however searches were not limited by date for e-cigarette use, or for prevention of tobacco use in the young adult population (19 to 25-year olds). Surveillance was conducted through February 7, 2020. Search strategies are available in **Appendix A1.** Search terms included "tobacco, smoking, cigarettes, electronic cigarettes, e-cigarettes, nicotine, and electronic nicotine delivery system," among other terms. Investigators also reviewed reference lists of relevant articles to identify studies.

Study Selection

We selected studies based on the inclusion and exclusion criteria developed for each key question (**Appendix A2**). After an initial dual review of citations and abstracts, investigators retrieved full-text articles of potentially relevant material. Two reviewers conducted full-text review of articles and discrepancies were resolved through consensus or with input from a third reviewer. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists excluded studies with reasons for exclusion.

For Key Questions 1 and 2, we included randomized and nonrandomized controlled trials of children and adolescents with a minimum of 6 months (or 24 weeks) of followup postbaseline. We included comparative observational studies along with randomized and nonrandomized controlled trials to describe potential harms of interventions (Key Question 3).

Intervention trials designed to prevent tobacco use in children or adolescents, or trials that promoted the cessation of tobacco use published since the search of the last review (September 2012) were eligible for inclusion. Included interventions were primary care-relevant behavioral counseling interventions (e.g., face-to-face individual and/or group counseling, telephone or technology-based counseling; text-messages; interactive websites), pharmacotherapy (i.e., NRT, bupropion, or varenicline tartrate), and complementary and alternative medicine interventions (e.g., acupuncture and hypnosis). We included trials that targeted parents or caregivers as a means to prevent or reduce tobacco or nicotine use in children and adolescents, the child/adolescent directly, or both parent and child/adolescent. We also included studies of interventions aimed at preventing multiple risky behaviors (e.g., smoking, drinking, drug use, sex) or increasing safe or healthy behaviors (e.g., condom use, use of additional services as needed) if the trials reported outcomes of interest separately from other outcomes.

Prevention or cessation studies of all types of tobacco products (e.g., cigarettes, smokeless tobacco, cigars, pipes, e-cigarettes) were eligible for inclusion provided they reported health outcomes (e.g., respiratory, cardiovascular, oral health outcomes), tobacco or nicotine use, or frequency or quantity of alcohol use or use of other psychotropic substances. We included trials of baseline nonsmokers that reported initiation of smoking, trials of baseline smokers that reported cessation of smoking, and trials of combined smokers and nonsmokers that reported smoking prevalence as study outcomes. Outcomes were typically 7-day point prevalence, 30-day point prevalence, or continuous abstinence. See **Table 2** for common tobacco use measures. Eligible intervention studies that followed children and adolescents to adulthood and reported adult tobacco and/or e-cigarette use were also included. We excluded trials that reported only perceptions or attitudes about tobacco use or intentions to quit. We also excluded head-to-head studies of one smoking intervention compared with another smoking intervention and required control groups to include no smoking intervention or a minimal smoking intervention (e.g., usual care, attention control, wait list control, no intervention).

We excluded most trials conducted in schools because of the interaction of students with each other, the influence of peer relationships, and the inability to replicate these conditions within clinical practice, but included trials that were conducted in school buildings after hours or trials where the school nurse counseled individual students. We also excluded any studies that used e-

cigarettes as a cessation or prevention intervention for children and adolescents due to concerns over the harms of using e-cigarettes in this population (e.g., nicotine addiction, harm to the developing brain, nicotine toxicity). We included studies of adolescents up to 18 years of age for cessation interventions and up to 25 years of age for prevention interventions.

Data Abstraction and Quality Rating

For the included trials, investigators abstracted the following data: study design, setting, population characteristics, intervention characteristics, and results for each outcome. Two investigators independently applied criteria developed by the USPSTF[43] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Studies that were rated poor-quality were excluded because results are likely to be biased and highly unreliable.[43] Discrepancies were resolved through a consensus process.

Data Synthesis

Self-reported smoking status was the primary outcome. We analyzed trials by whether they targeted smokers, nonsmokers, or both. When able, we calculated relative risks (RRs) using raw data counts and pooled trials using random effects meta-analyses on the natural log scale and back transformed the results; we assessed statistical heterogeneity with the I^2 statistic. The meta-analyses were adjusted for cluster randomization for six trials using the sample sizes, number of clusters, and an estimated intraclass correlation coefficient (ICC), in accordance with the Cochrane Handbook.[44] As in the prior USPSTF review,[2,3] we used an ICC of 0.01. Sample sizes in the text of the report included these adjusted numbers. We pooled studies in meta-analysis and meta-regression using Stata 14.2 (StataCorp, College Station, Texas). In instances where trials had more than one intervention group, we included in meta-analyses the group with the most intensive intervention. We conducted meta-regression to evaluate effects of study-level characteristics on estimates, used backward stepwise meta-regression with a p-value less than or equal to 0.20 for entry into the model, and controlled for the response in the control group. We also conducted stratified analyses of dichotomous variables (e.g., study conducted in the United States vs. Europe) and categorized continuous variables (i.e., duration of trial in weeks, age of participants in years, percent female, percent nonwhite, number of contacts) to explore their role on effect size. Additionally, we performed sensitivity analyses based on intensity of intervention (excluding highly intensive interventions). Analyses were based on data at 12 months postbaseline. When 12-month data were not available, we used end-of-trial data or data nearest to 12 months.

We assessed the aggregate internal validity (quality) of the body of evidence for each key question ("insufficient", "low", "moderate", and “high”) using methods developed by the USPSTF, based on the number, quality and size of studies, consistency of results between studies, and precision of effects.[43]

Expert Review and Public Comment

The draft Research Plan was posted on the USPSTF Website from June 22 to July 19, 2017. In response to comments, the USPSTF made the following changes to the Research Plan. The USPSTF added pregnant adolescents as an included population, as well as studies in subgroups of adolescents with health problems common to primary care, such as depression and asthma. The USPSTF increased the upper age limit to 25 years for tobacco and nicotine use prevention and changed pharmacotherapy use for tobacco and nicotine cessation in children and adolescents from a contextual question to an included intervention. The USPSTF also included cardiovascular outcomes in addition to respiratory and oral/dental health outcomes.

A draft version of this report was reviewed by content experts (**Appendix A6**), representatives of Federal partners, USPSTF members, and AHRQ Medical Officers. Reviewer comments were presented to the USPSTF during its deliberations and subsequently addressed in revisions of this report. In addition, the draft report was posted for public comment from June 25, 2019 to July 22, 2019. In response to public comments received, we made minor editorial clarifications to the report that did not include changes to the evidence or to conclusions drawn.

Chapter 3. Results

We identified 26 trials, reported in 33 publications,[45-77] examining the effects and harms of interventions designed to prevent the initiation of tobacco use and/or promote cessation among children and adolescents (**Table 3**). Twenty-five of the 26 included trials reported smoking prevalence at 6 months or longer followup; one additional trial did not report health outcomes or tobacco prevalence at 6 months or longer followup and thus, was only included for harms (Key Question 3).[78] Seven trials were newly identified as part of this update and 19 were carried forward from the previous review. Overall, five trials were rated good-quality[58,59,68,74,76] and the remainder were rated fair-quality largely due to unspecified methods of allocation concealment, lack of reporting of baseline participant characteristics by randomized group, and high attrition (**Appendix B1**). We did not include three studies rated poor-quality. **Tables 4, 5, and 6** present study, population, and intervention characteristics for all included trials. **Appendix B2** presents detailed descriptions of the behavioral interventions.

Key Question 1. Do Primary Care Interventions to Prevent Tobacco and Nicotine Use or Improve Tobacco and Nicotine Cessation Rates in Children and Adolescents Improve Health Outcomes (i.e., Respiratory, Dental, Cardiovascular, and Oral Health) and Reduce the Likelihood of Tobacco and Nicotine Use in Adulthood?

Summary

The previous USPSTF review[2,3] found no eligible evidence on the effects of primary care interventions on smoking status as adults or on health outcomes. One long-term followup paper of a previously included trial[64] found no long-term effect of counseling by a dentist on the likelihood of adult smoking at 16 years of followup (odds ratio [OR] 0.78, 95% confidence interval [CI] 0.56 to 1.09), although the effect estimate favored the intervention.[73] One new trial found no effect of a nurse visitation program on smoking during late pregnancy (56% in both intervention and control groups) or on mental health outcomes at 2 years postpartum.[72] However, the intervention was not well-defined. Both trials were rated fair-quality due to unclear allocation concealment,[64] unclear if randomized groups were similar at baseline,[64] and high attrition.[64,72] We identified no trials of e-cigarette use.

Evidence

The prior review found no evidence for this key. One trial[64] included previously enrolled 12 year olds (n=2,586) at their routine dental exam in Finland and assigned them to brief counseling by a dentist or usual care. Adolescents who did not smoke (94.3%) were counseled against smoking. Both adolescents who smoked and those who did not smoke were shown photos of teeth discolored by smoking and invited to check their own teeth with a hand mirror for discolorations.

The brief counseling was provided to participants up to four times during routine dental visits over approximately 2.5 years. The prevalence of smoking at the 2-year followup was 18.1 percent in the group that received counseling by the dentist and 20.8 percent among those assigned to usual care and was not statistically significantly different. A companion publication reported long-term followup when the study participants were 29 years old and found that in the 1,020 participants who returned the survey (39.4% of the original sample), 15.3 percent in the intervention group and 18.5 percent in the usual care group were smokers (OR 0.78, 95% CI, 0.56 to 1.09).[73] Most started smoking at 15 years old (median), which was not different between the groups.

One non-blinded, randomized trial of a combined intervention enrolled 1,645 pregnant women 19 years or younger and less than 25 weeks gestation to an intensive program of home visits by nurses in the United Kingdom (Family Nurse Partnership [FNP]) plus usual care or to usual care alone (publically funded health care and social care).[72] This study was based on a U.S. model of home visitation that covered parent education on fetal and infant development, informal support, and referrals to other services as needed. However, details of the intervention in the U.K. trial were not provided and it is unknown how closely the U.K. trial followed the U.S. model. In the U.K. trial, primary outcomes included self-reported tobacco use in late pregnancy. Secondary outcomes included maternal depression, problems with alcohol and drug use, and emergency department visits and hospital admissions not related to the birth of the child through 24 months postpartum. Both smokers (57%) and nonsmokers (43%) were enrolled and assigned to treatment groups through minimization. Self-reported smoking or cotinine levels were missing from 486 participants (30%). Of the 1,092 women analyzed for smoking, there were no differences in self-reported smoking during late pregnancy (56% both groups) or in the number of cigarettes smoked per day. While there were no differences between groups on maternal non-delivery related emergency department visits and hospital admissions, maternal psychological distress scores, depressive symptoms score, or problems with alcohol and drug use scores at 24 months postpartum, it is uncertain if these outcomes would be substantially affected by the smoking intervention and may not be the best benchmark for evaluating the value of the intervention.

Key Question 2. Do Primary Care Interventions Prevent Tobacco and Nicotine Use or Improve Tobacco and Nicotine Cessation Rates in Children and Adolescents?

Summary

The prior review[2,3] included 18 trials and seven new trials were identified for this update.[51,56,57,71,72,74,75] Across all 25 trials, 14 provided evidence on preventing tobacco initiation among nonusers, 12 provided evidence on tobacco cessation among users, and nine provided evidence on the overall tobacco prevalence. Similar to the prior review,[2,3] behavioral interventions were associated with reduced smoking initiation compared with controls (k=13, n=21,700, 7.4% vs. 9.2%, RR 0.82, 95% CI, 0.73 to 0.92, I^2=15%).[45,48,51-53,55,57-59,62,66,69,71,75] However, as in the prior review,[2,3] there was no effect of behavioral intervention trials on smokers (n=2,516) quitting smoking and most continued to smoke after the intervention (80.7% vs. 84.1%, RR 0.97, 95% CI, 0.93 to 1.01, I^2=29%).[46,49,50,56,58,66,68,69,71] One new medication trial

(n=257) found no effect of NRT on smoking cessation.[74] Behavioral interventions had a significant effect on decreasing smoking prevalence in trials that included both smokers and nonsmokers at baseline (n=10,533, 16.8% vs. 20.1%, RR 0.91, 95% CI, 0.83 to 0.995, p=0.04, I^2=19%). However, these results were sensitive to inclusion of two trials with behavioral interventions that were less applicable to primary care. We identified no prevention, cessation, or combined prevention and cessation trials of e-cigarette use, either as a target of the intervention or as a means to smoking cessation.

Most trials were rated fair-quality, including six of the seven new trials, due to unclear allocation concealment, uncertainty about whether important baseline characteristics were similar between randomized groups, lack of blinding or not reporting blinding, and high loss to followup (**Appendix B1**). One new trial was rated good-quality.[74]

Evidence

Prevention Interventions

The prior review[2,3] found less smoking initiation with behavioral interventions (k=9, n=17,721, 8.8% vs. 10.4%, RR 0.81, 95% CI, 0.70 to 0.93, I^2=38%) based on two good-quality[58,59] and seven fair-quality trials.[48,51-53,55,66,69] Four new, fair-quality studies of behavioral interventions were identified that reported smoking initiation.[51,57,71,75] **Table 7** provides characteristics of behavioral interventions by the four methods of delivering the intervention (i.e., face-to-face counseling, telephone counseling, print materials, and through the use of a computer).

Characteristics of Prevention Studies

Included trials were heterogeneous in type, target, and intensity of the interventions (**Table 4**). All trials were conducted in the United States[48,52,55,58,59,62,66,69,71] or in Europe (i.e., The Netherlands,[45,51,57,75] the United Kingdom[53]). Nine trials enrolled only nonsmokers[45,51-53,55,57,59,62,75] and five enrolled baseline smokers and nonsmokers but reported results by smoking status.[46,58,66,69,71] Being a nonsmoker was defined as never smoking, not even one puff,[45,48,62] never smoked or smoked one to two puffs but not in the past year,[69] no smoking in the past 30 days,[58] never smoked but susceptible to smoking or smoked previously but not in the past 30 days,[66] no tobacco use in past 30 days and never used tobacco more than 100 times,[59] smokes less than one cigarette per week,[53] never smoked weekly or more,[71] never smoked not even one puff or tried smoking but do not smoke anymore or stopped smoking after smoked at least once a week (or less),[51] or was not reported.[52,55,57]

Interventions took place in primary care clinics,[58,69,71] dental clinics,[59,66] homes,[45,48,51-53,55,57,62,75] and a school.[55] The intervention that took place in a school was conducted after school hours and was not a school-based intervention. Eight trials targeted the youth to receive the intervention,[45,51,53,58,59,66,69,71] two targeted the parent[48,75] and four targeted both child and parent.[52,55,57,62] Three trials targeted behaviors in addition to smoking—alcohol use,[48,55] marijuana and other illegal drug use,[55] sexual activity,[55] and condom use.[71] One trial also assessed the intervention's effect on the proportion who initiated the use of chewing tobacco.[48]

Trials used a single mode of intervention delivery[45,51,53,55,57,62,75] or used multiple means of delivery[48,52,58,59,66,69,71] Print materials were used most commonly to deliver part or all of the intervention[45,48,52,53,57-59,62,75] followed by face-to-face encounters with a counselor, health educator, or primary care medical or dental provider.[55,58,59,66,69,71] Several trials also employed telephone support or booster calls[52,58,66,69,75] and three trials were internet-based or used an interactive computer program.[51,58,71] The control groups consisted of usual care,[51,52,59,69] an attention control,[58] a low intensity smoking intervention,[55,62,66,71,75] no interaction,[53] or was not described.[45,48,57]

The content of the interventions, like the methods for intervention delivery, were heterogeneous. Studies focused on: 1) increasing parental communication, support, and guidance for the adolescent (antismoking socialization);[48,52,55,57,62] 2) providing health education on the harms of smoking;[52,53,59,66] 3) providing messages that smoking makes one's teeth less attractive;[59,66] 4) describing the advantages of remaining a nonsmoker;[45,53] 5) exposing the adolescent to nonsmoking information, animated videos, and computer games;[51] and 6) assessing a participants readiness to act or change and providing strategies and processes to facilitate action or behavior change.[45,58,66,69,71] One trial targeted smoking parents who received up to seven telephone calls by Dutch national quit line counselors who provided information on nicotine dependence and utilized cognitive behavioral therapy (CBT) techniques to assist parents in quitting smoking.[75] The outcome of interest in this trial was the effect of the parent receiving the intervention and possibly quitting smoking on the child's smoking initiation.

The duration of the interventions ranged from 7 weeks[55] to 25 months[51] with a mean number of six contacts, ranging from three contacts (1 visit and 2 telephone calls[58 6] or 3 mailings[45,53]) to 15 contacts (3 computer-tailored feedback messages and 6 prompt messages per year for 2 years).[51] The duration of the prevention trials ranged from 6[45] to 36 months.[57] The primary smoking outcomes reported were 30-day point prevalence of smoking,[45,52,58,66] 30-day point prevalence of any tobacco use,[59] taken even one puff of a cigarette,[48,57,62,75] and smoking or starting to smoke or smoking initiation.[51,53,55,69,71]

Characteristics of Participants in Prevention Studies

The weighted mean age of study participants was 12.8 years (the age range is unknown since not all of the trials reported the age range of those actually enrolled). Calculation of the mean age did not include one trial that enrolled 10 to 15 year olds but did not report a mean age[53] and assumes a mean age of 7.5 years in one trial that enrolled 7 to 8 year olds.[62] Only one study enrolled more males than females (51.4% vs. 48.6%);[55] the weighted mean percent females was 53.9 percent (range: 48.6% to 100%). Studies enrolled primarily whites (weighted mean proportion white 77.6%, range: 7.9% to 98.3%). Three studies did not report the racial breakdown (**Table 4**).[52,53,75]

Results From Prevention Studies

Meta-analysis of the nine trials from the prior review[2,3] and the four new trials found that behavioral interventions were associated with reduced smoking initiation at 6 months or longer compared with controls (k=13, n=21,700, 7.4% vs. 9.2%, RR 0.82, 95% CI, 0.73 to 0.92, I^2=15%, **Figure 2 and Table 8**).[45,48,51-53,55,57-59,62,66,69,71,75] Outcomes reported at 12 months were

pooled when available. Eight trials provided outcomes at 12 months, and one trial each provided outcomes at 7 months,[48] 18 months,[71] 20 months,[52] 24 months,[59] and 36 months.[62] One prevention trial (n=3,349) that could not be pooled found an out-of-school intervention (3 letters mailed to participants homes that contained smoking prevention messages) associated with a decreased likelihood of initiating smoking compared with a control group at 6 months (10.4% vs. 18.1%, $p<0.05$).[45] However, this comparison included 1,068 adolescents in the intervention group who also received the school-based social influence program entitled "Don't play with Fire."

Six trials not only reported outcomes at 12 months, but also reported outcomes beyond 12 months.[48 26,51,55,57,58,75] Results beyond 12 months were consistent with the 12-month findings for each trial with the exception of one trial where outcomes at 24 months were no longer statistically significant (OR 0.80, 95% CI, 0.62 to 1.03).[58] One trial, that found no difference between the intervention and control groups at 12 months, reported significant findings at 6 months (1.8% initiated smoking vs. 3.5%, $p<0.05$).[69] Additionally, one trial reported the effect of the intervention on initiation of chewing tobacco and found no differences between intervention and control groups, but very few adolescents began chewing tobacco (approximately 3% in both groups).[48]

Three of the four new prevention trials were conducted in Europe, did not take place in a medical setting, and targeted smoking behaviors only.[51,57,75] The fourth trial was conducted in the United States in a family planning clinic, enrolled only females, and focused on condom use in addition to smoking behaviors.[71] The duration of the interventions ranged from 3[75] to 25 months,[51] and involved no contact time with an interventionist[51,57] to up to seven telephone counseling sessions.[75] Two trials targeted the youth,[51,71] one targeted the parent,[75] and one targeted both child and parent.[57] None of these trials individually demonstrated a treatment effect (RRs 0.61 to 1.08).

Three individual trials (total n=4,923) from the prior review[2,3] demonstrated significant effects of the intervention in the pooled analysis (RRs 0.62 to 0.76).[53,58,62] The trials focused solely on smoking behavior and all interventions were 12 months in duration. One trial was conducted in pediatric and family medicine clinics and involved approximately 15 minutes of contact with a health counselor in addition to the use of an interactive computer program, print materials, and two telephone booster calls.[58] The other two trials limited the intervention to print materials.[53,62]

Exploratory meta-regression of multiple study-level characteristics were conducted (**Appendix C1**) and results consistently demonstrated that no variable or group of variables predicted the magnitude of the intervention effect for prevention trials. Results were similar with stratified analyses (**Appendix C2**). That is, results from trials conducted in the United States were similar to those conducted in Europe; trials employing face-to-face counseling had similar findings as those that did not; and prevention only trials had similar results as trials that combined prevention and cessation interventions. The only exceptions were the unexpected findings that trials that used a single mode of delivering the intervention were more likely to report less smoking initiation than trials that employed multiple methods and that trials with fewer contacts with the participant (e.g., visits, telephone calls, mailings) were more likely to demonstrate an

intervention effect than did trials with more contacts. However, the meta-regression was limited by few studies and the significance of these findings are unclear.

Cessation Interventions

Behavioral Intervention Trials

The prior review[2,3] included seven trials that enrolled smokers.[46,49,50,58,66,68,69] Pooled analysis of the seven trials found no effect of the behavioral intervention (n=1,882, RR 0.96, 95 percent CI, 0.90 to 1.02) based on two good-quality[46,49,50,58,66,68,69] and five fair-quality studies.[46,49,50,58,66,68,69] Two new, fair-quality cessation trials were identified for this update review (n=634).[56,71]

Characteristics of Cessation Interventions in Behavioral Trials

Similar to the prevention studies, cessation trials were also heterogeneous in study design (**Table 5**). All trials were conducted in the United States,[46,49,50,58,66,68,69,71] except for one trial that was conducted in Switzerland.[56] Four behavioral trials enrolled only smokers[49,50,56,68] and the remainder enrolled both smokers and nonsmokers but reported results by smoking status.[46,58,66,69,71] Being a smoker was generally defined as smoking at least one cigarette in the past 30 days.[46,58,66,68] Other definitions included daily smoking in the past 30 days,[49] weekly smoking in the past 30 days,[50] or smoked at least weekly and still smoking.[71] One study did not define what being a "smoker" constituted.[56]

The trials were conducted in primary care clinics,[58,69,71] a school health clinic,[68] a dental clinic,[66] and homes.[46,56] The location was not specified in two trials.[49,50] Seven trials targeted the youth,[49,56,58,66,68,69,71] one targeted the parent, [46] and one targeted both child and parent.[50] Two trials targeted behaviors in addition to smoking: alcohol use[46] and condom use.[71]

Two trials employed one method of delivering the intervention[56,68] while the other utilized multiple means of intervention delivery.[46,49,50,58,66,69,71] Face-to-face counseling was used the most often,[49,50,58,66,68,69,71] followed by telephone counseling.[49,50,58,66,69] One trial sent text messages to participants,[56] four trials made use of print materials,[46,49,50,58] and two trials used a computer to deliver part of the intervention.[58,71] The control groups consisted of usual care,[69] an attention control,[58] a low intensity smoking intervention,[49,50,66,68,71] an assessment only group,[56] or was not described.[46] Most trials assessed the adolescent's readiness to stop smoking and provided strategies and processes to facilitate behavior change.[49,50,56,58,66,68,69,71] Other behavioral intervention strategies included focusing on increasing parental communication, support, and guidance for the adolescent (antismoking socialization);[46] providing health education on the harms of smoking;[49,50,66,68] and providing messages that smoking makes one's teeth less attractive.[66]

The duration of the intervention ranged from 1 week[49] to 12 months[58] with a median of four contacts and a range of two contacts (1 visit and 1 booster call)[49] to 66 contacts (all text messages, including 11 assessment messages).[56] The duration of the cessation trials with behavioral interventions ranged from 6[49,50,56] to 24 months.[58] Smoking outcomes included 30-day

point prevalence of smoking,[46,49,58,66,68] 7-day point prevalence of smoking,[49,50,56] or was not reported.[69,71]

Characteristics of Participants in Cessation Trials of Behavioral Interventions

Whereas the weighted mean age in prevention trials was 12.8 years, the average age of participants in cessation trials was much older at 16.6 years. All but two studies enrolled more females than males[49,68] and one trial enrolled only females.[71] The weighted mean proportion of females was 54 percent (range: 47.5% to 100%). Similar to the prevention trials, more whites than nonwhites were enrolled (weighted mean proportion of whites 84.4%, range 7.9% to 92.6%). One trial, conducted in Switzerland, did not report racial breakdown (**Table 5**).[56]

Results for Cessation Studies of Behavioral Interventions

Similar to the prior review[2,3] meta-analysis of the nine cessation trials found that behavioral interventions to quit smoking were not associated with less smoking post intervention when compared with controls (n=2,516, 80.6% vs. 84.1%, RR 0.97, 95% CI, 0.93 to 1.01, I^2=29%, **Figure 3 and Table 9**).[46,49,50,56,58,66,68,69,71] Four trials reported outcomes at 12 months,[58,66,68,69] three at 6 months,[49,50,56] and one trial each at 7 months[48] and 18 months.[71] Two trials provided data beyond 12 months,[46,58] and had similar findings as those reporting at 12 months. One trial that found no intervention effect at 12 months reported significantly less smoking at 6 months compared with usual care (63.6% still smoking vs. 75.4%, p<0.05).[69]

Of the two new trials, one trial was conducted in a U.S. family planning clinic and was also a prevention trial,[71] while the other was conducted in Switzerland and consisted of text messages sent to vocational students at least three times a week over 3 months.[56] Text messages included a review of outcome expectations, social support, and tips for coping with cravings. Having an intention to quit smoking was not an inclusion criterion for this trial. Neither of the new trials demonstrated a significant treatment effect (RR1.06, 95% CI, 0.84 to 1.33[71]; RR 0.97, 95% CI, 0.91 to 1.03[56]).

