JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Primary Care–Relevant Interventions for Tobacco and Nicotine Use Prevention and Cessation in Children and Adolescents

Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Interventions to discourage the use of tobacco products (including electronic nicotine delivery systems or e-cigarettes) among children and adolescents may help decrease tobacco-related illness and injury.

OBJECTIVE To update the 2013 review on primary care–relevant interventions for tobacco use prevention and cessation in children and adolescents to inform the US Preventive Services Task Force.

DATA SOURCES The Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PsyINFO, and EMBASE (September 1, 2012, to June 25, 2019), with surveillance through February 7, 2020.

STUDY SELECTION Primary care–relevant studies; randomized clinical trials and nonrandomized controlled intervention studies of children and adolescents up to age 18 years for cessation and age 25 years for prevention. Trials comparing behavioral or pharmacological interventions with no or a minimal tobacco use intervention control group (eg, usual care, attention control, wait list) were included.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality. Studies were pooled using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Tobacco use initiation; tobacco use cessation; health outcomes; harms.

RESULTS Twenty-four randomized clinical trials (N = 44 521) met inclusion criteria. Behavioral interventions were associated with decreased likelihood of cigarette smoking initiation compared with control interventions at 7 to 36 months' follow-up (13 trials, n = 21 700; 7.4% vs 9.2%; relative risk [RR], 0.82 [95% CI, 0.73-0.92]). There was no statistically significant difference between behavioral interventions and controls in smoking cessation when trials were restricted to smokers (9 trials, n = 2516; 80.7% vs 84.1% continued smoking; RR, 0.97 [95% CI, 0.93-1.01]). There were no significant benefits of medication on likelihood of smoking cessation in 2 trials of bupropion at 26 weeks (n = 523; 17% [300 mg] and 6% [150 mg] vs 10% [placebo]; 24% [150 mg] vs 28% [placebo]) and 1 trial of nicotine replacement therapy at 12 months (n = 257; 8.1% vs 8.2%). One trial each (n = 2586 and n = 1645) found no beneficial intervention effect on health outcomes or on adult smoking. No trials of prevention in young adults were identified. Few trials addressed prevention or cessation of tobacco products other than cigarettes; no trials evaluated effects of interventions on e-cigarette use. There were few trials of pharmacotherapy, and they had small sample sizes.

CONCLUSIONS AND RELEVANCE Behavioral interventions may reduce the likelihood of smoking initiation in nonsmoking children and adolescents. Research is needed to identify effective behavioral interventions for adolescents who smoke cigarettes or who use other tobacco products and to understand the effectiveness of pharmacotherapy.

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Audio and Supplemental content

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It was estimated that each day in 2018, approximately 1600 children in the US smoked their first cigarette.[1] In 2020, the Surgeon General's report on smoking cessation found that tobacco use continues to be the leading cause of preventable death in the US.[2] Use of electronic cigarettes (e-cigarettes) has increased rapidly in adolescents, in whom it is more common than cigarette smoking.[3,4] In 2019, the estimated prevalence of e-cigarette use was 27.5% among high school students and 10.5% among middle school students, and the estimated prevalence of smoking cigarettes was 5.8% and 2.3%, respectively.[5] e-Cigarette use in youth is also associated with increased likelihood of initiation of smoking conventional tobacco products.[6-11] Potential harms associated with nicotine exposure in adolescents include nicotine addiction, nicotine toxicity, and harmful long-term effects to the developing brain, including negative effects on cognition. Potential harms of e-cigarette use also include lung injury and death, depending on the ingredients included in e-cigarette fluids.[12]

In 2013, the US Preventive Services Task Force (USPSTF) recommended that primary care clinicians provide interventions, including education or brief counseling, to prevent initiation of tobacco use among school-aged children and adolescents (B recommendation).[13] This was based on moderate certainty that primary care–relevant behavioral interventions can prevent tobacco use in children and adolescents with moderate net benefit. The current systematic review provides an update to include studies conducted since the last review, including literature on preventing and reducing use of newer tobacco products to inform the USPSTF for an updated recommendation statement.

Methods

Scope of Review

Detailed methods and additional study details are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/uspstf/document/UpdateSummaryFinal/tobacco-and-nicotine-use-prevention-in-children-and-adolescents-primary-care-interventions. The full report also provides the result of trials that examined the prevalence of smoking before and after an intervention when baseline smokers and nonsmokers are combined. **Figure 1** shows the analytic framework and key questions that guided the review. For this update, the inclusion criteria were expanded for prevention studies to young adults (ages 19-25 years).

Data Sources and Searches

The Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, MEDLINE, PsycINFO, and EMBASE were searched for English-language studies articles published from September 1, 2012, to June 25, 2019 (eMethods 1 in the Supplement), with surveillance through February 7, 2020. No search date restrictions were applied for e-cigarette use. Searches were supplemented by review of reference lists of included studies and the prior USPSTF report.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria. For all key questions, randomized clinical trials and nonrandomized controlled intervention studies of children and adolescents that evaluated interventions for prevention or cessation of any tobacco product (eg, cigarettes, cigars, e-cigarettes); reported health outcomes, effects on tobacco use, or frequency or quantity of alcohol or other substance use; and had a minimum of 6 months of follow-up were eligible.