The two trials from the prior review that did demonstrate a treatment effect (RR 0.79, 95% CI, 0.65 to 0.96;[49] RR 0.88, 95% CI, 0.79 to 0.97[58]) were conducted in the United States and targeted the youth or young adult.[49,58] One trial was also a prevention trial,[58] conducted in primary care, and involved 15 minutes of motivational interviewing with a health counselor supplemented with handouts, a session with an interactive computer program, and two booster calls.[58] The other trial limited the role of primary care to recruitment only and consisted of one visit plus one booster call within 1 week.[49] Most patients in this trial (81%) had no immediate plans to quit smoking.

Exploratory meta-regression of multiple study-level characteristics in cessation trials were conducted (**Appendix C1**) and results consistently demonstrated no ability of any variable or group of variables to predict the magnitude of the intervention effect for cessation trials. Results were similar with stratified analyses (**Appendix C3**).

In one trial, *post hoc* analysis of baseline smokers found that the intervention effect was greater among nonwhite adolescents (OR 4.10, 95% CI, 1.01 to 16.71) compared with white adolescents

(OR 2.16, 95% CI, 1.14 to 4.08), although this difference was not statistically significant.[58] Also, in one study of a school nurse-delivered, patient-centered counseling program, the school nurse met with adolescent smokers for four individual sessions (2 to 20 minute sessions before the quit smoking date and 2 to 15 minute sessions after the quit date) over 1 month.[68] Although there was a significant effect of the intervention at 3 months among males (no effect was seen among females), this was not seen at 12 months. The lack of intervention effect could be due to the intensity of the attention control condition. Adolescents assigned to the attention control group also met with the school nurse for four weekly visits. In addition, control adolescents were asked about smoking status and given an anti-smoking informational pamphlet each visit.

Medication Intervention Trials

Two fair-quality medication trials[65,67] from the prior review[2,3] evaluated the use of bupropion slow release (SR) in addition to behavioral counseling to encourage smokers to quit smoking (**Table 5**). No new trials of bupropion for smoking cessation in adolescents were identified for the update. One new, good-quality trial of NRT, in addition to a short behavioral intervention, on quitting smoking in children aged 12 to 18 years was identified.[74] The three medication trials were relatively small (n range: 211 to 312), recruited from schools, used placebo as a control, included a 6-month followup assessment, and enrolled adolescents who were motivated to quit smoking[74] or who had at least one [65] or two previous quit attempts.[67] One trial recruited through the media and various community venues (e.g., shopping malls, doctors' offices), as well as from schools.[67] One trial included outcomes at 12 months, as well as at 6 months.[74]

The new NRT trial was conducted in the Netherlands and enrolled 265 adolescents, who smoked at least seven cigarettes per day and were randomized to receive NRT or a placebo patch.[74] Those who smoked less than 20 cigarettes per day at baseline received the patch for 6 weeks (3 weeks at 14 mg/day followed by 3 weeks at 7 mg/day) and those who smoked more than 20 cigarettes per day at baseline received the patch for 9 weeks (3 weeks at 21 mg/day then 3 weeks at 14 mg/day then 3 weeks at 7 mg/day). All participants also received a behavioral intervention that consisted of a 75-minute information meeting covering preparation and expectations of quitting smoking and instructions on using NRT. Smoking cessation was defined as 30-day point prevalence abstinence at 6 and 12 months. Although NRT was associated with increased smoking cessation at the end of treatment among highly compliant adolescents (adjusted OR [AOR] 1.09, 95% CI, 1.01 to 1.17),[74] there was no effect after 6 months or 12 months among all participants (6 months: 8.1% vs. 5.7%, AOR 2.09, 95% CI, 0.20 to 22; 12 months: 8.1% vs. 8.2%, AOR 1.13, 95% CI, 0.17 to 7.44) or among only the more compliant youth (AOR 0.99, 95% CI, 0.91 to 1.07; AOR 0.99, 95% CI, 0.92 to 1.07, respectively, **Table 9**).[74]

Both trials of bupropion SR were conducted in the United States. One trial compared bupropion SR 150 mg and placebo,[65] while the other compared bupropion SR 150 mg, 300 mg, and placebo.[67] The three armed trial included 14 to 17 year olds who smoked six or more cigarettes per day, and in addition to bupropion SR 150 mg, 300 mg, or placebo, participants received 10 to 20 minutes of standardized individual cessation counseling. There were several time points when self-reported smoking abstinence with bupropion 300 mg was greater than with placebo (i.e., at weeks 1, 3, 5, and 6 after the target quit date). However, at the 26-week followup, quit rates in

the 300 mg, 150 mg, and placebo groups were not significantly different from each other at 17 percent, 6 percent, and 10 percent, respectively (**Table 9**).

The other bupropion trial[65] included 15 to 18 year olds who smoked at least 10 cigarettes per day and in addition to bupropion 150 mg or placebo, participants also received NRT (dose based on number of cigarettes smoked per day) for 8 weeks and weekly group skills training designed to facilitate not smoking in high-risk situations. At week 26, self-reported abstinence rates were 24 percent with bupropion plus NRT versus 28 percent in the group that received placebo plus NRT and provided no evidence for a treatment effect. However, compliance in this trial was not high. At week 5, only 39 out of 103 participants had evidence of bupropion in their urine (38%) and only 22 percent reported taking all of their bupropion pills (**Table 9**).

Combined Prevention and Cessation Interventions

Two good-quality trials[58,76] and five fair-quality behavioral trials[47,64,66,69,70] from the prior review[2,3] and two new fair-quality behavioral trials[71,72] included both smokers and nonsmokers. Four combined trials reported only prevalence of smoking at postintervention.[64,70,72,76] The remaining five trials reported results by smoking status and are also included as prevention and cessation trials.[47,58,66,69,71]

Characteristics of Combined Studies

Most trials were conducted in the United States,[47,58,66,69-71,76] one trial was conducted in the United Kingdom,[72] and one trial was conducted in Finland (**Table 6**).[64] The intervention took place in primary care medical clinics,[58,69,71,76] dental clinics,[64,66] and at homes.[47,70,72] Six trials targeted the youth to receive the intervention,[58,64,66,69,71,72] two targeted the parent [47,70] and one targeted both the child and parent.[76]

Trials used a single mode of intervention delivery[64,70,72] or used multiple means of delivery.[47,58,66,69,71,76] Face-to-face counseling was used most frequently to deliver part or all of the intervention[58,64,66,69-72] followed by telephone counseling or booster calls.[58,66,69,76] Print materials were used to deliver the intervention in three trials[47,58,76] and two trials used a computer to deliver part of the intervention.[58,71] The control groups consisted of usual care,[64,69,72] an attention control,[58,70,76] a low intensity smoking intervention,[66,71] or was not described.[48] The content of the interventions included a focus on assessing a participant's readiness to act or change and providing strategies and processes to facilitate action or behavior change;[58,66,69,71,72] increasing parental communication, support, and guidance for the adolescent;[47,70,76] providing health education on the harms of smoking;[66,76] and providing messages that smoking makes one's teeth less attractive.[64,66]

The duration of the intervention ranged from 15 weeks[47] to 36 months[76] with a median of 10 contacts, ranging from two contacts (2 dental visits)[64] to a mean of 39 nurse home visits.[72] The duration of the combined trials ranged from 6 [66] to 36 months.[70,76] The primary smoking outcomes were 30-day point prevalence of smoking,[58,66] ever smoked at posttest,[76] taken even one puff of a cigarette,[48] smoked in the past 90 days,[70] smoking at late pregnancy,[72] and smoking or starting to smoke/smoking initiation.[64,69,71]

Characteristics of Participants in Combined Studies

The weighted mean age of study participants was 14.0 years. Only one study enrolled more males than females (51.4% vs. 48.6%);[55] the weighted mean percent females was 58.6 percent (range: 48.3% to 100%). Two studies enrolled only female adolescents or young adults.[71,72] Studies enrolled primarily whites (weighted mean proportion white 73.2%, range: 0 to 91.4%). One trial enrolled only Hispanic adolescents[70] and one trial enrolled over 84 percent black adolescents.[71] Two studies did not report the racial breakdown (**Table 6**).[64,76]

Results From Combined Studies

The prior review[2,3] found no difference in smoking prevalence at followup between adolescents in the intervention groups compared with the control groups in a pooled analysis of six trials (n=6,838, RR 0.91, 95% CI, 0.81 to 1.01). One combined trial did not provide adequate data for inclusion in the prior meta-analysis.[76] New statistical techniques now enable an estimate of the effect size to be calculated.[79] Findings from pooled analysis including all nine trials were similar to those from the prior review (n=11,471, 20.3% vs. 23.5%, RR 0.93, 95% CI, 0.86 to 1.01, I^2=24%, **Figure 4 and Table 10**). Sensitivity analysis removing the study with estimated results[76] yielded similar, nonsignificant intervention effects (n=7,501, RR 0.92, 95% CI, 0.85 to 1.01). Two trials, that combined smokers and nonsmokers, employed extremely intensive interventions that were quite different from the remaining trials and may not be available for referral from primary care.[70,72] A sensitivity analysis removing these two trials that provided 49 contact hours over 12 months,[70] and 64 nurse visits over more than 24 months,[72] resulted in a borderline significant estimate of effect (n=10,533, 16.8% vs. 20.1%, RR 0.91, 95% CI, 0.83 to 0.995, p=0.04, I^2=19%, **Figure 5**). This change in the effect estimate is likely multifactorial due to the sizable heterogeneity in study design and populations enrolled.

The new intensive, combined trial, enrolled 1,645 nulliparous women in early pregnancy in the United Kingdom who were 19 years or younger (mean age: 17.9 years, range: 16.9 to 18.8 years).[72] This trial was also discussed in Key Question 1. The intensive intervention (FNP) consisted of up to 64 structured nurse visits to participants' homes beginning in pregnancy until the child turned 2 years old in addition to usual care. The control intervention was usual care, which consisted of publically funded health care and social care. Self-reported tobacco use in late pregnancy was a primary outcome and occurred with similar frequency in both groups (304/547 with the intervention, 306/545 with usual care; 56% in both groups). Smoking status was verified by urine cotinine level. Trial authors suggest that the level of care routinely available to teenage mothers in the United Kingdom is higher than that in the United States and that this extra support may have diluted any effect of the FNP Program.

The other new trial was included in the previous sections on prevention and cessation; it also enrolled only female adolescents, was conducted in a family planning clinic, and the intervention consisted of completing a smoking module on a computer and up to four counseling sessions with a bachelors or masters level counselor.[71] Neither of these trials demonstrated an individual treatment effect (RR 0.86 and RR 0.99).

Two individual trials from the prior review[2,3] enrolled both smokers and nonsmokers and demonstrated a significant treatment effect on reducing smoking at followup (RR 0.84 both trials).[47,58] One trial discussed previously, was conducted in primary care, targeted the adolescent with a brief clinician message along with a computer assessment, a motivational interview conducted by health counselors, and two booster phone calls.[58] The only other combined trial with significant findings, targeted parents and included four activity books followed by four phone calls by health educators over 15 weeks.[47]

Meta-regression analyses identified the duration of the intervention, in weeks, as the only variable that predicted intervention response in the combined trials, with greater intervention effects seen with shorter intervention durations (p=0.047). However, after adjusting for the response in the control groups, statistical significance was lost (p=0.053, **Appendix C1**). Stratified analyses of intervention duration (using a 12-month cutoff) also did not demonstrate a significant effect (**Appendix C4**).

Key Question 3. What Adverse Effects Are Associated With Primary Care Interventions to Prevent Tobacco and Nicotine Use or Improve Tobacco and Nicotine Cessation Rates in Children and Adolescents?

Summary

We included all 26 trials for this key question (22 behavioral-based intervention trials, and 4 trials of medications for smoking cessation). Five trials were rated good-quality[58,59,68,74,76] and the remainder were rated fair-quality. As in the prior review[2,3] new trials of behavioral interventions did not report any specific harms. The prior review reported harms of the three bupropion trials.[54,65,67] One new trial of NRT also reported harms.[74] Of the four medication trials, no serious adverse events occurred that were attributed to the study medication. We identified no trials of e-cigarette use in children and/or adolescents.

Evidence

None of the 22 behavioral intervention trials reported adverse events or harms associated with the intervention. Nine trials reported greater percentages of smoking in the intervention group than control group after the intervention (RRs 1.01 to 1.90).[52,55,64,66,69-71,75,76] However, this difference between the intervention and control groups was generally small (RRs less than 1.10). In the trial with the greatest RR (1.90, 95% CI, 0.49 to 7.32), the effect estimate was imprecise due to the small sample size and few total adolescents smoking at 12 months (n=9 out of 154 participants). In no prevention, cessation, or combined trial was the proportion smoking in the intervention group significantly greater than that in the control group.

Four medication trials reported harms; three bupropion trials[54,65,67] from the prior review[2,3] and one new NRT trial.[75] All medication trials were small (n range: 134 to 257). The new trial of NRT reported that participants in the NRT group reported more headaches, cough, abnormal

dreams, muscle pain, and patch related adverse events ($p<0.05$) compared with participants in the placebo patch group who reported more sleeplessness ($p<0.01$).[74] Itchiness was a common complaint in patients regardless of treatment group. No serious adverse events were reported.

In one of the bupropion trials, eight patients discontinued the study drug due to adverse events: feeling depressed, irritable, angry, having sleep disturbances, headaches, urticarial, anxiety, palpitations, attempted suicide, anticholinergic crisis attributed to recreational drug use, and pregnancy.[67] The number who left due to adverse events in the placebo group was not reported. Two serious adverse events were reported (one due to an ingestion of Jimson weed for recreational purposes and the other an attempted suicide with an intentional overdose of bupropion along with other drugs and alcohol) but neither were attributed to the study medication.[67] In a separate publication of this trial, body mass index (BMI) changes associated with bupropion treatment were examined to see if quitting smoking with this medication led to weight increases sometimes associated with quitting smoking. There was no increase in BMI, either among those who achieved smoking abstinence or those who did not.[80] Although participants randomized to 300 mg of bupropion experienced a decrease of 0.16 BMI *z*-score at 6 weeks compared with placebo ($p=0.01$), this effect was not maintained at 26 weeks (BMI *z*-score increase 0.05, $p=0.50$).

In the second trial of bupropion, where all participants also received NRT by patch, the total number of participants who experienced an adverse event, serious adverse event, or left the study due to an adverse event was not reported.[65] None of the adverse events that were reported (e.g., nausea, rash, weakness) were judged to be serious and there were no significant elevations in blood pressure.

In the third trial of bupropion, adverse events were reported after only 12 weeks, so this trial did not meet inclusion criteria for efficacy but is included here for harms.[54] In this study 76 of the 134 participants (57%) experienced at least one adverse event, with no significant differences between intervention and control groups. Headaches and dream disturbances were common with bupropion, with all of the nine instances of dream disturbances being associated with bupropion. Three participants (4.1%) in the bupropion groups (with and without contingency management) and three participants (4.9%) in the placebo groups (with and without contingency management) withdrew from the study due to adverse events.

Contextual Question 1. What Is the Relationship Between Use of E-Cigarettes and Use of Other Tobacco Products?

As mentioned in the introduction, the most commonly cited reasons for use of e-cigarettes among youth (and young adults) were curiosity, flavoring, and low perceived harm relative to regular tobacco products.[23] A 2018 report on Public Health Consequences of E-cigarettes, by the National Academies of Science, Engineering, and Medicine (NASEM) contained a section on smoking among youth and young adults (up to 29 years), focused on whether there were differences in patterns of cigarette use between those who were e-cigarette users versus those who were not.[10] The report included one systematic review of nine studies (n=16,621) evaluated the association of having ever used e-cigarettes among those who had never smoked a cigarette

at baseline with those who had ever smoked a cigarette at followup.[81] Pooled analysis of the seven studies examining smoking initiation demonstrated increased initiation of cigarette smoking associated with e-cigarette use (23.2% for those who had ever used an e-cigarette vs. 7.2% for those who had never used an e-cigarette, AOR 3.5; 95% CI, 2.38 to 5.16). Findings were similar among adolescents and young adults in a study of 2,588 18 to 25 year olds published since the systematic review.[82] The use of e-cigarettes was associated with increased initiation of cigarette smoking compared with never having used e-cigarettes (AOR 1.36, 95% CI, 1.01 to 1.83). Past 30-day use of e-cigarettes was also associated with increased past 30-day use of cigarettes based on a pooled analysis of two studies (n=2,084, AOR 4.28, 95% CI, 2.52 to 7.27). Four additional studies (n=5,976), not included in the systematic review's meta-analysis,[81] examined cigarette initiation at 4 months to 1 year followup.[83-86] All studies found a significantly increased risk in initiation of cigarette smoking in adolescents who had used e-cigarettes, consistent with the systematic review.[83-86] One study found that having ever smoked a cigarette was associated with an increased risk of initiation of e-cigarettes (OR 3.69, 95% CI, 1.88 to 7.23).[85]

There is also evidence that the frequency of e-cigarette use is associated with the frequency of cigarette smoking based on findings from one study (n=1,070).[87] The AOR for one or two instances of e-cigarette use was 2.88 (95% CI, 1.96 to 4.22) compared with AOR 4.17 (95% CI, 2.03 to 8.57) for monthly or yearly use. Another study (n=3,084) published after the systematic review[81] examined the frequency and intensity of e-cigarette use in the past 30 days and its association with the frequency and intensity of combustible tobacco products during the same time period in adolescents and young adults.[88] The odds of smoking frequency and intensity were both increased with increased vaping levels (OR 1.37, 95% CI, 1.16 to 1.61; OR 1.26, 95% CI, 1.07 to 1.48), suggesting a dose response relationship. Another study also found a similar positive association between initial e-cigarette use frequency and smoking use frequency and intensity at 12 months followup.[89] The findings with regard to frequency were not significant but the analysis of intensity found a 13 percent increase in total cigarettes smoked for each category increase in initial e-cigarette use (e.g., going from 1 to 3 uses in 6 months to monthly use), (incidence rate ratio [IRR] 1.13%, 95% CI, 1.06 to 1.11). An additional study found an increase in initiation of conventional smoking among adolescents who escalated their e-cigarette use compared with those who maintained their e-cigarette use, over 4 to 6 months (AOR 7.89, 95% CI, 3.06 to 20.38).[85] The same study also found the risk of initiation of e-cigarettes was increased among adolescents who smoked conventional cigarettes and who escalated their smoking compared with those who maintained their smoking usage, over 4 to 6 months (AOR 5.79, 95% CI, 2.55 to 13.15).

Overall, these additional studies suggest that not only is the use of e-cigarettes in adolescents and young adults associated with increased risk for using combustible tobacco, the degree of e-cigarette use is likely also associated with increased frequency of smoking and number of cigarettes smoked. These risks are in addition to the youth-specific harms of e-cigarette use, namely nicotine addiction and harm to the developing brain.
One study also suggests that the risk of initiating e-cigarette use is increased among conventional cigarette smoking adolescents. It should be noted that, although studies of e-cigarette use in adolescents for smoking cessation were excluded from this review, the searches would have captured these studies, but none were identified.

Chapter 4. Discussion

Summary of Review Findings

This report updates a 2012 USPSTF review on primary care relevant interventions for tobacco use prevention and cessation in children and adolescents.[2,3] New to this update is the inclusion of e-cigarettes as a tobacco product and an expansion of the age for prevention trials to participants up to the age of 25. **Table 11** summarizes the evidence reviewed for this update. Most of the trial interventions in this review were of (or included, in the case of pharmaceutical trials) a behavioral intervention that often consisted of information to increase communication and positive parenting in trials that targeted parents and/or focused on educating the adolescent and assessing his or her readiness to act/change while providing strategies and processes to facilitate action or behavior change in trials that targeted the youth. While the prior review found no trials that reported health outcomes or intervention effects on subsequent adult smoking (Key Question 1), we identified one study for each. A trial conducted in the United Kingdom examined health outcomes in pregnant teenagers who received an average of 39 nurse home visits and were followed for up to 2 years postpartum. There were no differences between nurse visits and usual care on self-reported psychological distress, depression, and problems with alcohol or drug use. However, the details of the intervention were not described and extensive resources were available to those who received usual care, which may have diluted any effect of the nurse visits. A second trial of brief counseling by dentists on the effects of smoking on oral health found no difference in smoking prevalence after long-term followup (when participants were approximately 29 years old).

Pooled analysis of 13 prevention trials of behavioral interventions (Key Question 2) demonstrated significantly less smoking initiation among adolescents in the intervention groups than control groups (RR 7.3% vs. 9.2%, RR 0.82, 95% CI, 0.73 to 0.92, I^2=15%). As in the prior review, proportions of participants who continued to smoke after the behavioral cessation interventions was similar between intervention and control groups in nine trials (80.7% continued smoking with the intervention vs. 84.1% in control groups, RR 0.97, 95% CI, 0.93 to 1.01, I^2=29%). One new trial of NRT, in addition to two previous trials of bupropion, also found no differences with pharmacotherapy compared with placebo pills or patches. NRT was found to increase abstinence among highly compliant adolescents at the end of treatment, but the effect was lost after 6 months. One trial also found treatment with bupropion 300 mg successful during short-term followup, but not by the 26-week followup. In the other bupropion trial, all participants also received NRT and self-reported smoking cessation rates were fairly high in both arms of the study at 26 weeks (24% in the bupropion arm and 28% in the placebo arm). In a pooled analysis of the nine behavioral intervention trials that combined smokers and nonsmokers, fewer participants smoked after the intervention but the result was not statistically significant (20.3% vs. 23.5%, RR 0.93, 95% CI, 0.86 to 1.01, I^2=24%). However, two trials included very intense interventions that were unlike other interventions and less likely to be referable from primary care due to availability. Sensitivity analysis removing these two trials did find a statistically significant treatment effect (16.8% vs. 20.1%, RR 0.91, 95% CI, 0.83 to 0.995, I^2=19%) indicating less smoking at followup in adolescents who received more primary care applicable behavioral intervention compared with controls. Due to the heterogeneity of trial

study design and differences between trials in populations enrolled, it is likely this finding is multifactorial and not necessarily only a function of the intervention's intensity.

There were no harms reported in trials of behavioral interventions (Key Question 3). Bupropion carries a boxed warning for increased risk of suicidality in children, adolescents, and young adults, with other concerns for increased risk for seizure, hypertension, mania, visual problems, and unusual thoughts and behaviors.[90] Trials of bupropion in children and adolescents for attention-deficit/hyperactivity disorder and/or depression are few and small; and few studies report significant adverse events with bupropion. In the bupropion and NRT trials, there were no serious adverse events reported that were related to the study medication, although a few non-serious adverse events were more common with pharmacotherapy compared with controls (e.g., headache, cough) in some trials.

Exploratory meta-regressions of study level characteristics were conducted and results consistently demonstrated no ability of any variable or group of variables to predict the magnitude of the intervention effect for prevention, cessation, or combined trials. This is likely due to the small numbers of trials included in the meta-regressions and the extensive heterogeneity in multiple study design variables (e.g., target of the intervention, methods of intervention delivery, duration of the intervention, location of the intervention) and the populations enrolled (e.g., both sexes, all female, mostly white, mostly black, all Hispanic, younger adolescents, older adolescents) in the included prevention, cessation, and combined trials. The only exceptions were the unexpected findings that in prevention studies trials that used a single mode of delivering the intervention or fewer number of contacts as part of the intervention (in-person visits, telephone calls, mailings to the adolescent's home) were more likely to report less smoking initiation than trials that employed multiple methods or had more participant contacts. However, the significance of these findings is unclear.

Contextual Issues

Child, adolescent, and young adult use of e-cigarettes is not safe.[23] Concerns regarding e-cigarette use by youth include nicotine addiction, harm to the developing brain, progression to combustible tobacco use, nicotine toxicity, inhalation of toxins or carcinogens, and explosions and fires caused by the e-cigarette device. Although we identified no trials in children and adolescents that examine the prevention or cessation of e-cigarette use, there is strong evidence linking e-cigarette use in nonsmoking adolescents and young adults to subsequent cigarette smoking. According to a 2018 report by the NASEM ever having used e-cigarettes is associated with a statistically significant increased risk of ever using combustible tobacco products.[10] Additionally, increased degree of e-cigarette use is associated with increased frequency and intensity of smoking cigarettes.

Limitations

Although our searches were not limited to cigarette smoking, most studies were published more than 10 years ago and only examined cigarette smoking with few enquiries regarding other forms

of tobacco products. Many of the studies reviewed were rated fair-quality due to risks of bias associated with unclear randomization and allocation concealment, lack of blinding, and high attrition; we did not include trials that were rated poor-quality. Additionally, the behavioral interventions included were quite heterogeneous and not always well described. We conducted exploratory meta-regression and stratified analyses to help understand study design characteristics related to decreased smoking but could not explain why some trials demonstrated significant effects of the behavioral interventions and others did not. However, meta-regression was limited by the few number of studies and there were numerous statistical tests conducted, which increases the risk for a Type I error. The small number of trials also limited our ability to conduct statistical and graphical tests for publication bias, but most published trials did not demonstrate a significant intervention effect. There were also inconsistent definitions of baseline smoking status, initiation, and abstinence. When possible we pooled self-reported smoking rather than chemically verified smoking, which may be unreliable in children who smoke irregularly. In the three studies that included both self-reported smoking abstinence and biochemically-verified smoking abstinence, biochemically-verified abstinence was lower than self-report (e.g., 15.3% self-report vs. 5.3% verified) but did not change study conclusions or meta-analysis results in the one trial included in the meta-analysis. Only one trial each assessed health outcomes and adult smoking. There were few trials that assessed pharmacotherapy for smoking cessation and they were small. There were no cessation trials of e-cigarette use identified; there were also no prevention trials in young adults found, even though we conducted a separate search to identify trials in this population. Other limitations include the lack of reporting on adherence in most trials, both in the delivery of the intervention and in the participation of the adolescent, or low adherence (in delivery and/or participation) reported in a few trials that may cause an intervention to appear less effective than it otherwise might be. Most cessation studies also did not report results by baseline motivation to quit tobacco or by baseline degree of nicotine addiction so it is not clear whether an intervention's relative success is dependent on the degree of motivation to stop smoking or the degree of addiction to nicotine. Additional limitations are that we excluded results found only in abstracts due to insufficient information to rate study quality and we also excluded trials published in languages other than English.

Emerging Issues/Next Steps

As the technology of e-cigarette use evolves (e.g., smaller vape clouds, devices that look like thumb drives), it becomes easier for youth to use e-cigarettes without detection by parents, school officials, or primary care physicians, increasing the likelihood of potential harms with e-cigarette use. There is one trial (NCT03634839),[91] with an estimated completion date August 2021, that is studying the effect of different flavorings and different nicotine concentrations on 60 youth (aged 16 to 20 years) and has a primary outcome of change score in liking/wanting e-cigarettes. One cluster trial (NCT04054765) is recruiting 12 to 15 year olds for a virtual reality video game intervention on the prevention of e-cigarette use (December 2020 estimated completion date). One trial in young adults aged 18 years to 24 years that is currently recruiting will compare the effect of a text messaging intervention on e-cigarette cessation (NCT04251273). This trial is sponsored by the Truth Initiative[92] and has an estimated completion date of January 2021. Additionally, the Adolescent Brain Development Study is a longitudinal study of brain development and child health in the United States. The behavioral

and biological development of almost 12,000 9 to 10 year-olds at 21 research sites will be tracked into young adulthood. Substance use, including tobacco products, is being tracked as a part of this study and may provide additional insight into the effects of nicotine exposure on the developing adolescent brain.

Other emerging issues concern the use of pharmacotherapy for smoking cessation in this age group. The FDA has not approved any smoking cessation drug (e.g., bupropion, NRT, varenicline) for use in children and there are few published trials of these drugs. In addition, in 2019 the FDA noted that it is changing the label for varenicline to specifically note that it is not recommended for persons 16 years and younger, as it has not been proven effective.[93] Two recently completed studies of NRT (NCT01359709,[94] NCT01145001[95]) and one additional trial of varenicline (NCT01312909[96]) in adolescents were identified, that have not yet been published. These studies should shed additional light on the efficacy and safety of these medications in the pediatric population.

One varenicline randomized trial (n=157) included adolescents and young adults 14 to 21 years of age, but was excluded because the mean age was 19.1 years and results were not reported separately for those less than 18 years of age.[97] It found no difference between varenicline versus placebo in self-reported 7-day smoking abstinence at the end of 12-weeks of treatment (n=90, 31% vs. 27%). At 6-month followup, the difference between varenicline and placebo on 7-day abstinence had widened (n=83, 36% vs. 17%). Attrition was high (47%); in addition, it is unclear why varenicline would show a delayed effect. Results of this trial were similar to an unpublished varenicline trial in adolescents (NCT01312909[96]). There was no difference between varenicline and placebo on 4-week continuous abstinence rate (week 9 through week 12) but in participants who received low-dose varenicline (0.5 mg), continuous abstinence rates from weeks nine through weeks 24 and 52 weeks were improved with varenicline. Attrition in this trial was 40%.

Another emerging issue is the relationship between e-cigarette use and marijuana use. Prevalence of self-reported marijuana use has been increasing in adolescents and young adults. In 2018, 42.7 percent of youth who had ever used an e-cigarette, 53.5 percent of youth who were current e-cigarette users, and 71.6 percent of youth who used multiple tobacco products reported ever using marijuana in e-cigarettes, with the largest increase observed in youth who were current users of tobacco products (33.2% to 40.6% from 2017 to 2018).[98]

Relevance for Priority Populations

Children and adolescents are a vulnerable population with developing bodies, developing brains, and developing personalities. Most smokers initiate smoking in adolescence. Methods to reduce exposure to nicotine and known and unknown toxins and carcinogens found in cigarettes, cigars, e-cigarettes, and other tobacco products have tremendous consequences for short-term (e.g., nicotine addiction, harm to the developing brain, nicotine toxicity, burns from vaping device explosions) and long-term (e.g., lung cancer, mouth and throat cancer, myocardial infarction, stroke, chronic obstructive pulmonary disease) mental and physical health. Access to primary care relevant behavioral intervention may decrease the likelihood that a child will pursue cigarette smoking or use of other tobacco products, thereby extending the child's life and health.

Applicability

Most studies were conducted in the United States and the remainder were conducted in Western Europe and are highly applicable to U.S. settings. We required trials to be conducted in primary care settings or to be referable from primary care.. Because trials enrolled mostly white adolescents, it is unclear if there are differences based on race or ethnic background in the effects of various interventions. Additionally, since most studies did not report the proportion of youth smoking by baseline characteristics, it is not known, for example, if behavioral interventions are more successful among youth highly motivated to quit versus those less motivated.

Future Research

There is no trial evidence on the prevention or cessation of e-cigarette use, of cigar use, or of other forms of tobacco use in children and adolescents with the exception of cigarette use. Such trials, particularly trials of e-cigarette use, are desperately needed, given the high and rapidly increasing prevalence of e-cigarette use among middle and high school aged youth. Additional well-conducted randomized trials are also needed to ascertain the best methods to encourage and achieve smoking cessation. Trials of most behavioral interventions for smoking cessation favor the intervention with a pooled estimate that is very close to statistical significance. Larger trials, especially trials conducted in youth wanting to quit tobacco products, may show a clear indication for the benefit of behavioral interventions. Additionally, trials should examine health outcomes such as respiratory and cardiovascular disease and should follow adolescents into adulthood to determine the interventions effects on long-term outcomes. None of the medication trials were very large ($n \leq 312$) and no published trial of varenicline met inclusion criteria.

Conclusions

Behavioral interventions can reduce the likelihood of smoking initiation in nonsmoking youth and young adults. Research is needed to identify effective behavioral interventions for youth who smoke or who use other tobacco products and to understand the effectiveness of pharmacotherapy for cessation of tobacco use. Due to the rapid escalation of e-cigarette use among youth, both prevention and cessation trials that target and/or include e-cigarette use are imminently needed.

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Figure 1. Analytic Framework

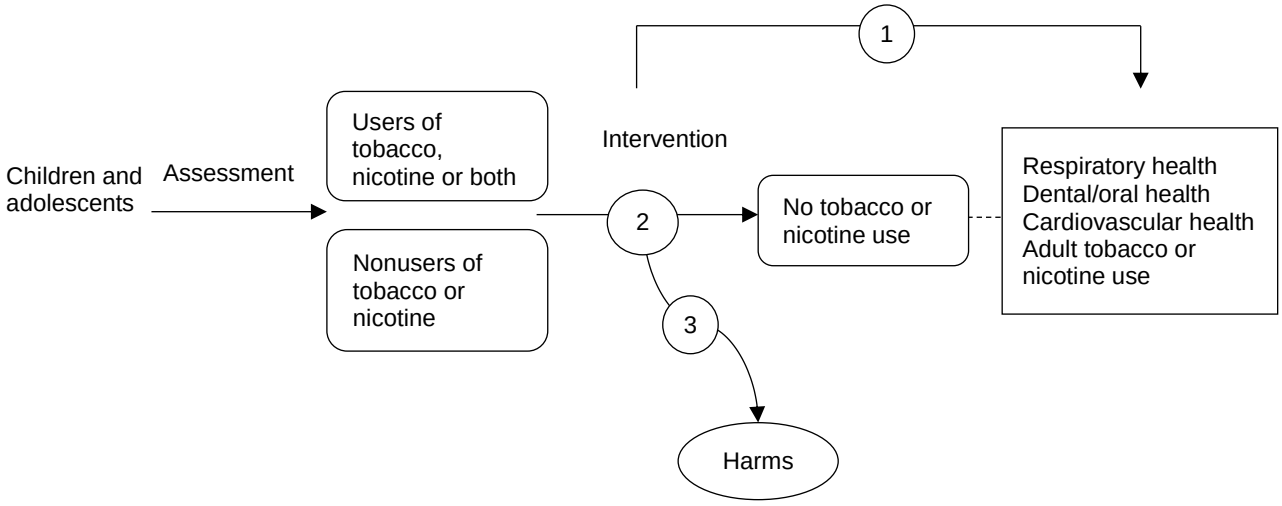
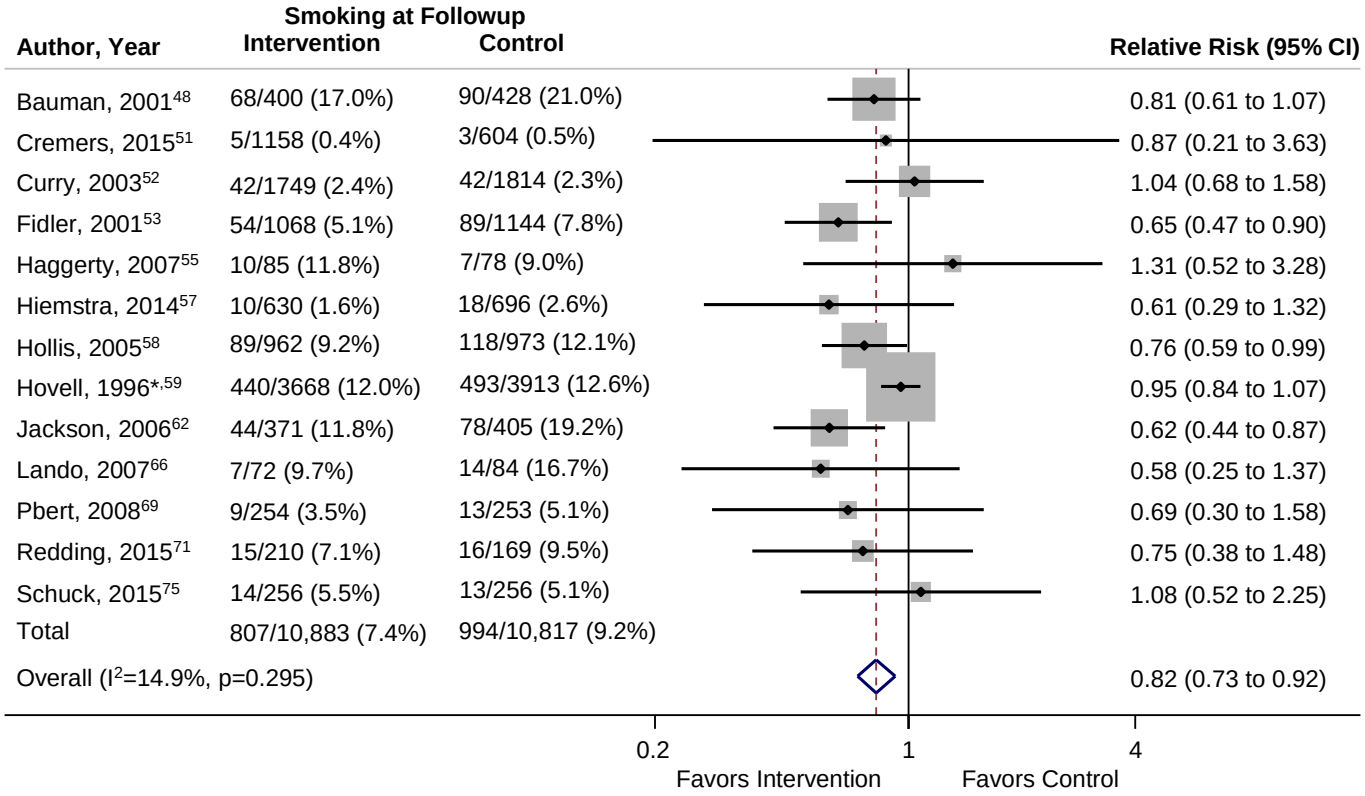


Figure 2. Meta-Analysis of Smoking Prevention Interventions to Reduce Smoking Initiation

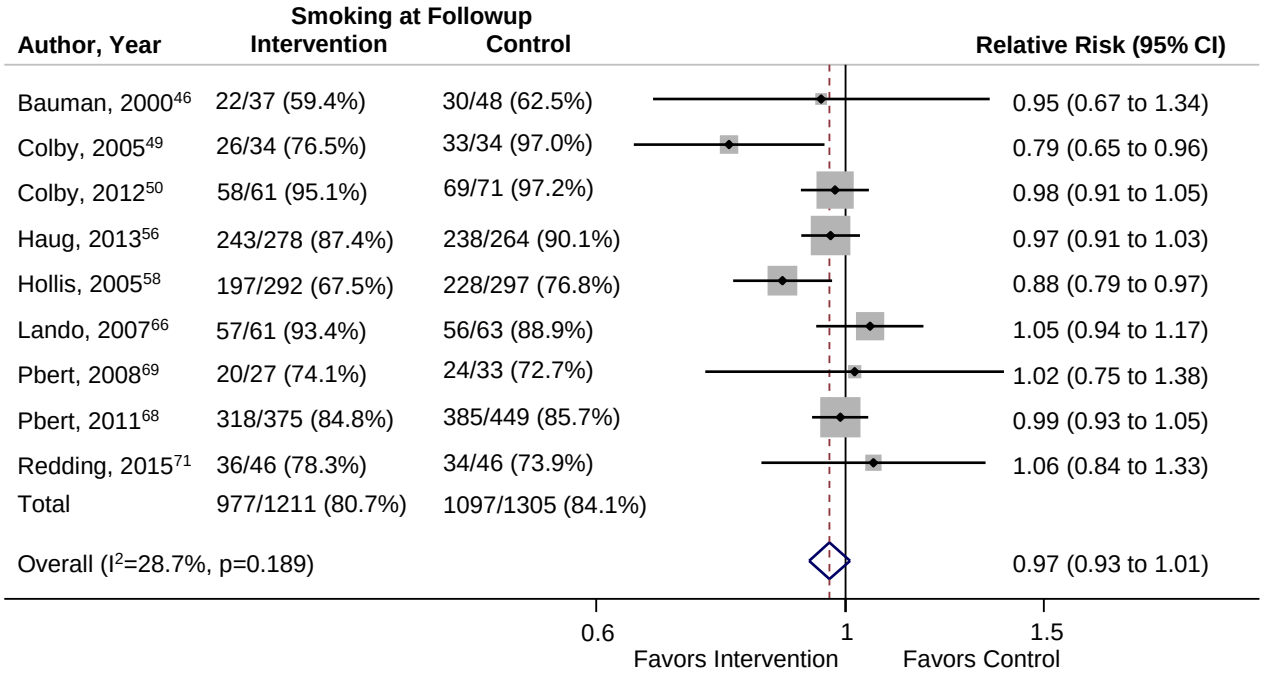


NOTE: Weights are from random effects analysis

*This study reports on any tobacco use at followup, not just smoking.

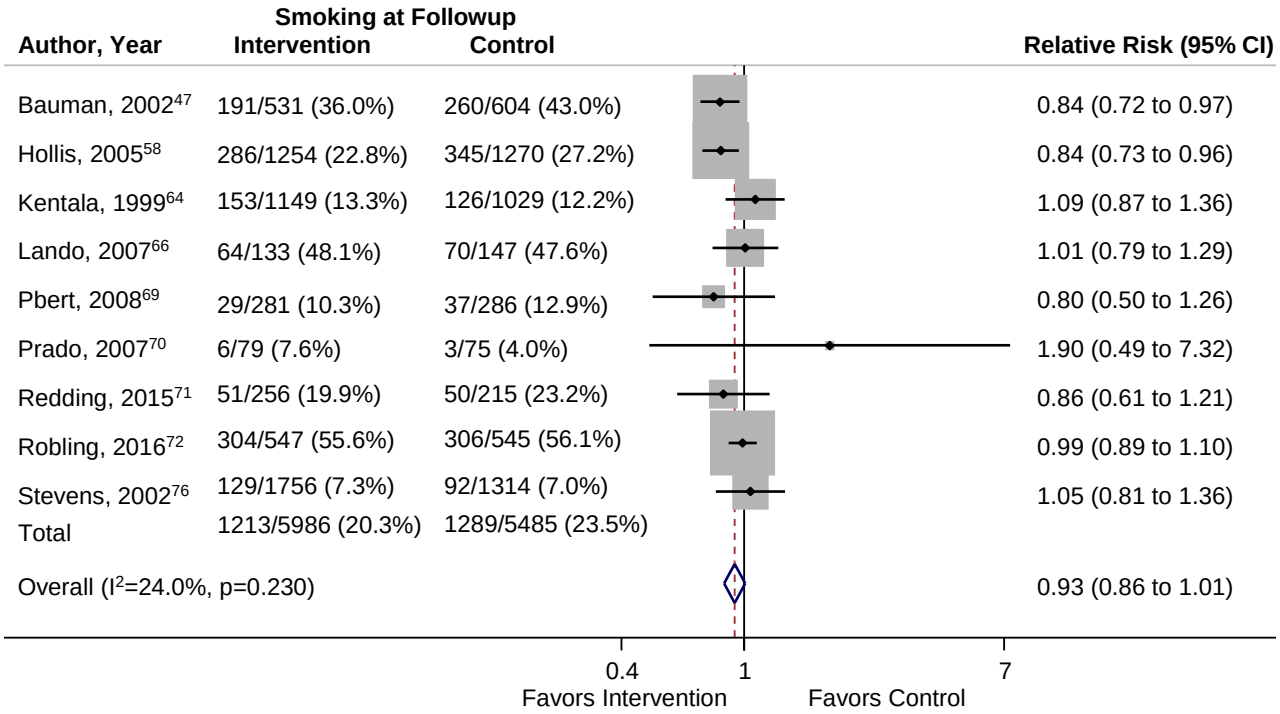
Abbreviations: CI=confidence interval.

Figure 3. Meta-Analysis of Smoking Cessation Behavioral Interventions Effect on Quitting



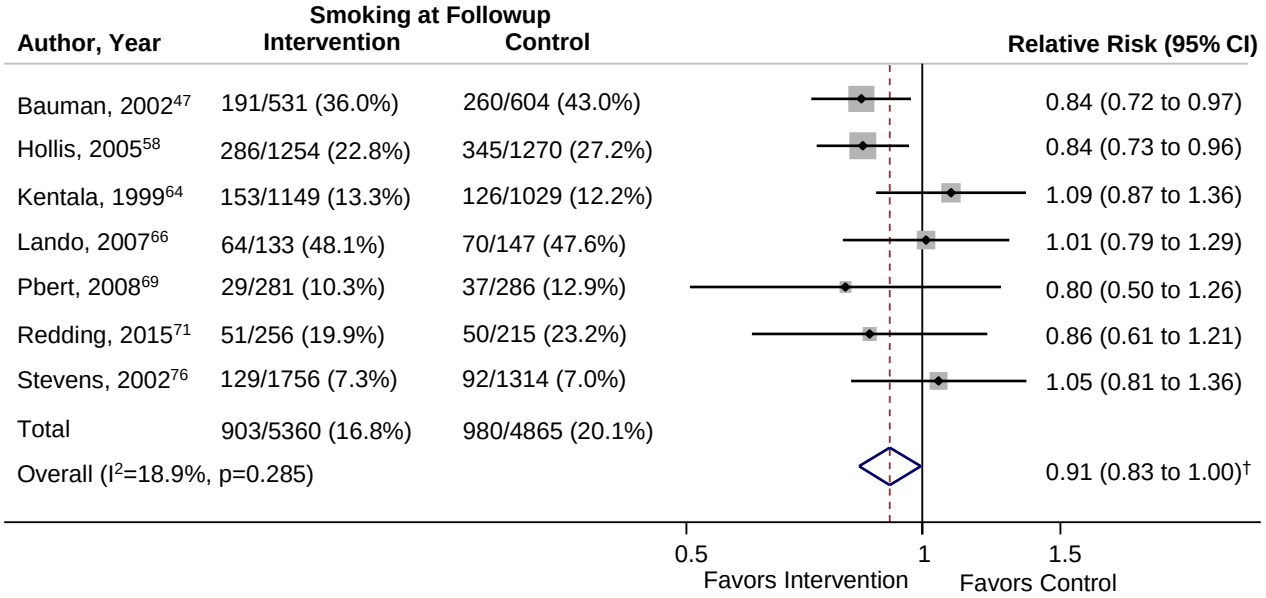
NOTE: Weights are from random effects analysis
Abbreviations: CI=confidence interval.

Figure 4. Meta-Analysis of Combined Interventions Effect on Tobacco Use



NOTE: Weights are from random effects analysis
Abbreviations: CI=confidence interval.

Figure 5. Sensitivity Analysis of Combined Interventions Effect on Tobacco Use*



NOTE: Weights are from random effects analysis

*Removed 2 trials of intensive interventions[68,70]
†Effect significance: p=0.04
Abbreviations: CI=confidence interval.

Table 1. Percentage of Middle and High School Students Who Currently Use* Tobacco, by Product and School Level—National Youth Tobacco Survey, United States, 2019

School level	Any tobacco† % (95% CI)	E-cigarettes % (95% CI)	Cigarettes % (95% CI)	Cigars % (95% CI)	Smokeless tobacco % (95% CI)	Hookah % (95% CI)	Pipe tobacco % (95% CI)	≥2 Tobacco products % (95% CI)
Middle school	12.5 (11.2 to 13.9)	10.5 (9.4 to 11.8)	2.3 (1.8 to 2.9)	2.3 (1.9 to 2.9)	1.8 (1.4 to 2.2)	1.6 (1.2 to 2.1)	---	4.0 (3.3- to 4.7)
High school	31.2 (29.1 to 33.5)	27.5 (25.3 to 29.7)	5.8 (4.6 to 7.3)	7.6 (6.6 to 8.8)	4.8 (3.7 to 6.3)	3.4 (2.7 to 4.2)	1.1 (0.8 to 1.5)	10.8 (9.4 to 12.4)

* Current use = use on ≥1 day in the past 30 days. Past 30-day use of e-cigarettes was determined by asking, "During the past 30 days, on how many days did you use e-cigarettes?" Past 30-day use of cigarettes was determined by asking, "During the past 30 days, on how many days did you smoke cigarettes?" Past 30-day use of cigars was determined by asking, "During the past 30 days, on how many days did you smoke cigars, cigarillos, or little cigars?" Past 30-day use of hookah was determined by asking, "During the past 30 days, on how many days did you smoke tobacco in a hookah or waterpipe?" Smokeless tobacco was defined as use of chewing tobacco, snuff, dip, snus, and/or dissolvable tobacco products. Past 30-day use of smokeless tobacco was determined by asking the following question for use of chewing tobacco, snuff, and dip: "During the past 30-days, on how many days did you use chewing tobacco, snuff, or dip?," and the following question for use of snus and dissolvable tobacco products: "In the past 30 days, which of the following products did you use on at least one day?" Responses from these questions were combined to derive overall smokeless tobacco use. Past 30-day use of pipe tobacco (not hookah) and bidis were determined by asking, "In the past 30 days, which of the following products have you used on at least one day?""

†Any tobacco use = use of any tobacco product (e-cigarettes, cigarettes, cigars, smokeless tobacco, hookah, pipe tobacco, and/or bidis) on ≥1 day in the past 30 days.

Abbreviations: CI=confidence interval.

Table 2. Common Tobacco Use Measures

Tobacco use term	Common measures and definitions
Susceptible	Defined as the absence of a firm resolve to not smoke in the future. Operationally determined with 3 questions: 1) Do you think you will try a cigarette soon [yes/no]? 2) If one of your best friends were to offer you a cigarette, would you smoke it [definitely yes/probably yes/probably not/definitely not]? 3) Do you think you will be smoking 1 year from now [definitely yes/probably yes/probably not/definitely not]? Youths are susceptible if they answer "yes" to the first question or if they fail to answer "definitely not" to the second or third question, or if they had smoked a cigarette in the past 30 days.
Experimentation	Often measured as ever smoking, even 1 or 2 puffs, or inferred from age at first smoking or youth's self-description of being an experimenter.
Lifetime ("ever") use	Ever smoked, even 1 or 2 puffs.
Former use	Ever smoked, but not in the past 30 days (some studies also use ever smoked, but not in the past year).
Current use	Any tobacco/cigarette use (even a puff) during the previous 30 days or ≥1 days in the past 30 days; this is also referred to as "monthly smoking" in some studies. Some studies consider current use to be in the past 7 or 90 days.
Daily smoking	Average of ≥1 cigarettes per day during the previous 30-day period.
Frequent smoking	≥20 cigarettes in the past 30 days.
Point prevalence abstinence	Not smoking at the point of followup; often measured as the past 7 or 30 days.
Continuous abstinence	No smoking through the followup period, also referred to as "sustained" abstinence.

Table 3. Included Studies by Intervention Type

Trial	Prevent initiation	Behavioral cessation	Pharmacotherapy cessation	Combined prevalence
Ausems, 2002[45]	X			
Bauman, 2000[46] Bauman, 2001[48] Bauman, 2002[47]	X	X		X
Colby, 2005[49]		X		
Colby, 2012[50]		X		
Cremers, 2015[51]	X			
Curry, 2003[52]	X			
Fidler, 2001[53]	X			
Gray, 2011[54]			X (Bupropion)	
Haggerty, 2007[55]	X			
Haug, 2013[56]		X		
Hiemstra, 2014[57]	X			
Hollis, 2005[58]	X	X		X
Hovell, 1996[59]	X			
Jackson, 2006[62]	X			
Kentala, 1999[64] Saari, 2012[73]				X
Killen, 2004[65]			X (Bupropion)	
Lando, 2007[66]	X	X		X
Muramoto, 2007[67]			X (Bupropion)	
Pbert, 2008[69]	X	X		X
Pbert, 2011[68]		X		
Prado, 2007[70]				X
Redding, 2015[71]	X	X		X
Robling, 2016[72]				X
Scherphof, 2014[74]			X (NRT)	
Schuck, 2015[75]	X			
Stevens, 2002[76]				X
Total Number of Studies (New)	**14 (4)**	**9 (2)**	**4 (1)**	**9 (2)**

Abbreviations: NRT=nicotine replacement therapy

Table 4. Characteristics of Behavioral Intervention Prevention Trials

Trial; quality; location; setting; N*	Target of intervention	Components included in intervention	Interventionist; mode of Intervention; role of PC	Duration of intervention (hours of contact);† followup	Control group	Mean age (range), years; female; nonwhite
Ausems 2002‡,45 Fair The Netherlands, home IG: 871; CG: 793	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: NA Mode of intervention: Print Role of PC: None	Duration: 9 weeks (0) Months to followup: 6 Followup: 91.5%	Not described	Age: 11.7 (NR) Female: 50.6% Nonwhite: NR
Bauman, 2001§,48 Fair U.S., home IG: 658; CG: 658	Person: Parent Based on smoking status: No	Multiple behaviors: Yes Group sessions: No MI: No	Interventionist: Health educators Mode of intervention: Phone, print Role of PC: None	Duration: 15 weeks (0.96) Months to followup: 7,‖ 16 Followup: 81.2%	Not described	Age: 13.9 (12–14) Female: 50.7% Nonwhite: 26.6%
Cremers, 2015[51] Fair The Netherlands, school and home IG1: 1207; IG2: 1003;¶ CG: 1003	Person: Youth Based on smoking status: No	Multiple behaviors: No Group sessions: No MI: No	Interventionist: Self-directed Mode of intervention: Computer Role of PC: None	Duration: 25 months (0) Months to followup: 12,‖ 25 Followup: 66.8%	Usual care	Age: 10.4 (10-11) Female: 50.6% Nonwhite: 11.7%
Curry, 2003[52] Fair U.S., home (optional primary care) IG: 2020; CG: 2006	Person: Both Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: Study-trained telephone counselor, PC Mode of intervention: Print, phone Role of PC: Recruitment only, optional PC	Duration: 6 weeks + 1 booster call within 14 months (NR) Months to followup: 20 Followup: 88.5%	Usual care	Age: 11. 0 (10–12) Female: 52.0% Nonwhite: NR
Fidler, 2001[53] Fair U.K., home IG: 1456; CG: 1486	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: NA Mode of intervention: Print Role of PC: Recruitment only	Duration: 12 months (0) Months to followup: 12 Followup: 75.3%	No interaction	Age: NR (10–15) Female: 55.3% Nonwhite: NR
Haggerty, 2007[55] Fair U.S., home (IG1) or after school (IG2)** IG1: 107; IG2: 118; CG: 83	Person: Both Based on smoking status: Yes	Multiple behaviors: Yes Group sessions: Yes MI: No	Interventionist: Study-trained workshop leaders Mode of intervention: Face Role of PC: None	Duration: 7 weeks (15.5) Months to followup: 12,‖ 24 Followup: 92.5%	Low intensity	Age: 13. 7 (NR) Female: 48.6% Nonwhite: 50.8%
Hiemstra, 2014[57] Fair The Netherlands, home IG: 728; CG: 750	Person: Both Based on smoking status: No	Multiple behaviors: No Group sessions: No MI: No	Interventionist: NA Mode of intervention: Print Role of PC: Recruitment only	Duration: 20 weeks + 1 booster module at 12 months (0) Months to followup: 6, 12,‖ 24, 36 Followup: 92.6%	Not described	Age: 10.1 (9-11) Female: 52.6% Nonwhite: 1.7%

Table 4. Characteristics of Behavioral Intervention Prevention Trials

Trial; quality; location; setting; N*	Target of intervention	Components included in intervention	Interventionist; mode of Intervention; role of PC	Duration of intervention (hours of contact);† followup	Control group	Mean age (range), years; female; nonwhite
Hollis, 2005[§,58] Good U.S., medical office IG: 1254; CG: 1272	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: PCP, health counselor,* self-directed Mode of intervention: Face, computer, print, phone Role of PC: Conducted in PC, provider delivered part	Duration: 1 visit + 2 booster sessions within 12 months (0.25) Months to followup: 12,‖ 24 Followup: 93.7%	Attention control	Age: 15.4 (14–17) Female: 59.2% Nonwhite: 21.8%
Hovell, 1996[59] Good U.S., orthodontic office IG: 7149; CG: 7626	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: Orthodontic staff Mode of intervention: Face, print Role of PC: Conducted in dental, provider delivered most	Duration: 2 years (NR) Months to followup: 24 Followup: 92.5%	Usual care	Age: 14.4 (11–19) Female: 54.0% Nonwhite: 27.0%
Jackson, 2006[62] Fair U.S., home IG: 426; CG: 447	Person: Both Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: NA Mode of intervention: Print Role of PC: None	Duration: 10 weeks + 1 booster guide within 12 months (NR) Months to followup: 36 Followup: 87.5%	Low intensity	Age: NR (7–8) Female: 52.6% Nonwhite: 23.7%
Lando, 2007[§,66] Fair U.S., dental clinic IG: 175; CG: 169	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: Dental staff Mode of intervention: Face, phone Role of PC: Conducted in dental, provider delivered part	Duration: 1 visit + 3 to 6 booster calls within 6 months (1.2) Months to followup: 12 Followup: 65.4%	Low intensity	Age: 15.4 (14–17) Female: 52.0% Nonwhite: 19.0%
Pbert, 2008[§,69] Fair U.S., pediatric clinic IG: 1346; CG: 1365	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: Peer counselors Mode of intervention: Face, phone Role of PC: Conducted in PC, provider delivered part	Duration: 1 visit + 4 booster calls over 21 weeks (1.1) Months to followup: 6, 12‖ Followup: 99.2%	Usual care	Age: 16.9 (13–17) Female: 54.1% Nonwhite: 8.6%
Redding, 2015[§,71] Fair U.S., medical office IG: 424; CG: 404	Person: Youth (female only) Based on smoking status: Yes	Multiple behaviors: Yes Group sessions: No MI: Yes	Interventionist: BA- or MA-level counselors, Self-directed Mode of intervention: Face, computer Role of PC: None	Duration: 9 months (NR, up to 4 counseling sessions) Months to followup: 12,‖ 18 Followup: 63.6%	Low intensity	Age: 16.4 (14-17) Female: 100% Nonwhite: 92.1%

Table 4. Characteristics of Behavioral Intervention Prevention Trials

Trial; quality; location; setting; N*	Target of intervention	Components included in intervention	Interventionist; mode of Intervention; role of PC	Duration of intervention (hours of contact);† followup	Control group	Mean age (range), years; female; nonwhite
Schuck, 2015[75] Fair The Netherlands, home IG: 256; CG: 256	Person: Parent Based on smoking status: Yes (parents), No (youth)	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: Dutch national quit line counselors Mode of intervention: Phone, print Role of PC: None	Duration: 3 months (NR, up to 7 telephone counseling sessions) Months to followup: 3, 12,‖ 30 Followup: 77.9%	Low intensity	Age: 10.5 (9-12) Female: 50.4% Nonwhite: NR

*Randomized.
†With interventionist
‡Study not included in meta-analysis.
§Study also included in combined prevention and cessation table and cessation only table (Tables 5 and 6).
‖Data from this followup point used.
¶Interventions were combined in the meta-analysis.
**Intervention group utilized in the meta-analysis.
Abbreviations: BA=bachelor degree; CG=control group; IG=intervention group; MA=master degree; MI=motivational interviewing; N=number; NA=not applicable; NR=not reported; PC=primary care; U.K.=United Kingdom; U.S.=United States.

Table 5. Characteristics of Cessation Trials

Trial; quality; location; setting; N*	Target of intervention	Components included in intervention	Interventionist; mode of intervention; role of PC	Duration of intervention (hours of contact);† followup	Control group	Mean age (range), years; female; nonwhite
Bauman, 2000‡,[46] Fair U.S., home IG: 658; CG: 658	Person: Parent Based on smoking status: No	Multiple behaviors: Yes Group sessions: No MI: No	Interventionist: Health educators Mode of intervention: Phone, print Role of PC: None	Duration: 15 weeks (0.96) Months to followup: 7,§ 16 Followup: 81.2%	Not described	Age: 13.9 (12–14) Female: 50.7% Nonwhite: 26.6%
Colby, 2005[49] Fair U.S., NR IG: 43; CG: 42	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: Study-trained interventionists Mode of intervention: Face, phone, print Role of PC: Recruitment only	Duration: 1 visit + 1 booster call within 1 week (0.875) Months to followup: 6 Followup: 80.0%	Low intensity	Age: 16. 3 (12–19) Female: 61.0% Nonwhite: 45.0%
Colby, 2012[50] Fair U.S., NR IG: 79; CG: 83	Person: Both Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: Study-trained interventionists Mode of intervention: Face, phone, print Role of PC: Recruitment only	Duration: 1 visit + 1 booster call within 1 week + 1 parent discussion (1.25) Months to followup: 6 Followup: 81.5%	Low intensity	Age: 16.2 (14-18) Female: 47.5% Nonwhite: 27.8%
Haug, 2013[56] Fair Switzerland, home IG: 372; CG: 383	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: NA Mode of intervention: Text messaging Role of PC: None	Duration: 3 months (0) Months to followup: 6 Followup: 74%	Assessment only	Age: 18.2 (NR) Female: 51.9% Nonwhite: NR
Hollis, 2005‡,[58] Good U.S., medical office IG: 1254; CG: 1272	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: PC, health counselor,* self-directed Mode of intervention: Face, computer, print, phone Role of PC: Provider delivered part	Duration: 1 visit + 2 booster sessions within 12 months (0.25) Months to followup: 12,§ 24 Followup: 93.7%	Attention control	Age: 15.4 (14–17) Female: 59.2% Nonwhite: 21.8%
Lando, 2007†,[66] Fair U.S., dental clinic IG: 175; CG: 169	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: Dental staff Mode of intervention: Face, phone Role of PC: Provider delivered part	Duration: 1 visit + 3 to 6 booster calls within 6 months (1.2) Months to followup: 12 Followup: 65.4%	Low intensity	Age: 15.4 (14–17) Female: 52.0% Nonwhite: 19.0%
Pbert, 2008†,[69] Fair U.S., pediatric clinic IG: 1346; CG: 1365	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: Peer counselors Mode of intervention: Face, phone Role of PC: Provider delivered part	Duration: 1 visit + 4 booster calls over 21 weeks (1.1) Months to followup: 6, 12§ Followup: 99.2%	Usual care	Age: 16.9 (13–17) Female: 54.1% Nonwhite: 8.6%

Table 5. Characteristics of Cessation Trials

Trial; quality; location; setting; N*	Target of intervention	Components included in intervention	Interventionist; mode of intervention; role of PC	Duration of intervention (hours of contact);† followup	Control group	Mean age (range), years; female; nonwhite
Pbert, 2011[68] Good U.S., school health clinic IG: 486; CG: 582	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: School nurse Mode of intervention: Face Role of PC: None	Duration: 4 weeks (1.5) Months to followup: 12 Followup: 88.4%	Low intensity	Age: 16.9 (NR) Female: 47.7% Nonwhite: 7.4%
Redding, 2015‡,[71] Fair U.S., medical office IG: 424; CG: 404	Person: Youth Based on smoking status: Yes	Multiple behaviors: Yes Group sessions: No MI: Yes	Interventionist: BA- or MA-level counselors, Self-directed Mode of intervention: Face, computer Role of PC: None	Duration: 9 months (NR, up to 4 counseling sessions) Months to followup: 12,§ 18 Followup: 63.6%	Low intensity	Age: 16.4 (14-17) Female: 100% Nonwhite: 92.1%
Killen, 2004‖,[65] Fair U.S., NR IG:103; CG: 108	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: Yes MI: No	Interventionist: Study-trained counselors Mode of intervention: Face Role of PC: None	Duration: 10 weeks (7.5) Months to followup: 6 Followup: 63.5%	Placebo	Age: 17.3 (15–18) Female: 31.3% Nonwhite: 49.8%
Muramoto, 2007‖,[67] Fair U.S., research clinic IG1: 105;¶ IG2: 104 CG: 103	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: NR Mode of intervention: Face Role of PC: None	Duration: 7 weeks (2.25) Months to followup: 6 Followup: 61.9%	Placebo	Age: 16.0 (14–17) Female: 45.8% Nonwhite: 26.0%
Scherphof, 2014‖,[74] Good The Netherlands, School IG: 135; CG: 122	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: NR Mode of intervention: Face Role of PC: None	Duration: 6 or 9 weeks depending on # cigarettes smoked per day (1.25) Months to followup: 6, 12§ Followup: 89.9%	Placebo	Age: 16.7 (NR) Female: 52.9%** Nonwhite: NR

*Randomized.
†With interventionist
‡Study also included on combined prevention and cessation table and prevention only table (Tables 4 and 6).
§Data from this followup point used.
‖Pharmacotherapy utilized in intervention group.
¶Intervention group utilized in the meta-analysis.
**Calculated based on presented data.
Abbreviations: BA=bachelor degree; CG=control group; IG=intervention group; MA=master degree; MI=motivational interviewing; N=number; NA=not applicable; NR=not reported; PC=primary care; U.K.=United Kingdom; U.S.=United States.

Table 6. Characteristics of Combined Prevention and Cessation Behavioral Intervention Trials

Trial; quality; location; setting; N*	Target of intervention	Components included in intervention	Interventionist; mode of intervention; role of PC	Duration of intervention (hours of contact);† followup	Control group	Mean age (range), years; female; nonwhite
Bauman, 2002‡,47 Fair U.S., home IG: 658; CG: 658	Person: Parent Based on smoking status: No	Multiple behaviors: Yes Group sessions: No MI: No	Interventionist: Health educators Mode of intervention: Phone, print Role of PC: None	Duration: 15 weeks (0.96) Months to followup: 7,§ 16 Followup: 81.2%	Not described	Age: 13.9 (12–14) Female: 50.7% Nonwhite: 26.6%
Hollis, 2005‡,58 Good U.S., medical office IG: 1254; CG: 1272	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: PC, health counselor,* self-directed Mode of intervention: Face, computer, print, phone Role of PC: Conducted in PC, provider delivered part	Duration: 1 visit + 2 booster sessions within 12 months (0.25) Months to followup: 12, § 24 Followup: 93.7%	Attention control	Age: 15.4 (14–17) Female: 59.2% Nonwhite: 21.8%
Kentala, 1999[64] Saari, 2012[73] Fair Finland, dental clinic IG: 1348; CG: 1238	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: No	Interventionist: Dental staff Mode of intervention: Face Role of PC: Conducted in dental, provider delivered most	Duration: 1-4 visits (0.17) Months to followup: 12, § 24 Followup: 84.2%	Usual care	Age: 13.1 (NR) Female: 49.0% Nonwhite: NR
Lando, 2007‡,66 Fair U.S., dental clinic IG: 175;CG: 169	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: Dental staff Mode of intervention: Face, phone Role of PC: Conducted in dental, provider delivered part	Duration: 1 visit + 3 to 6 booster calls within 6 months (1.2) Months to followup: 12 Followup: 65.4%	Low intensity	Age: 15.4 (14–17) Female: 52.0% Nonwhite: 19.0%
Pbert, 2008‡,69 Fair U.S., pediatric clinic IG: 1346; CG: 1365	Person: Youth Based on smoking status: Yes	Multiple behaviors: No Group sessions: No MI: Yes	Interventionist: Peer counselors Mode of intervention: Face, phone Role of PC: Conducted in PC, provider delivered part	Duration: 1 visit + 4 booster calls over 21 weeks (1.1) Months to followup: 6, 12§ Followup: 99.2%	Usual care	Age: 16.9 (13–17) Female: 54.1% Nonwhite: 8.6%
Prado, 2007[70] Fair U.S., home, community IG: 91; CG: 84	Person: Parent Based on smoking status: No	Multiple behaviors: Yes Group sessions: Yes MI: No	Interventionist: Study-trained facilitators Mode of intervention: Face Role of PC: None	Duration: 12 months (49) Months to followup: 12, § 24, 36 Followup: 88.0%	Attention control	Age: 13.4 (NR) Female: 53.7% Nonwhite: 100%
Redding, 2015‡,71 Fair U.S., medical office IG: 424; CG: 404	Person: Youth Based on smoking status: Yes	Multiple behaviors: Yes Group sessions: No MI: Yes	Interventionist: BA- or MA-level counselors, Self-directed Mode of intervention: Face, computer Role of PC: None	Duration: 9 months (NR, up to 4 counseling sessions) Months to followup: 12, § 18 Followup: 63.6%	Low intensity	Age: 16.4 (14-17) Female: 100% Nonwhite: 92.1%

Table 6. Characteristics of Combined Prevention and Cessation Behavioral Intervention Trials

Trial; quality; location; setting; N*	Target of intervention	Components included in intervention	Interventionist; mode of intervention; role of PC	Duration of intervention (hours of contact);† followup	Control group	Mean age (range), years; female; nonwhite
Robling, 2016[72] Fair U.K., home IG: 823; CG: 822	Person: Youth (pregnant) Based on smoking status: No	Multiple behaviors: Yes Group sessions: No MI: Yes	Interventionist: Family nurses Mode of intervention: Face Role of PC: Home visits by nurse	Duration: 24 months (mean nurse visits 39) Months to followup: 24 Followup: 66.4%	Usual care	Age: 17.9 (16.9-18.8) Female: 100% Nonwhite: 11.9%
Stevens, 2002‖,[76] Good U.S., pediatric office IG: 1780; CG: 1331	Person: Parent and youth Based on smoking status: No	Multiple behaviors: Yes Group sessions: No MI: No	Interventionist: PCP Mode of intervention: Face, phone, print Role of PC: Provider delivered part	Duration: 36 months (NR) Months to followup: 12, § 24, 36 Followup: 95.5%	Attention control	Age: 11. 0 (NR) Female: 48.3% Nonwhite: NR

*Randomized.
†With interventionist
‡Study also included on prevention only and cessation only tables (Tables 4 and 5).
§Data from this followup point used in meta-analysis.
‖Study not included in meta-analysis.
Abbreviations: BA=bachelor degree; CG = control group; IG = intervention group; MA=master degree; N = number; NR = not reported; PC=primary care; U.S. = United States.

Table 7. Behavioral Intervention Implementation Table

Mode of prevention intervention delivery	Print	Face-to-face	Telephone	Computer
Study Findings	k=8, n=18,733 RR 0.81 (95% CI, 0.70 to 0.94)	k=6, n=10,751 RR 0.91 (95% CI, 0.81 to 1.01)	k=6, n=7,501 RR 0.82 (95% CI, 0.69 to 0.96)	k=3, n=4,076 RR 0.76 (95% CI, 0.60 to 0.97)
Example Interventions*	Fidler, 2001;[51] Jackson, 2006;[60] Hovell,1996[57]	Hollis, 2005;[56] Pbert, 2008[67]	Pbert, 2008;[67] Hollis, 2005[56]	Redding, 2015;[69] Hollis, 2005[56]
Intensity of Delivery	Handouts may be reinforcement of information given or sole intervention; from newsletters and stickers to children to booklets and activity guides for parents	Face-to-face may be primary means of intervention delivery or one part of intervention; ranged from 1 visit to 8 visits	Telephone counseling was never used alone but always accompanied print material or face-to-face counseling; often took the form of 1 to 4 booster calls	Computer programs were interactive or web-based as in Fun Without Smokes; use of the computer ranged from 1 use to 6 uses
Materials provided for practice*	Prescriptions with preprinted anti-tobacco messages were given to the adolescents covering: tobacco-free office, tobacco advertising, tobacco and sports, smokeless tobacco, nicotine and tobacco addiction, passive smoking, tobacco and the adolescent's teeth, and negative consequences of tobacco use.[57]	Use of 5A model: Provider asked about smoking, advised continued abstinence and referred to peer counselor who continued the model (assess, assist, arrange followup) using motivational interviewing and behavior change counseling.[67]	Use of 5A model: Provider asked about smoking, advised continued abstinence and referred to peer counselor who continued the model (assess, assist, arrange followup) using motivational interviewing and behavior change counseling.[67]	Computer screenshots: Redding, 2015[69]
Primary Population	The age range for studies targeting youth only was 10 to 19 years: 10 to 19 years for print materials, 11 to 19 years for face-to-face and telephone counseling, and 10 to 17 years for computer assessment and counseling. The age range of the child in studies that targeted the parent only was 9 to 14 years for print materials and telephone counseling. There were no studies of face-to-face or computer counseling that targeted the parents only. The age range of the child in studies that targeted both the child and the parent was 7 to 12 years: 7 to 12 years for print materials, 10 to 12 years for telephone counseling; one study of face-to-face counseling did not report age range. The weighted mean ages of youth exposed to print materials was 12.9 years, to face-face-counseling was 14.8 years, to telephone counseling was 12.9 years, and to computer assessment/counseling was 13.3 years. The weight mean ages of studies targeting only the youth was 13.6 years, targeting only the parent was 12.6 years, and targeting both the youth and the parent was 10.9 years. Three studies did not report mean age of participants.			
Primary Outcome	Initiation of smoking in baseline nonsmokers			
Behavior change goals & techniques	Designed to prevent youth from smoking; there was no difference between trials that targeted smoking behavior only (10 trials, n=20,330, RR 0.80, 95% CI, 0.69 to 0.93) and trials that targeted other behaviors such as alcohol consumption (3 trials, n=1,370, RR 0.83, 95% CI, 0.65 to 1.07)			
Duration of Interventions	Duration ranged from very brief (1 week) to 25 months; there was no difference between trials that were shorter than 12 months (6 trials, n=2,545, RR 0.82, 95% CI, 0.66 to 1.02) and trials of longer interventions (7 trials, n=19,155, RR 0.79, 95% CI, 0.66 to 0.95)			
Settings of Studies	Trials occurred in primary (medical) care (2 trials, n=2,442), primary (dental) care (2 trials, n=7,738), family planning clinic (1 trials, n=379), and not in a medical setting (9 trials, n=14,490)			

Table 7. Behavioral Intervention Implementation Table

Target of Intervention	Interventions targeted the child, the parent or caregiver, or both; there were no differences based on whether the intervention targeted the child (7 trials, n=14,532, RR 0.82, 95% CI, 0.71 to 0.95), the parent (2 trials, n=1,340, RR 0.84, 95% CI, 0.64 to 1.09), or both (4 trials, Ns=5,828)
Evidence of effect modification	Single mode of intervention delivery (5 trials, n=6,239, RR 0.66, 95% CI, 0.53 to 0.82) vs. multiple modes (8 trials, n=15,461, RR 0.90, 95% CI, 0.82 to 0.99); ≤6 contacts (8 trials, n=11,210, RR 0.74, 95% CI, 0.64 to 0.86) vs. >6 contacts (5 trials, n=10,490, RR 0.92, 95% CI, 0.83 to 1.03); p-values in meta-regression controlling for responses in control groups are p=0.044 and p=0.032, respectively
Comparison group	Usual care, attention control, low intensity intervention, no intervention, not described
Interventionist and training required	Prevention trials used physicians or other medical providers, dentists, dental hygienists, health educators, health counselors, peer counselors, study-trained counselor, study-trained workshop leader
Reported adherence to intervention	From the 6 individual studies that reported child, parent, or counselor/educator's adherence: 70% of students read their letters; 62% of families completed all 4 booklets; 51% to 83% of parents completed tasks, 47% of parents reported speaking with a counselor for a booster counseling call, 60% of kids read the comic book, 48% of kids watched the video; 81% of family activities completed; 67% of adolescents actually received the counseling and < 50% completed both interviews; 72% of protocol given to nonsmokers and former smokers, 84% of protocol given to nonsmokers

*We included the only 3 studies that had significant findings (Fidler, 2001;[51], Hollis, 2005;[56] and Jackson, 2006[60]) and the only 3 studies that provided practice materials (Hovell et al., 1996;[57] Pbert, 2008;[67] Redding, 2015[69]); although other studies referenced practice materials, websites were no longer active or referenced outdated modes of communication (VHS tape) or referenced material in a foreign language

Abbreviations: CI=confidence interval; RR=relative risk.

Table 8. Results of Behavioral Intervention Prevention Trials

Trial, quality	Person targeted	Role of PC	Mode of intervention	Time point analyzed	% Initiating smoking at followup (IG vs. CG)	Relative risk (95% CI)
Ausems, 2002[45] Fair	Youth	None	Print	6 months	10.4* vs. 18.0	NR*
Bauman, 2001[48] Fair	Parent	None	Phone, print	7 months	17.0 vs. 21.0	0.81 (0.61 to 1.07)
Cremers, 2015[51] Fair	Youth	None	Computer	12 months	0.59 (IG1) and 1.06 (IG2) vs. 1.02	NR†
Curry, 2003[52] Fair	Both	Recruitment only	Phone, print	20 months	2.4‡ vs. 2.3‡	1.04 (0.68 to 1.58)
Fidler, 2001[53] Fair	Youth	Recruitment only	Print	12 months	5.1 vs. 7.8	0.65 (0.47 to 0.90)
Haggerty, 2007[55] Fair	Both	None	Face	12 months	11.8§ vs.9.0§	1.31 (0.52 to 3.28)
Hiemstra, 2014[57] Fair	Both	Recruitment only	Print	12 months	10.8 vs. 12.0	NR‖
Hollis, 2005[58] Good	Youth	Conducted in PC, provider delivered part	Face, computer	12 months	9.3 vs. 12.1	0.76 (0.59 to 0.99)
Hovell, 1996[59] Good	Youth	Conducted in dental, provider delivered most	Face, print	24 months	12.0¶ vs. 12.6¶	0.95 (0.84 to 1.07)
Jackson, 2006[62] Fair	Both	None	Print	36 months	11.9 vs. 19.3	0.62 (0.44 to 0.87)
Lando, 2007[66] Fair	Youth	Conducted in dental, provider delivered part	Face, phone	12 months	9.7 vs. 16.7	0.58 (0.25 to 1.37)
Pbert, 2008[69] Fair	Youth	Conducted in PC, provider delivered part	Face, phone	12 months	3.2 vs. 4.5	0.69 (0.30 to 1.58)
Redding, 2015[71] Fair	Youth	Conducted in family planning clinics, PC not involved	Face, computer	18 months	8.5 vs. 7.3	NR**
Schuck, 2015[75] Fair	Parent	None	Phone, print	12 months	20.1 vs. 14.7	NR††

*The number of baseline nonsmokers and the number of children initiating smoking at followup were not reported. The percentage of children initiating smoking at followup (as reported in the article) were 10.4% (95% CI, 6.9% to 14.0%) in the intervention group and 18.1% (95% CI, 12.5% to 23.7%) in the control group.

†Adjusted OR (age, gender, ethnicity, SES, among others for Prompt-reinforced intervention: 0.53 (95% CI, 0.12 to 2.47); No prompt-reinforced intervention: OR 1.01 (95% CI, 0.24 to 4.21).

‡Among the assessment cohort (n=492), 2.5% of the IG and 0% of the CG reported smoking in the past 30 days at baseline. Author does not report whether baseline smokers were included in the followup.

§At baseline, 22.0% of the IG and 21.7% of the CG reported smoking; these individuals were excluded from the analysis at followup.

‖ITT Adjusted OR (adjusted for parental smoking): 1.01 (95% CI, 0.82 to 1.24); adjusted for asthma: OR 0.91 (95% CI, 0.32 to 2.60); adjusted for SES: OR 1.06 (95% CI, 0.71 to 1.59).

¶Baseline smokers were excluded from the analysis (specific numbers not reported).

**GEE analysis indicated no significant differences between groups.

††OR 0.70 (95% CI, 0.41 to 1.20).

Abbreviations: CG=control group; CI=confidence interval; Face=face-to-face; GEE=generalized estimating equation; IG=intervention group; ITT=intention to treat; NR=not reported; PC=primary care; OR=odds ratio; SES=socioeconomic status.

Table 9. Results of Cessation Trials

Trial, quality	Role of PC	Mode of intervention	Time point analyzed	Definition of smoker at baseline	% Smoking at followup (IG vs. CG)	% Quitting at followup (IG vs. CG)	Relative risk (95% CI)
Bauman, 2000[46] Fair	None	Phone, print	7 months	Smoked ≥1 days in past 30 days	59.5 vs. 62.5	40.5 vs. 37.5	0.95 (0.67 to 1.34)
Colby, 2005[49] Fair	Recruitment only	Face, phone, print	6 months	Daily smoking for the past 30 days	76.5 vs. 97.1	23.5 vs. 2.9	0.79 (0.65 to 0.96)
Colby, 2012[50] Fair	Recruitment only	Face, phone, print	6 months	Smoked ≥1 time a week for past 30 days	95.1 vs. 97.2	4.9 vs. 2.8	0.98 (0.91 to 1.05)
Haug, 2013[56] Fair	None	Text messaging	6 months	Daily or occasional cigarette smoking (≥4 cigarettes in preceding month and ≥1 cigarette in preceding week)	87.5 vs. 90.4	12.5 vs. 9.6	NR*
Hollis, 2005[58] Good	Conducted in PC, provider delivered part	Face, computer	12 months	Smoked ≥1 cigarettes in past 30 days	67.5† vs. 76.8†	32.5† vs. 23.2†	0.88 (0.79 to 0.97)
Lando, 2007[66] Fair	Conducted in dental, provider delivered part	Face, phone	12 months	Smoked in past 30 days	93.4 vs. 88.9	6.6 vs. 11.1	1.05 (0.94 to 1.17)
Pbert, 2008[69] Fair	Conducted in PC, provider delivered part	Face, phone	12 months	Smoked occasionally or regularly	74.4 vs. 72.4	25.6 vs. 27.6	1.02 (0.75 to 1.38)
Pbert, 2011[68] Good	None	Face	12 months	Smoked in past 30 days and interested in quitting in next 2 weeks	84.8 vs. 85.7	15.2 vs. 14.3	0.99 (0.93 to 1.05)
Redding, 2014[71] Fair	Conducted in family planning clinics, PC not involved	Face, Computer	18 months	Ever smoked more than weekly	71.1 vs. 76.7	28.9 vs. 23.3	NR‡
Killen, 2004[65] (medication) Fair	None	Face	6 months	Smoked ≥10 cigarettes per day, smoked ≥6 months, had made one or more failed quit attempts, and scored ≥10 on mFTQ	87.5 vs. 90.0	12.5 vs. 10.0	0.97 (0.86 to 1.10)
Muramoto, 2007[67] (medication) Fair	None	Face	6 months	Smoked >6 cigarettes per day, had an exhaled CO level ≥10 ppm, and had at least 2 previous quit attempts and motivated to quit; excluded those using other tobacco products	93.8 vs. 89.7	6.3 vs. 10.3	1.05 (0.94 to 1.16)
Scherphof, 2014[74] (medication) Good	None	Face	12 months	Smoked ≥7 cigarettes per day, parent aware of smoking behavior, and motivated to quit smoking	95.6 vs. 93.4	4.4 vs. 6.6	NR§

*OR 1.03 (95%CI, 0.59 to 1.79); 4-week abstinence: 6.3% vs. 5.5%; OR 0.97 (95%CI, 0.50 to 1.90).

Table 9. Results of Cessation Trials

†Includes self-described experimenters and smokers.
‡GEE analysis indicated no difference between groups.
§Adjusted OR (gender, compliance, interaction of compliance and group, and other variables significantly correlated with smoking cessation in the study: 1.13 (95% CI, 0.17 to 7.44).
Abbreviations: CG=control group; CI=confidence interval; CO=carbon monoxide; Face=face-to-face; IG=intervention group; ITT=intention to treat; Med=medication; mFTQ=modified Fagerström Tolerance Questionnaire; NR=not reported; OR=odds ratio; PC=primary care.

Table 10. Results of Combined Primary Prevention and Cessation Behavioral Intervention Trials

Trial, quality	Targeted multiple behaviors	Person targeted	Role of PC	Mode of intervention	Time point analyzed	% Smoking at baseline (IG* vs. CG*)	% Smoking at followup (IG† vs. CG†)	Relative risk (95% CI)
Bauman, 2002[47] Fair	Yes	Parent	None	Phone, print	7 months	19.3‡ vs. 24.8‡	36.0 vs. 43.0	0.84 (0.72 to 0.97)
Hollis, 2005[58] Good	No	Youth	Conducted in PC, provider delivered part	Face, computer	12 months	23.3§ vs. 23.4§	22.8 vs. 27.2	0.84 (0.73 to 0.96)
Kentala, 1999[64] Fair	No	Youth	Conducted in dental, provider delivered most	Face	12 months	5.5 vs. 6.0	13.3 vs. 12.2	1.09 (0.87 to 1.36)
Lando, 2007[66] Fair	No	Youth	Conducted in dental, provider delivered part	Face, phone	12 months	34.9‡ vs. 37.3‡	48.1 vs. 47.6	1.01 (0.79 to 1.29)
Pbert, 2008[69] Fair	No	Youth	Conducted in PC, provider delivered part	Face, phone	12 months	8.7 vs. 10.6	9.4 vs. 11.7	0.80 (0.50 to 1.26)
Prado, 2007[70] Fair	Yes	Parent	None	Face	12 months	3.3 vs. 1.2	7.6 vs. 4.0	1.90 (0.49 to 7.32)
Redding, 2015[71] Fair	Yes	Youth	Conducted in family planning clinics, PC not involved	Face, computer	18 months	18.4‡ vs. 22.3‡	20.6‡ vs. 22.4‡	NR‖
Robling, 2016[72] Fair	No	Youth	Home visits by nurse	Face	24 months (postpartum)	56 vs. 58	56 vs. 56	0.90 (0.64 to 1.28)
Stevens, 2002¶,[76] Good	Yes	Both	Conducted in PC, provider delivered part	Face, phone, print	12 months	5.3‡ vs. 4.5‡	NR	NR**

*Among those randomized.
†Among those analyzed at followup.
‡Calculated based on presented data.
§Calculated based on data requested from the author.
‖GEE analysis indicated no difference between groups.
¶ Not included in meta-analysis.
**The adjusted OR for having ever smoked for the intervention group compared with the control group was 1.05 (95% CI, 0.80 to 1.39).
Abbreviations: CG=control group; CI=confidence interval; Face=face-to-face; GEE=generalized estimating equation; IG=intervention group; ITT=intention to treat; NR=not reported; OR=odds ratio; PC=primary care.

Table 11. Summary of Evidence

Key question	Populations or interventions	Studies (k); observations (n); study designs	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
Key Question 1 Efficacy of Interventions	Reduce tobacco product use in adulthood	1 trial (n=2,178)	Enrolled 12 year olds and evaluated smoking at age 29; prevalence of smoking 15.3% vs. 18.5% (OR 0.78, 95% CI, 0.56 to 1.09)	Unknown consistency; imprecise estimate	Only 39% responded to followup survey;	Insufficient	Finnish trial—U.S. applicable
Key Question 1 Efficacy of interventions	Improve adolescent health outcomes	1 trials (n=1,092)	Enrolled pregnant adolescents, maternal ED/hospital admission (OR 1.32, 95% CI, 0.99 to 1.76), psychological distress scores, depressive symptom scores, and problems with alcohol and drug use scores not different with nurse home visits vs. control	Unknown consistency; imprecise estimate	Description of intervention not provided; details of usual care services accessed not provided	Insufficient	UK trial; services in control group exceed U.S.; intensive nurse visits less applicable to primary care practice
Key Question 2 Efficacy of behavioral interventions	Prevent smoking initiation in nonsmokers	14 trials (n=25,049)	Pooled analysis of 13 trials (n=21,700, 7.4% vs. 9.2%, RR 0.82, 95% CI, 0.73 to 0.92); I^2=15%	Consistent; precise	Most trials have moderate risk of bias	Moderate for benefit	Most trials U.S.
Key Question 2 Efficacy of behavioral interventions	Smoking cessation in baseline smokers	9 trials (n=2,516)	Pooled analysis of 9 trials (80.7% vs. 84.1%, RR 0.97, 95% CI, 0.93 to 1.01); I^2=29%	Consistent; precise	Most trials have moderate risk of bias	Low for no effect	Most trials U.S.
Key Question 2 Efficacy of behavioral interventions	Smoking prevalence in baseline smokers and nonsmokers	9 trials (n=11,471)	Pooled analysis of 7 trials (n=10,533, 16.8% vs. 20.1%, RR 0.91, 95% CI, 0.83 to 0.995); I^2=19%	Consistent; precise	Most trials have moderate risk of bias	Low for benefit	Most trials U.S.
Key Question 2 Efficacy of bupropion	Smoking cessation in baseline smokers	2 trials in (n=523)	2 trials of bupropion demonstrated no benefit over placebo	Consistent; estimates imprecise	Low retention (<70%)	Low for no effect	Trials conducted in US
Key Question 2 Efficacy of NRT	Smoking cessation in baseline smokers	1 trial (n=265)	6 months: 8.1% vs. 5.7%, AOR 2.09, 95% CI, 0.20 to 22; 12 months: 8.1% vs. 8.2%, AOR 1.13, 95% CI, 0.17 to 7.44	Unknown consistency, imprecise estimate	None	Insufficient	Netherlands trial—US applicable
Key Question 3 Harms of behavioral interventions	Baseline smokers and nonsmokers	No studies	No studies	No studies	No studies	No studies	No studies

Table 11. Summary of Evidence

Key question	Populations or interventions	Studies (k); observations (n); study designs	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
Key Question 3 Harms of bupropion	Baseline smokers	3 trials (n=657)	No difference between bupropion and control in experiencing a serious or severe adverse event (2 trials), 4% withdrew with bupropion due to adverse events (2 trials); bupropion associated with more headache (2 trials), cough (1 trial), dream disturbance (1 trial), insomnia (1 trial), irritability (1 trial) than control	Consistent, imprecise	Trials rated moderate risk of bias	Low for harms	All trials conducted in U.S.
Key Question 3 Harms of NRT	Baseline smokers	1 trial (n=257)	NRT associated with more headache, cough, abnormal dreams, muscle pain, and patch-related adverse events than placebo	Consistency unknown; estimate imprecise	None	Insufficient	Dutch study—U.S. applicable

Abbreviations: CI=confidence interval; NRT=nicotine replacement therapy; OR=odds ratio; RR=relative risk; U.S.=United States.

Databases Searched for Overall Project

OVID MEDLINE® Database Searches

Search Strategy:

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1 Smoking/
2 exp "Tobacco Use Cessation"/
3 "Tobacco Use Disorder"/
4 Electronic Cigarettes/
5 (smoking$ or cigarette$ or tobacco or nicotine or vape or vaping or "e-cigarette$" or "electronic cigarette$").ti.
6 (prevent$ or prevention or use$ or usage or cessation or quit$ or stop$).ti,ab.
7 pc.fs.
8 (or/1-5) and (or/6-7)
9 (child$ or adolescen$ or teen$ or youth or "young adult").ti,ab.
10 8 and 9
11 10 and (random$ or control$ or trial or study).ti,ab.
12 limit 10 to (meta analysis or systematic reviews)
13 11 or 12
14 limit 13 to (english language and humans)
15 (201209$ or 20121$ or 2013$ or 2014$ or 2015$ or 2016$ or 2017$).ed,dp.
16 14 and 15
17 10 and (control$ or cohort or compare$ or comparison or comparative or observational).ti,ab.
18 17 and (ae or co or mo).fs.
19 17 and (harm$ or adverse).ti,ab,kw,tw.
20 18 or 19
21 limit 20 to (english language and humans)
22 21 and (201209$ or 20121$ or 2013$ or 2014$ or 2015$ or 2016$ or 2017$).ed,dp.
23 16 or 22

EBM Reviews - Cochrane Central Register of Controlled Trials

Search Strategy:

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1 Smoking/
2 exp "Tobacco Use Cessation"/
3 "Tobacco Use Disorder"/
4 Electronic Cigarettes/
5 (smoking$ or cigarette$ or tobacco or nicotine or vape or vaping or "e-cigarette$" or "electronic cigarette$").ti.
6 (prevent$ or prevention or use$ or usage or cessation or quit$ or stop$).ti,ab.
7 pc.fs.
8 (or/1-5) and (or/6-7)
9 (child$ or adolescen$ or teen$ or youth or "young adult").ti,ab.
10 8 and 9
11 limit 10 to english language
12 limit 11 to yr="2012 -Current"

Appendix A1. Search Strategies

EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
---
1 (smoking$ or cigarette$ or tobacco or nicotine or vape or vaping or "e-cigarette$" or "electronic cigarette$").ti.
2 (child$ or adolescen$ or teen$ or youth or "young adult").ti.
3 1 and 2

PsycINFO
Search Strategy:
---
1 exp smoking cessation/
2 exp electronic cigarettes/
3 exp tobacco smoking/
4 (smoking$ or cigarette$ or tobacco or nicotine or vape or vaping or "e-cigarette$" or "electronic cigarette$").ti.
5 exp prevention/
6 (prevent$ or prevention or use$ or usage or cessation or quit$ or stop$).ti,ab.
7 (child$ or adolescen$ or teen$ or youth or "young adult").ti,ab.
8 (or/1-4) and (5 or 6)
9 7 and 8
10 limit 9 to ("0300 clinical trial" or "0830 systematic review" or 1200 meta analysis)
11 9 and (random$ or control$ or trial or cohort or comparative or comparison or compare$).ti,ab.
12 10 or 11
13 intervention.id.
14 (intervention$ or treatment or therapy or counseling).ti,ab.
15 exp Drug Therapy/
16 12 and (13 or 14 or 15)
17 limit 16 to yr="2012 -Current"

Elsevier Embase®
Search Strategy:

((('smoking'/exp AND 'smoking related phenomena' OR 'smoking cessation'/exp OR 'vaping'/exp OR 'electronic cigarette'/exp OR 'electronic cigarette') AND ('prevention and control'/exp OR 'prevention and control')) AND ('clinical trial'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'double blind procedure'/de OR 'meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ([child]/lim OR [adolescent]/lim OR [young adult]/lim) AND [english]/lim) AND (2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py) AND [embase]/lim NOT [medline]/lim

Update Search: Young Adult Prevention Age Gap

OVID MEDLINE® Database Searches

Search Strategy:

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1 (smoking$ or cigarette$ or tobacco or nicotine or vape or vaping or "e-cigarette$" or "electronic cigarette$").ti.
2 (prevent$ or prevention or use$ or usage).ti,ab.
3 pc.fs.
4 (adolescen$ or teen$ or youth or "young adult").ti,ab.
5 1 and (2 or 3) and 4
6 5 and (random$ or control$ or trial or cohort or compare$ or comparison or comparative or observational).ti,ab.
7 limit 6 to english language
8 limit 7 to yr="1902 - 2012"
9 5 and (control$ or cohort or compare$ or comparison or comparative or observational).ti,ab.
10 9 and (ae or co or mo).fs.
11 9 and (harm$ or adverse).ti,ab,kw,tw.
12 10 or 11
13 limit 12 to english language
14 limit 13 to yr="1902-2012"
15 8 or 14

EBM Reviews - Cochrane Central Register of Controlled Trials

Search Strategy:

---

1 Smoking/
2 "Tobacco Use Disorder"/
3 Electronic Cigarettes/
4 (smoking$ or cigarette$ or tobacco or nicotine or vape or vaping or "e-cigarette$" or "electronic cigarette$").ti.
5 (prevent$ or prevention or use$ or usage or quit$ or stop$).ti,ab.
6 pc.fs.
7 (or/1-4) and (5 or 6)
8 (adolescen$ or teen$ or youth or "young adult").ti,ab.
9 7 and 8

EBM Reviews - Cochrane Database of Systematic Reviews

Search Strategy:

---

1 (smoking$ or cigarette$ or tobacco or nicotine or vape or vaping or "e-cigarette$" or "electronic cigarette$").ti.
2 (adolescen$ or teen$ or youth or "young adult").ti.
3 1 and 2

Appendix A1. Search Strategies

PsycINFO
Search Strategy:
---
1 exp smoking cessation/
2 exp electronic cigarettes/
3 exp tobacco smoking/
4 (smoking$ or cigarette$ or tobacco or nicotine or vape or vaping or "e-cigarette$" or "electronic cigarette$").ti.
5 exp prevention/
6 (prevent$ or prevention or use$ or usage).ti,ab.
7 (adolescen$ or teen$ or youth or "young adult").ti,ab.
8 (or/1-4) and (5 or 6)
9 7 and 8
10 limit 9 to ("0300 clinical trial" or "0830systematic review" or 1200 meta analysis)
11 9 and (random$ or control$ or trial or cohort or comparative or comparison or compare$).ti,ab.
12 10 or 11
13 intervention.id.
14 (intervention$ or treatment or therapy or counseling).ti,ab.
15 exp Drug Therapy/
16 12 and (13 or 14 or 15)
17 limit 16 to yr="1861 - 2011"

Appendix A2. Inclusion and Exclusion Criteria

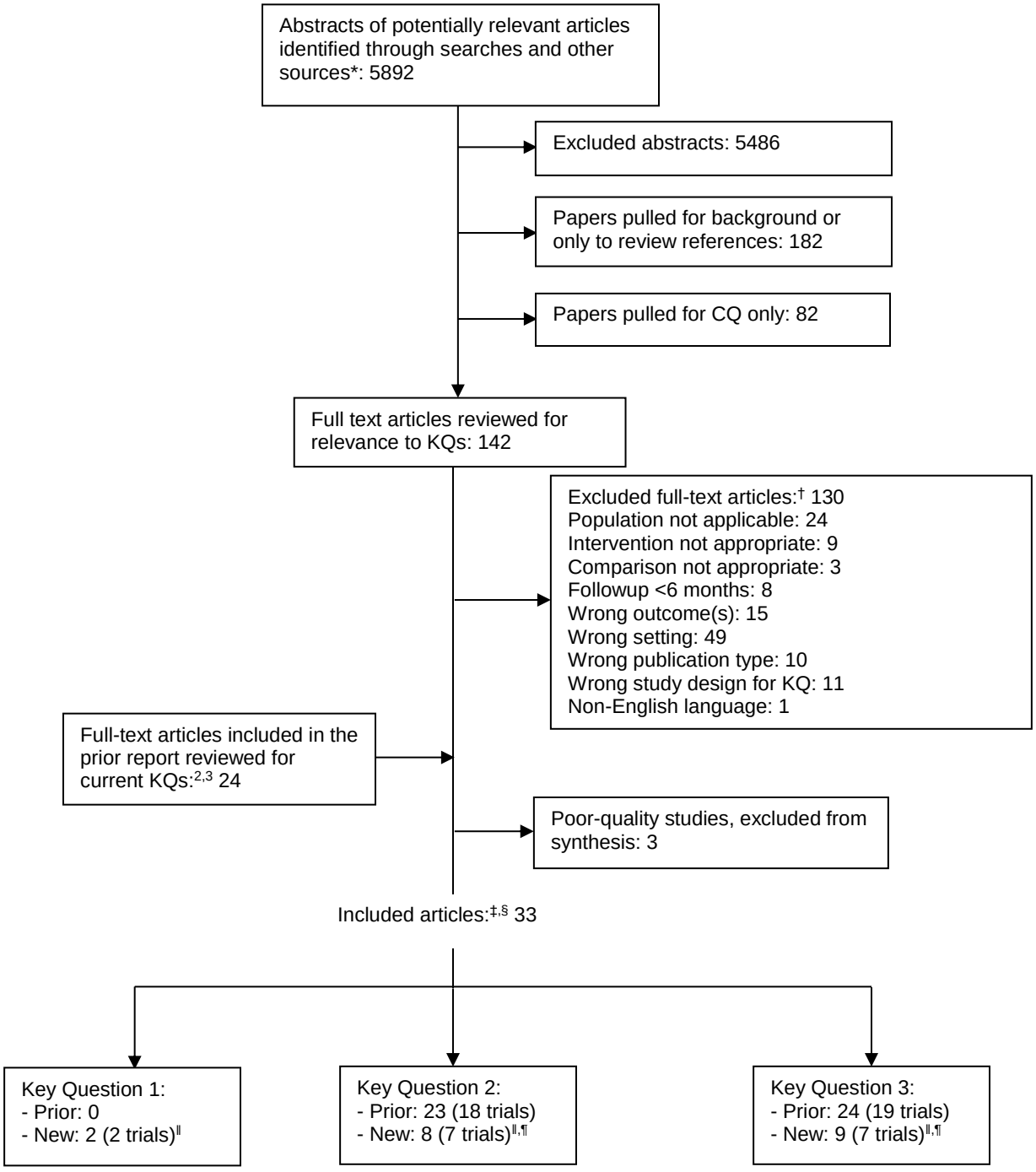
	Included	Excluded
Setting	Primary care, other health care, research clinic/office, dental clinic, or school-based health clinic	• Schools (other than health clinics delivering primary care) • Inpatient settings • Institutional/residential facilities
Populations	• Adolescents (ages 13 to 18 years) and children (age <13 years) for cessation; children and adolescents (to age 25 years) for prevention • More than 50% of study participants must be in included age group • Pregnant adolescents	• Adults (age >18 years for cessation >25 for prevention), unless subgroup results for adolescents are reported separately from adults • Trials limited to children or adolescents with health issues that would limit generalizability to general primary care patients
Condition	• Use of tobacco or nicotine, including cigarettes, smokeless tobacco, cigars, pipes, and e-cigarettes	Studies that target marijuana use alone
Interventions	• Primary care–relevant behavioral counseling interventions, including individual, group, phone, or technology-based sessions; telephone quit lines; apps; and health care system–level interventions • Adjunctive use of pharmacotherapy (nicotine replacement therapy, bupropion, or varenicline tartrate) • Interventions targeting parents or caregivers as a means to prevent or reduce tobacco or nicotine use in children and adolescents • Complementary and alternative medicine treatments, such as acupuncture and hypnosis	• Broad public health or policy interventions • Use of e-cigarettes as a cessation or prevention intervention • Trials in which participants are highly likely to know one another (i.e., closed social groups, peer counseling) and participant interaction is likely
Comparisons	• Usual care • Minimal care (no more than one single brief contact per year or brief written materials, such as pamphlets) • No intervention • Attention control • Wait list	Active intervention (more intensive than a single, brief contact per year or brief written materials)
Outcomes	**KQ 1:** • Prevalence or severity of asthma, chronic bronchitis, or other respiratory disorders, health care utilization for respiratory disorders • Dental/oral health outcomes • Cardiovascular health outcomes • Rate, incidence, or prevalence of adult tobacco or nicotine use **KQ 2:** • Tobacco or nicotine use cessation • Frequency or quantity of alcohol use or use of other substances **KQ 3:** • Any adverse effect occurring after initiation of the intervention (e.g., paradoxical increase in tobacco or nicotine use, mental health issues)	Attitudes or knowledge about tobacco; intentions to quit

Appendix A2. Inclusion and Exclusion Criteria

	Included	Excluded
Study Design	**KQs 1, 2:** • Randomized and nonrandomized, controlled trials; systematic reviews • Trials with a minimum of 6 months (or 24 weeks) of followup postbaseline **KQ 3:** • Randomized and nonrandomized, controlled trials; comparative observational designs; systematic reviews • No minimum followup required	**KQs 1 to 3:** All other study designs **KQs 1, 2:** Studies with less than 6 months (or 24 weeks) of followup postbaseline
Study Quality	Fair- or good-quality studies	Poor-quality studies

Abbreviations: KQ=key question.

Appendix A3. Literature Flow Diagram



*Other sources include reference lists of relevant articles, systematic reviews, reviewer suggestions, etc.
†See Appendix 4 for the list of excluded studies and Appendix 2 for the list of exclusion criteria.
‡Studies that provided data and contributed to the body of evidence were considered 'included'.
§Studies may contribute data to more than one key question.
‖1 new publication[73] is an update of a previously included trial.[64]

Appendix A4. List of Excluded Studies

1. Allara E, Angelini P, Gorini G, et al. A prevention program for multiple health-compromising behaviors in adolescence: baseline results from a cluster randomized controlled trial. Prev Med. 2015 Feb;71:20-6. doi: 10.1016/j.ypmed.2014.12.002. PMID: 25500201. **Exclusion reason: wrong setting**.

2. Al-Sheyab N, Alomari M, Shah S, et al. 'Class smoke-free' pledge impacts on nicotine dependence in male adolescents: a cluster randomized controlled trial. Trop Med Int Health. 2015;20:255-6. **Exclusion reason: wrong setting**.

3. Andersen A, Krolner R, Bast LS, et al. Effects of the X:IT smoking intervention: a school-based cluster randomized trial. Int J Epidemiol. 2015 Dec;44(6):1900-8. doi: 10.1093/ije/dyv145. PMID: 26210612. **Exclusion reason: wrong setting**.

4. Andersen A, Krolner R, L SN, et al. Prevention of smoking among adolescents: first year results from the cluster randomised X:IT trial. IEA-EEF European Congress of Epidemiology 2012: Epidemiology for a Fair and Healthy Society. Eur J Epidemiol. 2012 Sep 5-8;27(1 SUPPL. 1):S29. **Exclusion reason: wrong publication type**.

5. Bailey SR, Hagen SA, Jeffery CJ, et al. A randomized clinical trial of the efficacy of extended smoking cessation treatment for adolescent smokers. Nicotine Tob Res. 2013 Oct;15(10):1655-62. doi: 10.1093/ntr/ntt017. PMID: 23460656. **Exclusion reason: wrong setting**.

6. Barry R. It's a bitch to quit: interview with Dr. Phoenix Matthews [Blog Interview]. 2012. http://thelstop.org/2012/11/its-a-bitch-to-quit-interview-with-dr-phoenix-matthews/. Accessed Sep 8, 2018. **Exclusion reason: wrong publication type**

7. Baskerville NB, Azagba S, Norman C, et al. Effect of a digital social media campaign on young adult smoking cessation. Nicotine Tob Res. 2016 Mar;18(3):351-60. doi: 10.1093/ntr/ntv119. PMID: 26045252. **Exclusion reason: population not applicable**.

8. Bast LS, Due P, Bendtsen P, et al. High impact of implementation on school-based smoking prevention: the X:IT study-a cluster-randomized smoking prevention trial. Implementation Science. 2016 Sep 17;11(1):125. doi: 10.1186/s13012-016-0490-7. PMID: 27640187. **Exclusion reason: wrong setting**.

9. Bast LS, Due P, Ersboll AK, et al. Association of school characteristics and implementation in the X:IT study-a school-randomized smoking prevention program. J Sch Health. 2017 May;87(5):329-37. doi: 10.1111/josh.12500. PMID: 28382673. **Exclusion reason: wrong setting**.

10. Bavarian N, Duncan R, Lewis KM, et al. Adolescent substance use following participation in a universal drug prevention program: examining relationships with program recall and baseline use status. Subst Abus. 2015;36(3):359-67. doi: 10.1080/08897077.2014.952364. PMID: 25148566. **Exclusion reason: wrong setting**.

11. Bernardes-Souza B, Patruz Ananias De Assis Pires F, Madeira GM, et al. Facial-aging mobile apps for smoking prevention in secondary schools in Brazil: appearance-focused interventional study. JMIR Public Health Surveill. 2018 Jul 17;4(3):e10234. doi: 10.2196/10234. PMID: 30021713. **Exclusion reason: wrong setting**.

12. Bowen DJ, Henderson PN, Harvill J, et al. Short-term effects of a smoking prevention website in American Indian youth. J Med Internet Res. 2012 May-Jun;14(3):185-92. doi: 10.2196/jmir.1682. PMID: 22659390. **Exclusion reason: followup less than 6 months**.

13. Bradley EG. Reducing adolescent smoking through a school-based motivational intervention: a pilot study. E-Journal of Applied Psychology. 2012;8(1):38-44. doi: 10.7790/ejap.v8i1.319. **Exclusion reason: wrong outcome**.

14. Brick LA, Redding CA, Paiva AL, et al. Intervention effects on stage transitions for adolescent smoking and alcohol use acquisition. Psychol Addict Behav. 2017 Aug;31(5):614-24. doi: 10.1037/adb0000302. PMID: 28714725. **Exclusion reason: wrong outcome**.

15. Brinker TJ, Owczarek AD, Seeger W, et al. A medical student-delivered smoking prevention program, education against tobacco, for secondary schools in Germany: randomized controlled trial. J Med Internet Res. 2017 Jun 06;19(6):e199. doi: 10.2196/jmir.7906. PMID: 28588007. **Exclusion reason: intervention not appropriate**.

16. Brinker TJ, Stamm-Balderjahn S, Seeger W, et al. Education Against Tobacco (EAT): a quasi-experimental prospective evaluation of a multinational medical-student-delivered smoking prevention programme for secondary schools in Germany. BMJ Open. 2015 Sep 18;5(9):e008093. doi: 10.1136/bmjopen-2015-008093. PMID: 26384722. **Exclusion reason: wrong setting**.

17. Burford O, Jiwa M, Carter O, et al. Internet-based photoaging within Australian pharmacies to promote smoking cessation: randomized controlled trial. J Med Internet Res. 2013 Mar 26;15(3):e64. doi: 10.2196/jmir.2337. PMID: 23531984. **Exclusion reason: population not applicable**.

18. Burford O, Kindarji S, Parsons R, et al. Using visual demonstrations in young adults to promote smoking cessation: preliminary findings from a French pilot study. Res Social Adm Pharm. 2018 04;14(4):398-400. doi: 10.1016/j.sapharm.2017.04.050. PMID: 28495124. **Exclusion reason: population not applicable**.

19. Caldwell AL, Tingen MS, Nguyen JT, et al. Parental smoking cessation: impacting children's tobacco smoke exposure in the home. Pediatrics. 2018;141(Suppl 1):S96-S106. PMID: 29292310. **Exclusion reason: wrong outcome**.

20. Carragher N, Krueger RF, Eaton NR, et al. ADHD and the externalizing spectrum: direct comparison of categorical, continuous, and hybrid models of liability in a nationally representative sample. Soc Psychiatry Psychiatr Epidemiol. 2014 Aug;49(8):1307-17. doi: 10.1007/s00127-013-0770-3. PMID: 24081325. **Exclusion reason: wrong outcome**.

21. Castro RP, Haug S, Filler A, et al. Engagement within a mobile phone-based smoking cessation intervention for adolescents and its association with participant characteristics and outcomes. J Med Internet Res. 2017 Nov;19(11):e356. PMID: 29092811. **Exclusion reason: wrong outcome**.

22. Chansatitporn N, Charoenca N, Sidhu A, et al. Three-month effects of Project EX: a smoking intervention pilot program with Thai adolescents. Addict Behav. 2016 Oct;61:20-4. doi:

10.1016/j.addbeh.2016.05.003. PMID: 27235988. **Exclusion reason: followup less than 6 months**.

23. Chen YF, Yu T, Brody GH. Parenting intervention at age 11 and cotinine levels at age 20 among African American youth. Pediatrics. 2017 Jul;140(1) doi: 10.1542/peds.2016-4162. PMID: 28615354. **Exclusion reason: wrong publication type**.

24. Clawson AH, Robinson LA, Ali JS. Physician advice to adolescents about smoking: who gets advised and who benefits most? J Adolesc Health. 2016 Feb;58(2):195-201. doi: 10.1016/j.jadohealth.2015.10.006. PMID: 26802992. **Exclusion reason: wrong study design**.

25. Coleman T, Cooper S, Thornton JG, et al. A randomized trial of nicotine-replacement therapy patches in pregnancy. Obstet Gynecol Surv. 2012;67(7):387-8. doi: 10.1097/OGX.0b013e31825fd62b. **Exclusion reason: population not applicable**.

26. Collins BN, Lepore SJ, Winickoff JP, et al. An office-initiated multilevel intervention for tobacco smoke exposure: a randomized trial. [Erratum appears in PMID: 29853625]. Pediatrics. 2018 Jan;141(Suppl 1):S75-S86. doi: 10.1542/peds.2017-1026K. PMID: 29292308. **Exclusion reason: wrong outcome**.

27. Cooper S, Taggar J, Lewis S, et al. Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial.[Erratum appears in Lancet Respir Med. 2014 Nov;2(11):e22]. Lancet Respir Med. 2014 Sep;2(9):728-37. doi: 10.1016/S2213-2600(14)70157-2. PMID: 25127405. **Exclusion reason: wrong outcome**.

28. Cremers HP, Mercken L, Oenema A, et al. A web-based computer-tailored smoking prevention programme for primary school children: intervention design and study protocol. BMC Public Health. 2012 Jun 11;12:277. doi: 10.1186/1471-2458-12-277. PMID: 22490110. **Exclusion reason: wrong publication type**.

29. Cummins SE, Tedeschi GJ, Anderson CM, et al. Telephone intervention for pregnant smokers: a randomized controlled trial. Am J Prev Med. 2016;51(3):318-26. doi: 10.1016/j.amepre.2016.02.022. **Exclusion reason: population not applicable**.

30. Daly JB, Mackenzie LJ, Freund M, et al. Interventions by health care professionals who provide routine child health care to reduce tobacco smoke exposure in children: a review and meta-analysis. JAMA Pediatrics. 2016 Feb;170(2):138-47. doi: 10.1001/jamapediatrics.2015.3342. PMID: 26719991. **Exclusion reason: wrong study design**.

31. Davis JM, Mills DM, Stankevitz KA, et al. Pilot randomized trial on mindfulness training for smokers in young adult binge drinkers. BMC Complement Altern Med. 2013 Sep 03;13:215. doi: 10.1186/1472-6882-13-215. PMID: 24006963. **Exclusion reason: population not applicable**.

32. Di Paco A, Boffi R, De Marco C, et al. A sequential school based smoke prevention program in secondary school adolescents. Monaldi Arch Chest Dis. 2013 Mar;79(1):8-11. doi: 10.4081/monaldi.2013.103. PMID: 23741940. **Exclusion reason: wrong setting**.

Appendix A4. List of Excluded Studies

33. Dotterud CK, Storro O, Simpson MR, et al. The impact of pre- and postnatal exposures on allergy related diseases in childhood: a controlled multicentre intervention study in primary health care. BMC Public Health. 2013 Feb 08;13:123. doi: 10.1186/1471-2458-13-123. PMID: 23394141. **Exclusion reason: wrong outcome**.

34. Eades SJ, Sanson-Fisher RW, Wenitong M, et al. An intensive smoking intervention for pregnant Aboriginal and Torres Strait Islander women: a randomised controlled trial. Med J Aust. 2012 Jul 2;197(1):42-6. PMID: 22762231. **Exclusion reason: population not applicable**.

35. Eakin MN, Rand CS, Borrelli B, et al. Effectiveness of motivational interviewing to reduce head start children's secondhand smoke exposure. a randomized clinical trial. Am J Respir Crit Care Med. 2014 Jun 15;189(12):1530-7. doi: 10.1164/rccm.201404-0618OC. PMID: 24821270. **Exclusion reason: wrong outcome**.

36. Elder JP, Woodruff SI, Eckhardt L. Participation in a telephone-based tobacco use prevention program for adolescents. Am J Health Promot. 1994;9(2):92-5. **Exclusion reason: wrong setting**.

37. Endrighi R, McQuaid EL, Bartlett YK, et al. Parental depression is prospectively associated with lower smoking cessation rates and poor child asthma outcomes. Ann Behav Med. 2018 Feb 17;52(3):195-203. doi: 10.1093/abm/kax011. PMID: 29538661. **Exclusion reason: wrong outcome**.

38. Espada JP, Gonzalvez MT, Guillen-Riquelme A, et al. Immediate effects of Project EX in Spain: a classroom-based smoking prevention and cessation intervention program. J Drug Educ. 2014;44(1-2):3-18. doi: 10.1177/0047237915573523. PMID: 25721322. **Exclusion reason: wrong setting**.

39. Espada JP, Gonzalvez MT, Orgiles M, et al. Pilot clinic study of Project EX for smoking cessation with Spanish adolescents. Addict Behav. 2015 Jun;45:226-31. doi: 10.1016/j.addbeh.2015.02.009. PMID: 25725191. **Exclusion reason: wrong setting**.

40. Espada JP, Gonzalvez MT, Orgiles M, et al. Preliminary results of Project EX in Spain: a classroom-based smoking prevention and cessation program. Drug Alcohol Depend. 2014;146(14). **Exclusion reason: wrong publication type**.

41. Espada JP, Gonzalvez MT, Orgiles M, et al. One-year effects of Project EX: a smoking intervention pilot program with Spanish adolescents. J Health Psychol. 2017 Jul;22(8):1067-74. doi: 10.1177/1359105315623628. PMID: 26826168. **Exclusion reason: wrong setting**.

42. Fallin A, Neilands TB, Jordan JW, et al. Wreaking "havoc" on smoking: social branding to reach young adult "partiers" in Oklahoma. Am J Prev Med. 2015 Jan;48(1 Suppl 1):S78-85. doi: 10.1016/j.amepre.2014.09.008. PMID: 25528713. **Exclusion reason: population not applicable**.

43. Fanshawe TR, Halliwell W, Lindson N, et al. Tobacco cessation interventions for young people. Cochrane Database Syst Rev. 2017 Nov 17;11:CD003289. doi: 10.1002/14651858.CD003289.pub6. PMID: 29148565. **Exclusion reason: wrong study design**.

44. Farsalinos KE, Romagna G. Chronic idiopathic neutrophilia in a smoker, relieved after smoking cessation with the use of electronic cigarette: a case report. Clin Med Insights Case Rep.

2013;6:15-21. doi: 10.4137/CCRep.S11175. PMID: 23439796. **Exclusion reason: wrong study design**.

45. Floden L, Taren DL, Muramoto ML, et al. BMI changes in adolescents treated with bupropion SR for smoking cessation. Obesity. 2016 Jan;24(1):26-9. doi: 10.1002/oby.21360. PMID: 26692579. **Exclusion reason: wrong study design**.

46. Fosco GM, Frank JL, Stormshak EA, et al. Opening the "Black Box": family check-up intervention effects on self-regulation that prevents growth in problem behavior and substance use. J Sch Psychol. 2013 Aug;51(4):455-68. doi: 10.1016/j.jsp.2013.02.001. PMID: 23870441. **Exclusion reason: wrong setting**.

47. Fridberg DJ, Cao D, King AC. Integrating alcohol response feedback in a brief intervention for young adult heavy drinkers who smoke: a pilot study. Drug Alcohol Depend. 2015 Oct 01;155:293-7. doi: 10.1016/j.drugalcdep.2015.08.017. PMID: 26341847. **Exclusion reason: intervention not appropriate**.

48. Fromme K, Brown SA. Empirically based prevention and treatment approaches for adolescent and young adult substance use. Cogn Behav Pract. 2000;7(1):61-4. **Exclusion reason: wrong study design**.

49. Gharlipour Z, Hazavehei SMM, Moeini B, et al. The effect of preventive educational program in cigarette smoking: Extended Parallel Process Model. J Educ Health Promot. 2015;4:4. doi: 10.4103/2277-9531.151875. PMID: 25767815. **Exclusion reason: wrong setting**.

50. Giannotta F, Vigna-Taglianti F, Rosaria Galanti M, et al. Short-term mediating factors of a school-based intervention to prevent youth substance use in Europe. J Adolesc Health. 2014 May;54(5):565-73. doi: 10.1016/j.jadohealth.2013.10.009. PMID: 2013-43584-001. **Exclusion reason: wrong setting**.

51. Gonzalvez MT, Espada JP, Orgiles M, et al. One-year effects of Project EX in Spain: a classroom-based smoking prevention and cessation intervention program. PLoS ONE [Electronic Resource]. 2015;10(6):e0130595. doi: 10.1371/journal.pone.0130595. PMID: 26090821. **Exclusion reason: wrong setting**.

52. Gonzalvez MT, Espada JP, Orgiles M, et al. Two-year effects of a classroom-based smoking prevention and cessation intervention program. Eur Addict Res. 2017;23(3):122-8. doi: 10.1159/000475985. PMID: 28595196. **Exclusion reason: wrong setting**.

53. Gorzkowski JA, Kaseeska KR, Wright M, et al. Implementation and impact of the 5As tobacco counseling intervention with adolescents in pediatric practice. J Adolesc Health. 2016 Mar 9-12;58(2016):S49. doi: 10.1016/j.jadohealth.2015.10.110. **Exclusion reason: wrong publication type**.

54. Gray KM, Carpenter MJ, Lewis A, et al. Varenicline versus bupropion XL for smoking cessation in older adolescents: a randomized, double-blind pilot trial. Nicotine Tob Res. 2012 Feb;14(2):235-9. doi: 10.1093/ntr/ntr130. PMID: 21778151. **Exclusion reason: population not applicable**.

Appendix A4. List of Excluded Studies

55. Guo J, Liao J, Chang L, et al. The effectiveness of an integrated multicomponent program for adolescent smoking cessation in Taiwan. Addict Behav. 2014 Oct;39(10):1491-9. doi: 10.1016/j.addbeh.2014.05.009. PMID: 2014-29596-021. **Exclusion reason: wrong setting**.

56. Haller DM, Pfarrwaller E, Cerutti B, et al. Primary care interventions to reduce cardiovascular risk behaviours in adolescents: a protocol for a systematic review. BMJ Open. 2016 Oct 18;6(10):e011936. doi: 10.1136/bmjopen-2016-011936. PMID: 27798001. **Exclusion reason: wrong publication type**.

57. Harrell MB, Arora M, Bassi S, et al. Reducing tobacco use among low socio-economic status youth in Delhi, India: outcomes from project ACTIVITY, a cluster randomized trial. Health Educ Res. 2016 Oct;31(5):624-38. doi: 10.1093/her/cyw039. PMID: 27540182. **Exclusion reason: intervention not appropriate**.

58. Harutyunyan A, Movsisyan N, Petrosyan V, et al. Reducing children's exposure to secondhand smoke at home: a randomized trial. Pediatrics. 2013 Dec;132(6):1071-80. doi: 10.1542/peds.2012-2351. PMID: 24190686. **Exclusion reason: population not applicable**.

59. Haug S, Paz Castro R, Kowatsch T, et al. Efficacy of a technology-based, integrated smoking cessation and alcohol intervention for smoking cessation in adolescents: results of a cluster-randomised controlled trial. J Subst Abuse Treat. 2017;82(pp 55-66) PMID: CN-01412025. **Exclusion reason: comparison not appropriate**.

60. Hawkins JD, Oesterle S, Brown EC, et al. Youth problem behaviors 8 years after implementing the communities that care prevention system: a community-randomized trial. JAMA Pediatrics. 2014 Feb;168(2):122-9. doi: 10.1001/jamapediatrics.2013.4009. PMID: 24322060. **Exclusion reason: intervention not appropriate**.

61. Heffner JL, Kealey KA, Marek PM, et al. Proactive telephone counseling for adolescent smokers: comparing regular smokers with infrequent and occasional smokers on treatment receptivity, engagement, and outcomes. Drug Alcohol Depend. 2016 Aug;165:229-35. doi: 10.1016/j.drugalcdep.2016.06.014. PMID: 27344195. **Exclusion reason: intervention not appropriate**.

62. Hodder RK, Freund M, Bowman J, et al. Effectiveness of a pragmatic school-based universal resilience intervention in reducing tobacco, alcohol and illicit substance use in a population of adolescents: cluster-randomised controlled trial. BMJ Open. 2017 Aug 18;7(8):e016060. doi: 10.1136/bmjopen-2017-016060. PMID: 28821523. **Exclusion reason: wrong setting**.

63. Idrisov B, Sun P, Akhmadeeva L, et al. Immediate and six-month effects of Project EX Russia: a smoking cessation intervention pilot program. Addict Behav. 2013 Aug;38(8):2402-8. doi: 10.1016/j.addbeh.2013.03.013. PMID: 23639851. **Exclusion reason: wrong setting**.

64. Isensee B, Hansen J, Maruska K, et al. Effects of a school-based prevention programme on smoking in early adolescence: a 6-month follow-up of the 'Eigenstandig werden' cluster randomised trial. BMJ Open. 2014 Jan 21;4(1):e004422. doi: 10.1136/bmjopen-2013-004422. PMID: 24448850. **Exclusion reason: wrong setting**.

Appendix A4. List of Excluded Studies

65. Isensee B, Morgenstern M, Stoolmiller M, et al. Effects of Smokefree Class Competition 1 year after the end of intervention: a cluster randomised controlled trial. J Epidemiol Community Health. 2012 Apr;66(4):334-41. doi: 10.1136/jech.2009.107490. PMID: 21071561. **Exclusion reason: wrong setting**.

66. Jones DJ, Olson AL, Forehand R, et al. A family-focused randomised controlled trial to prevent adolescent alcohol and tobacco use: the moderating roles of positive parenting and adolescent gender. Behav Ther. 2005;36(4):347-55. **Exclusion reason: wrong outcome**.

67. Kegler MC, Bundy L, Haardorfer R, et al. A minimal intervention to promote smoke-free homes among 2-1-1 callers: a randomized controlled trial. Am J Public Health. 2015 Mar;105(3):530-7. doi: 10.2105/AJPH.2014.302260. PMID: 25602863. **Exclusion reason: intervention not appropriate**.

68. Khalil GE, Wang H, Calabro KS, et al. From the experience of interactivity and entertainment to lower intention to smoke: a randomized controlled trial and path analysis of a web-based smoking prevention program for adolescents. J Med Internet Res. 2017 Feb 16;19(2):e44. doi: 10.2196/jmir.7174. PMID: 28209560. **Exclusion reason: comparison not appropriate**.

69. Kong G, Larsen H, Cavallo DA, et al. Re-training automatic action tendencies to approach cigarettes among adolescent smokers: a pilot study. Am J Drug Alcohol Abuse. 2015;41(5):425-32. doi: 10.3109/00952990.2015.1049492. PMID: 26186485. **Exclusion reason: wrong setting**.

70. Krist L, Lotz F, Burger C, et al. Long-term effectiveness of a combined student-parent and a student-only smoking prevention intervention among 7th grade school children in Berlin, Germany. Addiction. 2016 Dec;111(12):2219-29. doi: 10.1111/add.13537. PMID: 27447693. **Exclusion reason: wrong setting**.

71. Larsen H, Kong G, Becker D, et al. Cognitive bias modification combined with cognitive behavioral therapy: a smoking cessation intervention for adolescents. Drug Alcohol Depend. 2015;146(14):e168. doi: 10.1016/j.drugalcdep.2014.09.374. **Exclusion reason: wrong publication type**.

72. Leischow SJ, Muramoto ML, Matthews E, et al. Adolescent smoking cessation with bupropion: the role of adherence. Nicotine Tob Res. 2016 May;18(5):1202-5. doi: 10.1093/ntr/ntv179. PMID: 26567274. **Exclusion reason: followup less than 6 months**.

73. Levine MD, Cheng Y, Marcus MD, et al. Preventing postpartum smoking relapse: a randomized clinical trial. JAMA Internal Medicine. 2016 Apr;176(4):443-52. doi: 10.1001/jamainternmed.2016.0248. PMID: 26998789. **Exclusion reason: population not applicable**.

74. Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. Cochrane Database Syst Rev. 2015 Mar 02(3):CD006936. doi: 10.1002/14651858.CD006936.pub3. PMID: 25726920. **Exclusion reason: population not applicable**.

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75. Lovato C, Watts A, Brown KS, et al. School and community predictors of smoking: a longitudinal study of Canadian high schools. Am J Public Health. 2013 Feb;103(2):362-8. doi: 10.2105/AJPH.2012.300922. PMID: 23237165. **Exclusion reason: wrong study design**.

76. Luh DL, Chen HH, Yen AM, et al. Effect of self-reported home smoking restriction on smoking initiation among adolescents in Taiwan: a prospective cohort study. BMJ Open. 2015 Jun 26;5(6):e007025. doi: 10.1136/bmjopen-2014-007025. PMID: 26116613. **Exclusion reason: wrong study design**.

77. Luna-Adame M, Carrasco-Gimenez TJ, Rueda-Garcia Mdel M. Evaluation of the effectiveness of a smoking prevention program based on the 'Life Skills Training' approach. Health Educ Res. 2013 Aug;28(4):673-82. doi: 10.1093/her/cyt061. PMID: 23784075. **Exclusion reason: wrong setting**.

78. Ly C. The Texas Tobacco Prevention Program (T2P 2): An Update of the Minnesota Smoking Prevention Program (MSPP) [dissertation]. Houston: Texas Medical Center Dissertations (via ProQuest); 2015. **Exclusion reason: wrong setting**

79. Mall ASK, Bhagyalaxmi A. An informal school-based, peer-led intervention for prevention of tobacco consumption in adolescence: a cluster randomized trial in rural Gandhinagar. Indian J Community Med. 2017 Jul-Sep;42(3):143-6. doi: 10.4103/ijcm.IJCM_25_16. PMID: 28852276. **Exclusion reason: wrong setting**.

80. Marsiglia FF, Kulis SS, Booth JM, et al. Long-term effects of the keepin' it REAL model program in Mexico: substance use trajectories of Guadalajara middle school students. J Prim Prev. 2015 Apr;36(2):93-104. doi: 10.1007/s10935-014-0380-1. PMID: 25416154. **Exclusion reason: wrong setting**.

81. Mason M, Mennis J, Way T, et al. Real-time readiness to quit and peer smoking within a text message intervention for adolescent smokers: modeling mechanisms of change. J Subst Abuse Treat. 2015 Dec;59:67-73. doi: 10.1016/j.jsat.2015.07.009. PMID: 26297323. **Exclusion reason: wrong outcome**.

82. Mason M, Mennis J, Way T, et al. Text message delivered peer network counseling for adolescent smokers: a randomized controlled trial. J Prim Prev. 2016 Oct;37(5):403-20. doi: 10.1007/s10935-016-0439-2. PMID: 27388626. **Exclusion reason: wrong outcome**.

83. Mason MJ, Campbell L, Way T, et al. Development and outcomes of a text messaging tobacco cessation intervention with urban adolescents. Subst Abus. 2015;36(4):500-6. doi: 10.1080/08897077.2014.987946. PMID: 25551337. **Exclusion reason: wrong outcome**.

84. Masood M, Masood Y, Md Sabri BA, et al. Within-family discussion on harmful effects of smoking and intention to initiate smoking among European adolescents. J Addict Med. 2015 Jul-Aug;9(4):261-5. doi: 10.1097/ADM.0000000000000127. PMID: 26241085. **Exclusion reason: wrong outcome**.

85. Mata HJ. Development and evaluation of a personalized normative feedback intervention for Hispanic youth at high risk of smoking [dissertation]. El Paso: ETD Collection for University of Texas, El Paso; 2011. **Exclusion reason: followup less than 6 months**

Appendix A4. List of Excluded Studies

86. Matias MA, Steindl SR, Plonka KA, et al. Do school based anti-smoking campaigns delivered by oral health therapists work? Aust Dent J. 2013 Sep;58(3):301-5. doi: 10.1111/adj.12078. PMID: 23981210. **Exclusion reason: wrong study design**.

87. Matthews AK, Li CC, Kuhns LM, et al. Results from a community-based smoking cessation treatment program for LGBT smokers. J Environ Public Health. 2013;2013:984508. doi: 10.1155/2013/984508. PMID: 23840237. **Exclusion reason: population not applicable**.

88. Matthews AK, McConnell EA, Li CC, et al. Design of a comparative effectiveness evaluation of a culturally tailored versus standard community-based smoking cessation treatment program for LGBT smokers. BMC Psychol. 2014;2(1):12. doi: 10.1186/2050-7283-2-12. PMID: 25566383. **Exclusion reason: population not applicable**.

89. McClure EA, Baker NL, Gray KM. Cigarette smoking during an N-acetylcysteine-assisted cannabis cessation trial in adolescents. Am J Drug Alcohol Abuse. 2014 Jul;40(4):285-91. doi: 10.3109/00952990.2013.878718. PMID: 24720376. **Exclusion reason: intervention not appropriate**.

90. Mercken L, Moore L, Crone M, et al. The effectiveness of school-based smoking prevention interventions among low- and high-SES European teenagers. Health Educ Res. 2012 Jun;27(3):459-69. doi: 10.1093/her/cys017. PMID: 22350193. **Exclusion reason: wrong setting**.

91. Minary L, Cambon L, Martini H, et al. Efficacy of a smoking cessation program in a population of adolescent smokers in vocational schools: a public health evaluative controlled study. BMC Public Health. 2013 Feb 18;13:149. doi: 10.1186/1471-2458-13-149. PMID: 23418994. **Exclusion reason: wrong setting**.

92. Mohammed M, Eggers SM, Alotaiby FF, et al. Effects of a randomized controlled trial to assess the six-months effects of a school based smoking prevention program in Saudi Arabia. Prev Med. 2016 Sep;90:100-6. doi: 10.1016/j.ypmed.2016.06.032. PMID: 27386742. **Exclusion reason: wrong setting**.

93. Patten CA, Fadahunsi O, Hanza MM, et al. Tobacco cessation treatment for Alaska native adolescents: group randomized pilot trial. Nicotine Tob Res. 2014 Jun;16(6):836-45. doi: 10.1093/ntr/ntu004. PMID: 24532352. **Exclusion reason: wrong setting**.

94. Patten CA, Hughes CA, Lopez KN, et al. Web-based intervention for adolescent nonsmokers to help parents stop smoking: a pilot feasibility study. Addict Behav. 2012 Jan;37(1):85-91. PMID: 21955873. **Exclusion reason: population not applicable**.

95. Pbert L, Druker S, Flint AJ, et al. Perspectives in implementing a pragmatic pediatric primary care-based intervention trial. Am J Prev Med. 2015 Sep;49(3 Suppl 2):S200-7. doi: 10.1016/j.amepre.2015.03.037. PMID: 26296555. **Exclusion reason: wrong study design**.

96. Perez-Milena A, Navarrete-Guillen AB, Mesa-Gallardo MI, et al. Efficiency of two motivational interventions for adolescent smokers (brief and intensive) conducted in high schools. Adicciones. 2012;24(3):191-200. doi: 10.20882/adicciones.90. **Exclusion reason: non-English language**.

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97. Perry CL, Maccoby N, McAlister. Adolescent smoking prevention: a third year follow-up. World smoking & health. 1980;5:40-5. **Exclusion reason: wrong study design**.

98. Peterson AV, Jr., Kealey KA, Mann SL, et al. Group-randomized trial of a proactive, personalized telephone counseling intervention for adolescent smoking cessation. J Natl Cancer Inst. 2009 Oct 21;101(20):1378-92. doi: 10.1093/jnci/djp317. PMID: 19822836. **Exclusion reason: intervention not appropriate**.

99. Peterson AV, Jr., Marek PM, Kealey KA, et al. Does effectiveness of adolescent smoking-cessation intervention endure into young adulthood? 7-year follow-up results from a group-randomized trial. PLoS ONE [Electronic Resource]. 2016;11(2):e0146459. doi: 10.1371/journal.pone.0146459. PMID: 26829013. **Exclusion reason: intervention not appropriate**.

100. Primack BA, Douglas EL, Land SR, et al. Comparison of media literacy and usual education to prevent tobacco use: a cluster-randomized trial. J Sch Health. 2014 Feb;84(2):106-15. doi: 10.1111/josh.12130. PMID: 25099425. **Exclusion reason: wrong setting**.

101. Prochaska JJ, Fromont SC, Ramo DE, et al. Gender differences in a randomized controlled trial treating tobacco use among adolescents and young adults with mental health concerns. Nicotine Tob Res. 2015 Apr;17(4):479-85. doi: 10.1093/ntr/ntu205. PMID: 25762759. **Exclusion reason: population not applicable**.

102. Raja M, Saha S, Mohd S, et al. Cognitive behavioural therapy versus basic health education for tobacco cessation among tobacco users: a randomized clinical trial. J Clin Diagn Res. 2014;8(4):ZC47–ZC9. doi: 10.7860/JCDR/2014/8015.4279. **Exclusion reason: followup less than 6 months**.

103. Ramo DE, Thrul J, Chavez K, et al. Feasibility and quit rates of the Tobacco Status Project: a Facebook smoking cessation intervention for young adults. J Med Internet Res. 2015 Dec 31;17(12):e291. doi: 10.2196/jmir.5209. PMID: 26721211. **Exclusion reason: population not applicable**.

104. Reynolds B, Harris M, Slone SA, et al. A feasibility study of home-based contingency management with adolescent smokers of rural Appalachia. Exp Clin Psychopharmacol. 2015 Dec;23(6):486-93. doi: 10.1037/pha0000046. PMID: 26280592. **Exclusion reason: wrong setting**.

105. Richmond R, Indig D, Butler T, et al. A randomized controlled trial of a smoking cessation intervention conducted among prisoners. Addiction. 2013 May;108(5):966-74. doi: 10.1111/add.12084. PMID: 23228222. **Exclusion reason: population not applicable**.

106. Riesch SK, Brown RL, Anderson LS, et al. Strengthening families program (10-14): effects on the family environment. West J Nurs Res. 2012 Apr;34(3):340-76. doi: 10.1177/0193945911399108. PMID: 21403057. **Exclusion reason: wrong setting**.

107. Saraf DS, Gupta SK, Pandav CS, et al. Effectiveness of a school based intervention for prevention of non-communicable diseases in middle school children of rural North India: a randomized

controlled trial. Indian J Pediatr. 2015 Apr;82(4):354-62. doi: 10.1007/s12098-014-1562-9. PMID: 25209052. **Exclusion reason: wrong setting**.

108. Scherphof CS, van den Eijnden RJ, Lugtig P, et al. Adolescents' use of nicotine replacement therapy for smoking cessation: predictors of compliance trajectories. Psychopharmacology (Berl). 2014 Apr;231(8):1743-52. doi: 10.1007/s00213-014-3511-8. PMID: 24595505. **Exclusion reason: followup less than 6 months**.

109. Schinke SP, Gilchrist LD, Snow WH. Skills intervention to prevent cigarette smoking among adolescents. Am J Public Health. 1985;75(6):665-7. PMID: 4003636. **Exclusion reason: wrong setting**.

110. Schinke SP, Gilchrist LD, Snow WH, et al. Skills-building methods to prevent smoking by adolescents. J Adolesc Health Care. 1985;6(6):439-44. PMID: 4055463. **Exclusion reason: wrong setting**.

111. Schuck K, Otten R, Kleinjan M, et al. Predictors of cessation treatment outcome and treatment moderators among smoking parents receiving quitline counselling or self-help material. Prev Med. 2014 Dec;69:126-31. doi: 10.1016/j.ypmed.2014.09.014. PMID: 25278424. **Exclusion reason: population not applicable**.

112. Sharifirad GR, Eslami AA, Charkazi A, et al. The effect of individual counseling, line follow-up, and free nicotine replacement therapy on smoking cessation in the samples of Iranian smokers: examination of transtheoretical model. J Res Med Sci. 2012;17(12):1128-36. PMID: 23853630. **Exclusion reason: population not applicable**.

113. Shi HJ, Jiang XX, Yu CY, et al. Use of mobile phone text messaging to deliver an individualized smoking behaviour intervention in Chinese adolescents. J Telemed Telecare. 2013 Jul;19(5):282-7. doi: 10.1177/1357633X13495489. PMID: 24163238. **Exclusion reason: followup less than 6 months**.

114. Simon P, Connell C, Kong G, et al. Self-efficacy mediates treatment outcome in a smoking cessation program for adolescent smokers. Drug Alcohol Depend. 2014;146(14). **Exclusion reason: comparison not appropriate**.

115. Sims TH, McAfee T, Fraser DL, et al. Quitline cessation counseling for young adult smokers: a randomized clinical trial. Nicotine Tob Res. 2013 May;15(5):932-41. doi: 10.1093/ntr/nts227. PMID: 23080378. **Exclusion reason: population not applicable**.

116. Skarstrand E, Sundell K, Andreasson S. Evaluation of a Swedish version of the Strengthening Families Programme. Eur J Public Health. 2014 Aug;24(4):578-84. doi: 10.1093/eurpub/ckt146. PMID: 24078373. **Exclusion reason: wrong setting**.

117. Skov-Ettrup LS, Ringgaard LW, Dalum P, et al. Comparing tailored and untailored text messages for smoking cessation: a randomized controlled trial among adolescent and young adult smokers. Health Educ Res. 2014 Apr;29(2):195-205. doi: 10.1093/her/cyt112. PMID: 24399268. **Exclusion reason: population not applicable**.

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118. Stamm-Balderjahn S, Groneberg DA, Kusma B, et al. Smoking prevention in school students: positive effects of a hospital-based intervention. Deutsches Arzteblatt International. 2012 Nov;109(44):746-52. doi: 10.3238/arztebl.2012.0746. PMID: 23189108. **Exclusion reason: wrong setting**.

119. Stotts AL, Green C, Northrup TF, et al. Feasibility and efficacy of an intervention to reduce secondhand smoke exposure among infants discharged from a neonatal intensive care unit. J Perinatol. 2013 Oct;33(10):811-6. doi: 10.1038/jp.2013.43. PMID: 23619375. **Exclusion reason: population not applicable**.

120. Stucki S, Kuntsche E, Archimi A, et al. Does smoking within an individual's peer group affect intervention effectiveness? An evaluation of the Smoke-Free Class Competition among Swiss adolescents. Prev Med. 2014 Aug;65:52-7. doi: 10.1016/j.ypmed.2014.04.018. PMID: 24786759. **Exclusion reason: wrong setting**.

121. Sussman S, Sun P, Rohrbach LA, et al. One-year outcomes of a drug abuse prevention program for older teens and emerging adults: evaluating a motivational interviewing booster component. Health Psychol. 2012 Jul;31(4):476-85. doi: 10.1037/a0025756. PMID: 21988096. **Exclusion reason: wrong setting**.

122. Tahlil T, Woodman RJ, Coveney J, et al. Six-months follow-up of a cluster randomized trial of school-based smoking prevention education programs in Aceh, Indonesia. BMC Public Health. 2015 Oct 24;15:1088. doi: 10.1186/s12889-015-2428-4. PMID: 26499860. **Exclusion reason: wrong setting**.

123. Tewari A, Bassi S, Stigler MH, et al. Innovative intervention strategy for tobacco control in low SES communities in Delhi: Project ACTIVITY. Respir Med. 2013;107(10). **Exclusion reason: wrong setting**.

124. Thrul J, Buhler A, Herth FJ. Prevention of teenage smoking through negative information giving, a cluster randomized controlled trial. Drugs (Abingdon Engl). 2014 Feb;21(1):35-42. doi: 10.3109/09687637.2013.798264. **Exclusion reason: followup less than 6 months**.

125. Tingen MS, Andrews JO, Heath J, et al. Tailored Parental Cessation Delivered Concurrently with Tobacco Prevention in Children Enrolled in Urban and Rural Southern Elementary Schools. Proceedings of the Eighth AACR Conference on The Science of Health Disparities in Racial/Ethnic Minorities and the Medically Underserved; 2015 Nov 13-16; Atlanta. Philadelphia: AACR; Cancer Epidemiol Biomarkers Prev; 2016. **Exclusion reason: wrong publication type**

126. Tuisku A, Salmela M, Nieminen P, et al. Varenicline and nicotine patch therapies in young adults motivated to quit smoking: a randomized, placebo-controlled, prospective study. Basic Clin Pharmacol Toxicol. 2016 Jul;119(1):78-84. doi: 10.1111/bcpt.12548. PMID: 26709238. **Exclusion reason: population not applicable**.

127. Vandenbergh DJ, Schlomer GL, Cleveland HH, et al. An Adolescent Substance Prevention Model Blocks the Effect of CHRNA5 Genotype on Smoking During High School. Nicotine Tob Res.

2016 Feb;18(2):212-20. doi: 10.1093/ntr/ntv095. PMID: 25941207. **Exclusion reason: wrong setting**.

128. Wang Y, Storr CL, Green KM, et al. The effect of two elementary school-based prevention interventions on being offered tobacco and the transition to smoking. Drug Alcohol Depend. 2012 Jan;120(1-3):202-8. doi: 10.1016/j.drugalcdep.2011.07.022. PMID: 21868176. **Exclusion reason: wrong setting**.

129. Weichold K, Tomasik MJ, Silbereisen RK, et al. The effectiveness of the life skills program IPSY for the prevention of adolescent tobacco use: the mediating role of yielding to peer pressure. The Journal of Early Adolescence. 2016 Oct;36(7):881-908. doi: 10.1177/0272431615589349. **Exclusion reason: wrong setting**.

130. Xavier LEDF, Bernardes-Souza B, Lisboa OC, et al. A medical student-delivered smoking prevention program, Education Against Tobacco, for secondary schools in Brazil: study protocol for a randomized trial. JMIR Research Protocols. 2017 Jan 30;6(1):e16. doi: 10.2196/resprot.7134. PMID: 28137703. **Exclusion reason: wrong publication type**.

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to treat analysis for RCTs

Definition of ratings based on above criteria:
Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.
Fair: Studies are graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is used for RCTs.
Poor: Studies are graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs

Appendix A6. Expert Reviewers of the Draft Report

- Jonathan D. Klein, MD, MPH, Professor and Senior Associate Head (Chair) of the Department of Pediatrics at the University of Illinois at Chicago
- Suzanne M. Colby, PhD, Professor in Psychiatry and Human Behavior and Behavioral and Social Sciences at Brown University
- Kelvin Choi, PhD, MPH, National Institute on Minority Health and Health Disparities at the National Institutes of Health
- Alberta Becenti, MPH, Indian Health Service Health Promotion and Disease Prevention Coordinator
- Nazleen Bharmal, MD, PhD, U.S. Department of Health and Human Services - Surgeon General's Office
- Brandy Peaker, MD, MPH, Centers for Disease Control and Prevention

Note: Reviewers provided comments on a prior version of the draft report and may or may not agree with the report findings

Appendix B1. Quality Assessment Table

Trial	Adequate randomization	Adequate allocation concealment	Similar groups at baseline	Specified eligibility criteria	Masked outcome assessors	Masked care provider	Masked patient	Reported attrition and withdrawals	Differential /high loss to followup	People analyze in groups they were randomized	Quality
Ausems, 2002[45]	Uncertain	NR	Yes	No	NR	NA	NA	Yes	No/No	Yes	Fair
Bauman, 2002[47] Bauman, 2000[46]	NR	Yes	NR	Yes	Uncertain	NA	NA	Yes	Yes/No	Yes	Fair
Colby, 2005[49]	NR	NR	Yes	Yes	Yes	NA	NA	Yes, not per group	NR/No	Yes	Fair
Colby, 2012[50]	Yes	Yes	No	Yes	Yes	NA	NA	Yes	No/No	Yes	Fair
Cremers, 2015[51]	Yes	NR	Yes	Yes	NA/NR	NA/NR	NR	Yes	Yes/Yes	Yes	Fair
Curry, 2003[52]	Uncertain	NR	Yes	Yes	NR	NA	NA	Yes	No/No	Yes	Fair
Fidler, 2001[53]	No	No	NR	Yes	NR	NA	NA	Yes	No/Yes	Yes	Fair
Gray, 2011[54]	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	Fair
Haggerty, 2007[55]	NR	NR	Yes	Yes	NR	NA	NA	Yes	No/No	Yes	Fair
Haug, 2013[56]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	Fair
Hiemstra, 2014[57]	Yes	Unclear	No	Yes	No	No	Yes	Yes	No/No	Yes	Fair
Hollis, 2005[58]	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	No/No	Yes	Good
Hovell, 1996[59]	Yes	NR	Yes	Yes	NR	NA	NA	Yes	No/No	Yes	Good
Jackson, 2006[62]	NR	Yes	NR	Yes	Adequate	NA	NA	Yes, not per group	NR/No	Yes	Fair
Kentala, 1999[64] Saari, 2012[73]	No	NR	NR	Yes	NR	NA	NA	Yes	No/Yes	Yes	Fair
Killen, 2004[65]	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	Fair
Lando, 2007[66]	Yes	NR	NR	Yes	NR	NA	NA	Yes	No/Yes	Yes	Fair
Muramoto, 2007[67]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	Fair
Pbert, 2008[69]	NR	Yes	Yes	Yes	NR	Yes	Yes	Yes	No/No	Yes	Fair
Pbert, 2011[68]	Yes	Yes	Yes	Yes	NR	NA	Unclear	Yes	No/No	Yes	Good

Appendix B1. Quality Assessment Table

Trial	Adequate randomization	Adequate allocation concealment	Similar groups at baseline	Specified eligibility criteria	Masked outcome assessors	Masked care provider	Masked patient	Reported attrition and withdrawals	Differential /high loss to followup	People analyze in groups they were randomized	Quality
Prado, 2007[70]	Yes	Un	Yes	Yes	Yes	NA	NA	Yes	No/No	Yes	Fair
Redding, 2015[71]	Yes	Yes	NR	Yes	Yes	NR	NR	Yes	No/Yes	No	Fair
Robling, 2016[72]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No/Yes	Yes	Fair
Scherphof, 2014[74]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Schuck, 2015[75]	Yes	Unclear	Yes	Yes	Unclear/NR	No	No	Yes	No/No	Yes	Fair
Stevens, 2002[76]	Yes	NR	Yes	Yes	NR	NA	NA	Yes	No/No	Yes	Good

Abbreviations: NA=not applicable; NR=not reported.

Appendix B2. Behavioral Intervention Details

Focus	Trial, quality	Behavioral intervention description	Behavioral intervention duration	Primary smoking outcome
Prevention only	Ausems, 2002[45] Fair	3 tailored newsletters mailed at 3-week intervals addressed to the student. Included essential components of successful social influence programs. Contents of letters were individualized. The first letter contained information regarding students' beliefs about smoking and the short-term consequences of smoking. The second letter focused on the influence of the social environment and intentions to not smoke in the future. The third letter described refusal techniques and included an exercise about cigarette refusal.	3 newsletters mailed at 3-week intervals (Intervention ran from November 1997 to early February 1998).	% of baseline nonsmokers (not even one puff) reporting ever smoking or smoking in the past 30 days at posttest
	Cremers, 2015[51] Fair	Personalized log-in codes to access Fun without Smokes website. Website contained smoking and nonsmoking information, games concerning nonsmoking, web-based questionnaire, and computer-tailored feedback messages. Received 3 computer-tailored feedback messages based on info children provided in Web-based questionnaire on 3 consecutive days via email as a PDF file and also available on the website. Aim was to repeatedly expose children to nonsmoking information during the course of the year in addition to the feedback messages.	No Prompt Group: received messages on 3 consecutive days via email. They could reuse the website but were not prompted to do so Prompt Group: received messages on 3 consecutive days via email, and 6 prompt messages via email or SMS every year to encourage them to reuse the Fun without Smokes website.	% smoking initiation
	Curry, 2003[52] Fair	5 intervention components addressed important individual, interpersonal, and environmental factors known to influence the smoking onset process: the child's attitudes, beliefs, and knowledge; dispositional factors such as high risk taking; the beliefs, attitudes, and behaviors of parents and peers; and tobacco marketing and availability. Families received a packet with materials for parents and children and a video with viewing guide. Parents received two counseling telephone calls and a mailed newsletter. Parent handbook provided information to encourage, motivate, and reinforce parent-child communication about tobacco. Children's packet included a pen and stickers with antitobacco messages and a comic book that described the dangers of tobacco, advertising deceptiveness, and how to resist peer pressure to smoke. Could receive motivational message during any routine primary care appointments. (22% of IG and 15% of CG said their provider discussed tobacco with their child; 17% of IG and 3% of CG said the provider mentioned the Steering Clear project.)	One counseling call 3 to 6 weeks after receipt of written materials, additional call 14 months after enrollment. 28-minute video.	% of full sample* reporting smoking (even a puff) in past 30 days at posttest

Appendix B2. Behavioral Intervention Details

Focus	Trial, quality	Behavioral intervention description	Behavioral intervention duration	Primary smoking outcome
	Fidler, 2001[53] Fair	Age-related materials about the advantages of remaining a nonsmoker. Some materials addressed other smoking-related issues and only incidentally referred to the dangers and health effects of smoking. Sent certificates affirming their nonsmoking decision and status and were encouraged to contact the project team if they wished.	4 mailings over 12 months.	% of full sample reporting "starting to smoke" at posttest (specific measure NR)
	Haggerty, 2007[55] Fair	Universal substance abuse and problem behavior preventive intervention for families (at least one parent and their teen together) including parenting, youth, and family components. The workbook includes the following components: roles (relating to your teen), risks (identifying and reducing them), protection (bonding with your teen to strengthen resilience), tools (working with your family to solve problems), involvement (allowing everyone to contribute), policies (setting family policies on health and safety issues), and supervision (supervising without invading).	IG1: Completed activities at home within 10 weeks. Contacted by phone once per week. IG2: Seven group and family sessions over 7 weeks, 2.5 hours for sessions 1, 4, and 7; 2 hours for sessions 2, 3, 5, and 6. Home practice encouraged.	% of baseline nonsmokers (specific measure NR) reporting initiating smoking postintervention (specific measure NR)
Prevention only	Hiemstra, 2014[57] Fair	Based on the U.S. version of Smoke-free Kids. Concentrates on stimulating antismoking socialization within families in order to prevent children from smoking. Each module dealt with different socialization constructs and included different assignments, such as games and scripted role-plays, to gradually increase parental skills and comfort in communicating with children about smoking, addictions, and expectations regarding abstinence. Each module also included a communication sheet for mothers, providing background information about the subjects discussed in the modules and communication tips for mothers.	Families received 5 printed activity modules by mail at 4-week intervals. A booster module was delivered 12-months post-baseline.	% who initiated smoking
	Hovell, 1996[59] Good	Staff created a tobacco-free environment by formalizing a nonsmoking office policy, removing tobacco ads, discontinuing magazines with such ads, and displaying tobacco prevention information. Patients received antitobacco "prescriptions" with a specific antitobacco message preprinted on the form (topics: announcement of tobacco-free office, tobacco advertising, tobacco and sports, smokeless tobacco, nicotine and tobacco addiction, passive smoking, tobacco and teeth, and negative consequences of tobacco use), a space for their name to be filled in, and a place to sign the prescription. Assume there was also a brief counseling session with the orthodontist.	0 to >7 prescriptions delivered individually over 2 years.	% of baseline nonusers (no 30-day tobacco use or having ever used tobacco more than 100 times)† reporting tobacco use in the past 30 days at posttest
	Jackson, 2006[62] Fair	Participants received 5 core activity guides mailed to their homes at approximate 2-week intervals (1 additional booster guide was received 1 year after baseline). Delivery of newsletters, tip sheets, and incentives was timed as appropriate to complement or reinforce each program guide.	5 activity guides mailed at 2-week intervals; 1 booster guide received 1 year after baseline.	% of full sample reporting ever smoking (even a puff) at posttest

Appendix B2. Behavioral Intervention Details

Focus	Trial, quality	Behavioral intervention description	Behavioral intervention duration	Primary smoking outcome
Cessation only	Colby, 2005[49] Fair	Motivational interviewing. Pros and cons of smoking and quitting, highlighted ambivalence and identified salient aspects of smoking. Personalized feedback sheet that summarized information from baseline assessment. Corrective normative feedback; personalized information about health effects, CO, and dependence level; and financial costs. Detailed action plan, anticipation of barriers, strategizing methods to overcome barriers. Enhanced self-efficacy. Same handouts as CG, feedback sheet, goal sheet, and information about strategies for quitting and coping with withdrawal. Telephone booster call to reinforce initial progress toward goals, emphasized personal choice for change, discussed coping skills and problem-solving, and promoted self-efficacy.	1 baseline session (35 minutes); 1 15- to 20-minute telephone booster session at 1 week.	% of full sample reporting 7-day abstinence at posttest
	Colby, 2012[50] Fair	Same intervention as Colby 2005. One motivational interviewing session plus one booster phone call, as well as print materials. Additional component where parents of intervention participants were asked to participate in one session that focused on increasing parent support for the adolescent's goals for changing smoking, increasing clear communication, and establishing home smoking rules. Parents in both conditions were mailed informational materials on helping adolescents quit smoking.	One baseline session (45 minutes), one 15- to 20-minute telephone booster session at 1 week, and one 15- to 20-minute discussion with parents.	% of full sample reporting 7-day abstinence and biochemically confirmed expired CO <9 ppm and saliva cotinine <14 ng/mL
Cessation only	Haug, 2013[56] Fair	Online assessment of individual smoking behavior and attitudes toward smoking (assessed outcome expectancies of smoking cessation, situations or circumstances in which craving usually occurs, alternative strategies to handle craving situations, and costs per cigarette pack), a weekly SMS text message assessment of smoking-related target behaviors (based on Health Action Process Approach stage and included CBT and motivational components), 2 weekly text messages individually tailored to the data of the online and the SMS text message assessments (tailored to HAPA stage), and an integrated quit day preparation and relapse-prevention program (for those in the preparation and action stages).	Weekly SMS text message assessments. Those in either of the preparation and action stages were informed biweekly about the quit date preparation messaging option. If a quit date was entered, the program provided up to 2 daily text messages to prepare for quit date and prevent relapse after.	% 7-day abstinence rate at posttest

Appendix B2. Behavioral Intervention Details

Focus	Trial, quality	Behavioral intervention description	Behavioral intervention duration	Primary smoking outcome
	Pbert, 2011[68] Good	Based on the 5A model and adapted to be developmentally appropriate for adolescents. Advised the student to stop smoking. Assessed motivation to quit. Assisted the adolescent to quit by addressing pros/cons of smoking, personal reasons for quitting, anticipated problems, previous quit attempts, nicotine addiction, quit methods, setting a quit date, triggers, and strategies. Assisted the adolescent to quit by addressing managing triggers, handling social situations, withdrawal symptoms and their management, managing cravings, managing stress, minimizing weight gain, gaining support, taking control of one's environment, and rewarding oneself. Assisted in maintaining abstinence if the adolescent quit. Nurse asked open-ended questions to actively engage adolescent.	Weekly private one-on-one sessions for 4 weeks (2 30-minute).	% full sample reporting 30-day abstinence at posttest
	Schuck, 2015[75] Fair	Parent telephone counseling by Dutch national quit line, 3 didactic booklets entitled Smoke-free Parents. If smoked >10 cigarettes, NRT was recommended but not provided.	Up to 7 sessions in 3 month period.	% who initiated smoking (even just one puff)
Cessation only (medication)	Killen, 2004[65] Fair	Both IG and CG received the behavioral intervention. Group-based skills training. Groups met weekly and were supervised by trained counselors. Counselors demonstrated the use of specific, concrete, self-regulatory skills for coping with risky situations without resorting to smoking and helped participants develop action plans to promote nonsmoking in self-identified, high-risk situations. (Medication: IG: 150 mg bupropion + NRT; CG: placebo + NRT).	Weekly group sessions (~8 participants/group) for 10 weeks (assumed), 45 minutes each.	% of full sample reporting 7-day abstinence (not even a puff) and biochemically confirmed saliva cotinine level <20 ng/mL at posttest
	Muramoto, 2007[67] Fair	Both IG and CG received the behavioral intervention. Brief individual counseling sessions standardized to address a series of topics addressing teaching skills related to changing smoking behaviors (e.g., identifying social support, identifying motivations and barriers to quitting, recognition of triggers for smoking, management of nicotine craving and withdrawal symptoms, and stress management). Telephone number for state quit line provided for additional behavioral support. (Medication: IG1: 150 mg bupropion; IG2: 300 mg bupropion; CG: placebo)	Seven individual sessions over 7 weeks, 10- to 20-minutes each.	% of baseline smokers (≥6 cigarettes per day, exhaled CO level ≥10 ppm, ≥2 previous quit attempts, and were motivated to quit) reporting 7-day abstinence at posttest
	Scherphof, 2014[74] Good	75 minute informational meeting to obtain background information of the participant (e.g. smoking behavior, attitudes concerning smoking, and factors related to smoking [cessation]). Participants also received (a) information about the study, (b) a short behavioral intervention aiming at quitting smoking (e.g. preparations and expectations) and (c) instructions for the use of NRT.	1 informational meeting.	% of baseline smokers reporting 4 week abstinence at posttest

Appendix B2. Behavioral Intervention Details

Focus	Trial, quality	Behavioral intervention description	Behavioral intervention duration	Primary smoking outcome
Combined prevention and cessation	Bauman, 2000[46] Bauman, 2001[48] Bauman, 2002[47] Fair	Successive mailings of four booklets and health educator telephone discussions with parents 2 weeks after each mailing. Booklets focused on family motivation to participate and engage, family characteristics known to influence adolescents not specific to alcohol and tobacco use, tobacco- and alcohol-specific predictors that originate in the family, and predictors that originate outside the family. Booklets all had specific activities to reinforce content that the families completed on their own. Health educators encouraged participation of all family members, answered parents' questions, and recorded information. Adolescent was reached through family members and was not contacted directly by health educator.	4 booklets and related activities completed by family members over 15 weeks (total time ~4 hours and 25 minutes), ~8 phone calls with health educator over 15 weeks discussing program and completing standard protocol (total time ~57.5 minutes per family); for families that completed all four units, it required an average of nearly 6 months (173.2 days [SD, 71.3]) between booklet one and completion of the fourth unit.	% of full sample reporting ever smoking (even one puff) at posttest **Prevention:** % of baseline nonsmokers (not ever smoking, even one puff) reporting ever smoking (even one puff) at posttest **Cessation:** % of baseline smokers (≥1 days in the past 30 days) reporting having smoked ≥1 days in past 30 days at posttest
	Hollis, 2005[58] Good	Teen Reach (Research Approaches to Cancer in a Health Maintenance Organization). Staff provided primary care clinicians with a 30- to 60-second suggested advice message to encourage teens to stop smoking or to not start. Clinicians were asked to encourage the patient to talk briefly with a health counselor immediately after the visit. Teens had a 10- to 12-minute session on the computer with the PTC expert system, which assessed their stage of readiness to begin smoking or their stage of change to quit smoking and then delivered tailored advice and encouragement. The program included testimonial movies and graphics. Teens had 3 to 5 minutes of post-PTC motivational counseling. Handouts included a synopsis of stage-relevant advice and small quit kits. There were 2 booster sessions with the PTC and health counselor over the remaining 11 months.	1 30- to 60-second advice message from PCP; 1 to 3, 3- to 5-minute sessions with health counselor over 12 months; one 10- to 12-minute computer session.	% of full sample reporting smoking ≥1 cigarettes in the past 30 days at posttest‡ **Prevention:** % of baseline nonsmokers (no smoking in past 30 days) reporting smoking ≥1 cigarettes in the past 30 days at posttest‡ **Cessation:** % of baseline smokers (smoking ≥1 cigarettes in the past 30 days) reporting smoking ≥1 cigarettes in the past 30 days at posttest‡
	Kentala, 1999[64] Saari, 2012[73] Fair	Nonsmokers were given positive feedback regarding smoking abstinence. After the dental exam, all patients were shown photos showing effects of smoking on teeth. Smokers were given a mirror to assess signs of smoking on their own teeth. Smokers and nonsmokers received the usual dental exam.	Brief part of annual dental visit (only a couple minutes). Patients had 1 to 4 visits.	% of full sample reporting ever smoking (assumed) at posttest

Appendix B2. Behavioral Intervention Details

Focus	Trial, quality	Behavioral intervention description	Behavioral intervention duration	Primary smoking outcome
	Lando, 2007[66] Fair	Brief advice on smoking cessation and prevention during dental exam. Videos from the CDC and Massachusetts Department of Public Health. Motivational interviewing to either encourage cessation or encourage prevention. Brief supportive telephone calls.	60 seconds of advice from dental hygienist or dentist; one 15- to 20-minute session of motivational interviewing; 3 to 6 phone calls over 6 months (estimated 10 minutes per call).	% of full sample reporting smoking in past 30 days **Prevention:** % of baseline nonsmokers (never smoked but susceptible) and baseline former smokers (ever smoked, but not in past 30 days) reporting smoking in the past 30 days at posttest **Cessation:** % of baseline smokers (smoked in past 30 days) reporting smoking in past 30 days at posttest
Combined prevention and cessation	Pbert, 2008[69] Fair	Providers asked about smoking, advised cessation or continued abstinence, and referred the patient to a peer counselor. Peer counseling combined the 5A model with motivational interviewing and behavior change counseling.	Advice from the pediatrician given during normal clinic visit (assume brief). 15-30 minute session with peer counselor at the clinic. 4 10-minute phone calls over 21 weeks.	% of smokers (smoke "occasionally or regularly") and nonsmokers (never smoked or 1–2 puffs but not in the past year) not abstinent at posttest (specific measure NR) **Prevention:** % of baseline nonsmokers (never smoked or 1–2 puffs but not in the past year) abstinent at posttest (specific measure NR) **Cessation:** % of baseline smokers (smoke "occasionally or regularly") abstinent at posttest (specific measure NR)
	Prado, 2007[70] Fair	Providers asked about smoking, advised cessation or continued abstinence, and referred the patient to a peer counselor. Peer counseling combined the 5A model with motivational interviewing and behavior change counseling.	15 group sessions, 8 family visits, and 2 parent-adolescent circles. Approximately 49 hours over 1 year.	% of full sample reporting smoking in the past 90 days at posttest

Appendix B2. Behavioral Intervention Details

Focus	Trial, quality	Behavioral intervention description	Behavioral intervention duration	Primary smoking outcome
	Redding, 2015[71] Fair	Computer-delivered personalized feedback tailored to the participant's stage of readiness to use condoms consistently or stage of change for smoking acquisition (among nonsmokers) or smoking cessation (among smokers) followed by in-person counseling to discuss feedback. The intervention was designed to accelerate state progress among those in early stages of change or to prevent relapse among those further along. Scores for each behavior were calculated and generated immediate on-screen and print copies of reports to be discussed with their counselor at the end of the computer session.	During the 9-month intervention, participants could return to the clinic every 3 months for a total of 4 possible sessions that include both the computer-tailored feedback and in-person counseling. Each computer program took 20-30 minutes.	% who reached stage A or M (stopping smoking among those who smoke; initiating smoking among those who do not smoke)
	Robling, 2016[72] Fair	Family Nurse Partnership provided by specially recruited and trained family nurses with an aim of affecting risk and protective factors within prenatal health-related behaviors, sensitive and competent caregiving, and early parental life course.	64 structured home visits. Intervention takes place from early pregnancy until the child's 2nd birthday. On average, the intervention group received 39.28 visits from the Family Nurse Partnership program.	% who smoked at late pregnancy
	Stevens, 2002[76] Good	Dartmouth Prevention Cohort Study. Primary care clinician focused on alcohol and tobacco use. Discussed risks with the child and parent. Signed a contract that the family would talk about risks at home and develop a family policy about alcohol and tobacco. Family received signed letter by their clinician reinforcing the agreement and a refrigerator magnet to post the contract. Reminded of the importance of family communication regarding alcohol and tobacco at subsequent office visits for 36 months. Clinician's role was to provide risk behavior information, encourage family communication, and offer help. Brochure on effective communication. 12 newsletters for each of the parents and children mailed to reinforce messages. Biannual telephone calls.	1 baseline session with PCP; 24 newsletters over 36 months; 6 phone calls over 36 months; additional PCP encouragement if additional office visits.	% of full sample reporting ever smoked at posttest

*An estimated 1.2% of the sample had smoked in the past 30 days at baseline.
†Tobacco use includes the use of cigarettes, pipes, cigars, or smokeless tobacco.
‡Originally reported as the percentage of participants reporting no smoking; reversed for consistency.
Abbreviations: 5A=Ask, Advise, Assess, Assist, Arrange Followup; CDC=Centers for Disease Control and Prevention; CG=control group; CO=carbon monoxide; IG=intervention group; NR=not reported; NRT=nicotine replacement therapy; PCP=primary care practitioner; PDF=portable document format; PTC=Pathways to Change; SD=standard deviation; SMS=short message service.

Appendix C1. Meta-Regression Analysis

Study-level characteristic	Prevention P-value	Cessation P-value	Combination P-value
Univariate analysis			
Trial conducted in United States vs. Europe	0.542	0.936	*
Trial targets smoking vs. multiple behaviors	0.752	0.663	0.951
Trial targets parent	0.883	0.845	0.739
Trial targets youth	0.703	0.929	0.301
Role of primary care	0.094†	0.886	0.239
Use of single vs. multimodal intervention	**0.046**†	0.656	0.061†
Use of print materials in intervention	0.887	0.118†	0.644
Use of face-to-face counseling	0.290	0.961	0.241
Use of telephone counseling	0.750	0.452	0.081†
Use of computer counseling	0.535	0.206	0.180†
Use of motivational interviewing	0.684	0.672	0.672
Duration of intervention	0.198†	0.417	**0.047**†
Year of trial publication	0.140†	0.204	0.829
Prevention or cessation-only vs. combined trial	0.535	0.868	NA
Outcome 30-day point prevalence vs. NR or one puff	0.200†	0.694	0.892
NonWhite race	0.598	0.887	0.746
Number of contacts (visits, telephone calls, mailings)	0.232	0.849	0.436
Includes adjustment for proportion smoking in control group			
Trial conducted in United States vs. Europe	0.312	0.903	0.059†
Trial targets smoking vs. multiple behaviors	0.478	0.547	0.881
Trial targets parent	0.734	0.816	0.799
Trial targets youth	0.439	0.955	0.399
Role of primary care	0.186†	0.950	0.306
Use of single vs. multimodal intervention	**0.044**†	0.684	*
Use of print materials in intervention	0.793	0.120	0.058†
Use of face-to-face counseling	0.375	0.955	0.311
Use of telephone counseling	0.712	0.471	0.075†
Use of computer counseling	0.739	0.186†	0.182
Use of motivational interviewing	0.621	0.716	0.684
Duration of intervention	0.415	0.536	0.053†
Year of trial publication	0.070†	0.176†	0.722
Prevention-only vs. combined trial	0.733	0.774	NA
Outcome 30-day point prevalence vs. NR or one puff	0.486	0.431	0.715
NonWhite race	0.603	0.919	0.831
Number of contacts (visits, telephone calls, mailings)	**0.032**†	0.818	0.126†

*Model failed to converge

†Entered into backwards stepwise regression model

Abbreviations: NA=not applicable; NR=not reported.

Appendix C2. Stratified Effect Estimates for Smoking Prevention Interventions

Group 1 vs. group 2	k=# Studies; n=# Youth RR (95% CI) for Group 1	k=# Studies; n=# Youth RR (95% CI) for Group 2	Group 1 vs. group 2 p value
Prevention-only study vs. Combined study	k=8, n=17,895 0.83 (0.68 to 1.00)	k=5, n=3,805 **0.77 (0.64 to 0.91)**	p>0.05
U.S. studies vs. European studies	k=10; n=17,214 **0.83 (0.74 to 0.95)**	k=3; n=4,486 **0.71 (0.53 to 0.96)**	p>0.05
Intervention focused on smoking alone vs. Intervention included other behaviors (e.g., alcohol, sex)	k=10; n=20,330 **0.80 (0.69 to 0.93)**	k=3; n=1,370 0.83 (0.65 to 1.07)	p>0.05
Targeted parent vs. Did not target parent	k=6; n=7,168 **0.81 (0.66 to 0.99)**	k=7; n=14,532 **0.82 (0.71 to 0.92)**	p>0.05
Targeted youth vs. Did not target youth	k=11; n=20,360 **0.80 (0.69 to 0.92)**	k=2; n=1,340 0.84 (0.64 to 1.09)	p>0.05
Primary care had active role vs. Primary care had no role or recruitment only	k=4; n=10,179 0.87 (0.74 to 1.02)	k=8; n=7,958 **0.73 (0.62 to 0.86)**	p>0.05
Single mode of intervention delivery vs. Intervention delivered by multiple methods	k=5; n=6,239 **0.66 (0.53 to 0.82)**	k=8; n=15,461 **0.90 (0.82 to 0.99)**	**p<0.05**
Intervention included print materials vs. Intervention included no print materials	k=8; n=18,733 **0.81 (0.70 to 0.94)**	k=5, n=2,967 0.78 (0.53 to 1.15)	p>0.05
Intervention included face-to-face contact vs. Intervention included no face-to-face contact	k=6; n=10,751 0.91 (0.81 to 1.01)	k=7; n=10,979 **0.75 (0.64 to 0.88)**	p>0.05
Intervention included telephone contact vs. Intervention included no telephone contact	k=6; n=7,501 **0.82 (0.69 to 0.96)**	k=7; n=14,199 **0.77 (0.62 to 0.97)**	p>0.05
Intervention included use of computer vs. Intervention did not use a computer	k=3, n=4,076 **0.76 (0.60 to 0.97)**	k=10, n=17,624 **0.81 (0.70 to 0.95)**	p>0.05
Intervention included motivational interviewing vs. Intervention included no motivational interviewing	k=5; n=3,489 **0.77 (0.62 to 0.95)**	k=8; n=18,211 **0.82 (0.69 to 0.97)**	p>0.05
Duration of intervention at least 12 months vs. Duration of intervention shorter than 12 months	k=7; n=19,155 **0.79 (0.66 to 0.95)**	k=6; n=2,545 0.82 (0.66 to 1.02)	p>0.05
Proportion of females <53% vs. Proportion of females ≥53%	k=6; n=6,984 0.89 (0.72 to 1.09)	k=7; n=14,716 **0.76 (0.63 to 0.91)**	p>0.05
Age of participants < 14 years vs. Age of participants ≥ 14 years	k=7; n=8,930 **0.80 (0.67 to 0.96)**	k=5; n=10,558 0.90 (0.80 to 1.00)	p>0.05
Outcome 30-day point prevalence vs. Outcome even one puff	k=4; n=13,235 0.90 (0.78 to 1.04)	k=4; n=3,442 **0.74 (0.60 to 0.90)**	p>0.05
Nonwhite enrollment > 20% vs. Nonwhite enrollment ≤ 20%	k=6; n=11,662 **0.82 (0.70 to 0.97)**	k=4; n=3,751 0.65 (0.41 to 1.01)	p>0.05
Number of contacts (e.g., visits, phone calls, mailings) ≤ 6 vs. Number of contacts > 6	k=8, n=11,210 **0.74 (0.64 to 0.86)**	k=5; n=10,490 0.92 (0.83 to 1.03)	p>0.05

Abbreviations: CI=confidence interval; k=number of studies; n=number of participants; RR=relative risk.

Appendix C3. Stratified Effect Estimates for Smoking Cessation Interventions

Group 1 vs. group 2	k=# Studies; n=# Youth RR (95% CI) for Group 1	k=# Studies; n=# Youth RR (95% CI) for Group 2	Group 1 vs. group 2 p value
Cessation-only study vs. Combined study	k=4, n=1,566 0.97 (0.93 to 1.01)	k=5, n=950 0.98 (0.89 to 1.08)	p>0.05
U.S. studies vs. European studies	k=8; n=1,974 0.97 (0.91 to 1.02)	k=1; n=542 0.97 (0.91 to 1.02)	p>0.05
Intervention focused on smoking alone vs. Intervention included other behaviors (e.g., alcohol, sex)	k=7; n=2,339 0.96 (0.92 to 1.01)	k=2; n=177 1.02 (0.85 to 1.24	p>0.05
Targeted parent vs. Did not target parent	k=2; n=217 0.98 (0.91 to 1.05)	k=7; n=2,299 0.96 (0.91 to 1.02)	p>0.05
Targeted youth vs. Did not target parent	k=8; n=2,431 0.97 (0.93 to 1.01)	k=1, n=85 0.95 (0.67 to 1.34)	p>0.05
Primary care had active role vs. Primary care had no role or recruitment only	k=3; n=773 0.97 (0.84 to 1.11)	k=6; n=1,743 0.97 (0.94 to 1.01)	p>0.05
Single mode of intervention delivery vs. Intervention delivered by multiple methods	k=2; n=1,366 0.98 (0.94 to 1.02)	k=7; n=1,150 0.96 (0.89 to 1.03)	p>0.05
Intervention included print materials vs. Intervention included no print materials	k=4; n=874 0.91 (0.83 to 1.00)	k=5, n=1,642 0.99 (0.95 to 1.03)	p>0.05
Intervention included face-to-face contact vs. Intervention included no face-to-face contact	k=7; n=1,889 0.96 (0.91 to 1.02)	k=2; n=627 0.97 (0.91 to 1.03)	p>0.05
Intervention included telephone contact vs. Intervention included no telephone contact	k=7; n=1,600 0.96 (0.90 to 1.01)	k=2; n=916 0.99 (0.94 to 1.05)	p>0.05
Intervention included use of computer vs. Intervention did not use a computer	k=2; n=681 0.94 (0.79 to 1.11)	k=7; n=1,835 0.98 (0.94 to 1.02)	p>0.05
Intervention included motivational interviewing vs. Intervention included no motivational interviewing	k=6; n=1,065 0.95 (0.88 to 1.04)	k=3; n=1,451 0.98 (0.94 to 1.02)	p>0.05
Duration of intervention at least 20 weeks vs. Duration of intervention shorter than 20 weeks	k=4; n=1,315 0.98 (0.87 to 1.10)	k=5; n=1,201 0.97 (0.93 to 1.01)	p>0.05
Proportion of females <53% vs. Proportion of females ≥53%	k=5; n=1,707 0.99 (0.95 to 1.02)	k=4; n=809 0.90 (0.80 to 1.01)	p>0.05
Age of participants < 16 years vs. Age of participants ≥ 16 years	k=3; n=798 0.96 (0.83 to 1.10)	k=6; n=1,718 0.97 (0.94 to 1.01)	p>0.05
Outcome 30-day point prevalence vs. Outcome 7-day point prevalence	k=4; n=1,622 0.97 (0.90 to 1.05)	k=3, n=742 0.95 (0.88 to 1.02)	p>0.05
Nonwhite enrollment > 20% vs. Nonwhite enrollment ≤ 20%	k=5; n=966 0.93 (0.85 to 1.01)	k=3; n=1,008 1.00 (0.95 to 1.05)	p>0.05
Number of contacts (e.g., visits, phone calls, mailings) <5 vs. Number of contacts ≥ 5	k=6, n=1,790 0.95 (0.89 to 1.01)	k=3, n=726 0.99 (0.94 to 1.04)	p>0.05

Abbreviations: CI=confidence interval; k=number of studies; n=number of participants; RR=relative risk.

Appendix C4. Stratified Effect Estimates for Primary Smoking Prevention and Cessation Interventions

Group 1 vs. Group 2	k=# Studies; n=# Youth RR (95% CI) for Group 1	k=# Studies; n=# Youth RR (95% CI) for Group 2	Group 1 vs. Group 2 p value
U.S. studies vs. European studies	k=7; n=8,201 **0.88 (0.81 to 0.95)**	k=2; n=3,270 1.01 (0.92 to 1.11)	p>0.05
Intervention focused on smoking alone vs. Intervention included other behaviors (e.g., alcohol, sex)	k=4; n=5,451 0.93 (0.81 to 1.08)	k=5; n=-6,020 0.94 (0.84 to 1.04)	p>0.05
Targeted parent vs. Did not target parent	k=3; n=4,359 0.93 (0.75 to 1.16)	k=6; n=7,112 0.94 (0.86 to 1.03)	p>0.05
Targeted youth vs. Did not target youth	K=7; n=10,182 0.95 (0.88 to 1.03)	k=2; n=1,289 0.95 (0.53 to 1.69)	p>0.05
Primary care had active role vs. Primary care had no role or recruitment only	k=7; n=10,182 0.95 (0.88 to 1.03)	k=2; n=1,289 0.95 (0.53 to 1.69)	p>0.05
Single mode of intervention delivery vs. Intervention delivered by multiple methods	k=2; n=1,246 0.99 (0.89 to 1.10)	k=7; n=10,225 **0.91 (0.83 to 1.00)**	p>0.05
Intervention included print materials vs. Intervention included no print materials	k=3; n=6,729 **0.87 (0.78 to 0.97)**	k=6, n=4,742 0.99 (0.91 to 1.08)	p>0.05
Intervention included face-to-face contact vs. Intervention included no face-to-face contact	k=8; n=11,222 0.96 (0.88 to 1.03)	k=1; n=1,135 **0.84 (0.72 to 0.97)**	p>0.05
Intervention included telephone contact vs. Intervention included no telephone contact	k=5; n=8,619 **0.88 (0.80 to 0.96)**	k=4; n=2,852 1.00 (0.91 to 1.09)	p>0.05
Intervention included use of computer Intervention did not use a computer	k=2; n=2,995 **0.84 (0.74 to 0.96)**	k=7; n=8,476 0.96 (0.88 to 1.05)	p>0.05
Intervention included motivational interviewing vs. Intervention included no motivational interviewing	k=5; n=4,934 0.93 (0.85 to 1.01)	k=4; n=6,537 0.98 (0.81 to 1.17)	p>0.05
Duration of intervention longer than 12 months vs. Duration of intervention 12 months or less	k=3; n=6,340 1.01 (0.93 to 1.11)	k=6; n=5,131 **0.86 (0.79 to 0.94)**	p>0.05
Proportion of females <53% vs. Proportion of females ≥53%	k=4; n=6,663 0.97 (0.84 to 1.11)	k=5; n=4,808 0.91 (0.82 to 1.02)	p>0.05
Age of participants < 14 years Age of participants ≥ 14 years	k=4; n=6,537 0.98 (0.81 to 1.17)	k=5; n=4,934 0.93 (0.83 to 1.03)	p>0.05
Outcome 30-day point prevalence vs. Outcome even one puff or not reported	k=4; n=4,050 0.94 (0.83 to 1.06)	k=5; n=7,421 0.93 (0.82 to 1.06)	p>0.05
Nonwhite enrollment > 20% vs. Nonwhite enrollment ≤ 20%	k=4; n=4,284 **0.84 (0.77 to 0.93)**	k=3; n=1,939 0.98 (0.90 to 1.08)	p>0.05
Number of contacts (e.g., visits, phone calls, mailings) <6 vs. Number of contacts ≥ 6	k=5; n=5,894 0.91 (0.79 to 1.05)	k=4; n=5,577 0.95 (0.90 to 1.05)	p>0.05

Abbreviations: CI=confidence interval; k=number of studies; n=number of participants; RR=relative risk.