For harms, cohort studies were also eligible. Interventions were primary care–relevant behavioral counseling interventions (eg, face-to-face individual counseling, group counseling, or both; telephone- or technology-based counseling; text messages; interactive websites, print materials), pharmacotherapy (ie, nicotine replacement therapy [NRT], bupropion, varenicline tartrate), and complementary and alternative medicine treatments (eg, acupuncture and hypnosis). Interventions were compared with usual care, attention control, wait-list control, or other nonsmoking or minimal smoking intervention. Trials could target parents/caregivers, children/adolescents, or both. Trials of interventions for preventing multiple risky behaviors (eg, smoking, alcohol or drug use, sex) or increasing healthy behaviors (eg, condom use, use of additional services) were also included, if they reported included outcomes.

Data Abstraction and Quality Rating

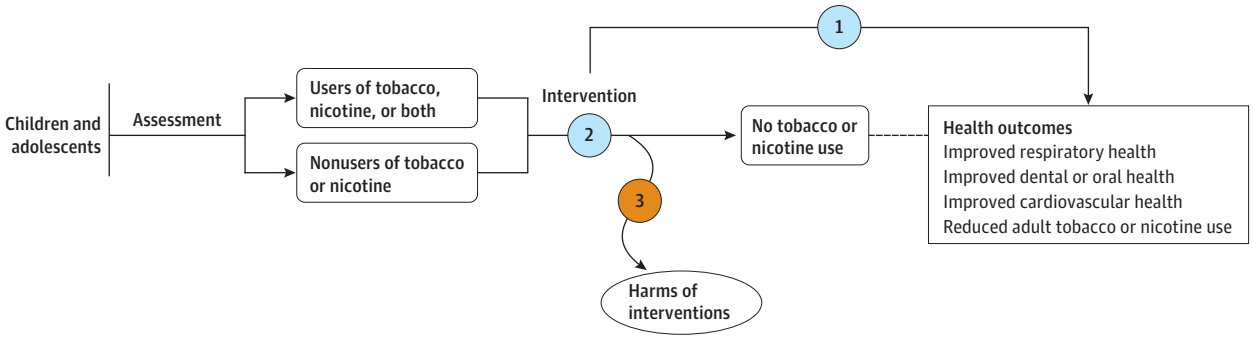
For each study, one investigator abstracted and another investigator checked the following data: study design, setting, population characteristics, intervention characteristics, and results for each outcome. Two investigators independently assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement); poor-quality studies were excluded from the synthesis of the results.[14] Quality ratings of individual studies are reported in eTable 1 in the Supplement.

Data Synthesis

Meta-analyses were conducted to calculate pooled relative risks (RRs) for smoking status for prevention and cessation interventions using the random-effects model in Stata version 14.2 (StataCorp). Statistical heterogeneity was assessed using the I^2 statistic. Meta-analyses were adjusted for cluster randomization using the sample sizes, number of clusters, and an estimated intraclass correlation coefficient.[15] As in the prior USPSTF review,[16,17] we used a coefficient of 0.01 to adjust for cluster randomization in trials. Analyses were based on data at or closest to 12 months after baseline. To evaluate the effects of trial-level characteristics on tobacco use, analyses were stratified by location (US vs Europe); duration (>20 weeks or ≤20 weeks); mode of intervention (multiple vs single); type of intervention; target of intervention (child, parent, or both); whether primary care had an active role in the trial (compared with no role or recruitment only); and outcome (30-day vs 7-day point prevalence of smoking). Meta-regression was also conducted to evaluate effects of study-level characteristics on estimates, using backward stepwise meta-regression with $P \leq .20$ for entry into the model, and controlling for the response in the control group. $P \leq .05$ (2-sided) was used to determine significance.

For all key questions and outcomes, the overall strength of the body of evidence was assessed as high, moderate, low, or insufficient using methods developed by the USPSTF, based on the overall quality of studies, consistency of results between studies, precision of findings, and risk of reporting bias.[14] The applicability of the findings to US primary care populations and settings was also assessed.

Figure 1. Analytic Framework: Primary Care–Relevant Interventions for Tobacco and Nicotine Use Prevention and Cessation in Children and Adolescents



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 (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?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line indicates a health outcome that immediately follows an intermediate outcome.

Results

Across all KQs, 24 randomized clinical trials (n = 44 521) reported in 31 publications were included (**Figure 2**).[18-48] Seven trials were newly identified as part of this update and 17 were carried forward from the previous review. An additional 2 trials that reported smoking prevalence in a combined group of baseline smokers and nonsmokers are included in the full report.[49,50] Twenty trials were of behavioral interventions for tobacco prevention, cessation, or both[18-28,30-38,40,42-47]; the remaining 4 trials assessed pharmacotherapy for quitting smoking.[29,39,41,48] No trials on the prevention or cessation of e-cigarettes were identified. Only 1 trial reported health outcomes.[44] Most trials enrolled predominately white adolescents; adolescents in prevention trials were younger than those in cessation trials (mean age, 12.8 years vs 16.6 years). Four of the trials were rated good-quality[33,34,42,46] and the remainder were rated fair-quality. Methodological shortcomings included unclear allocation concealment methods, lack of clarity of whether groups were similar at baseline, and high attrition. It was also not possible to effectively blind trials of behavioral interventions.

Benefits of Tobacco Prevention and Cessation

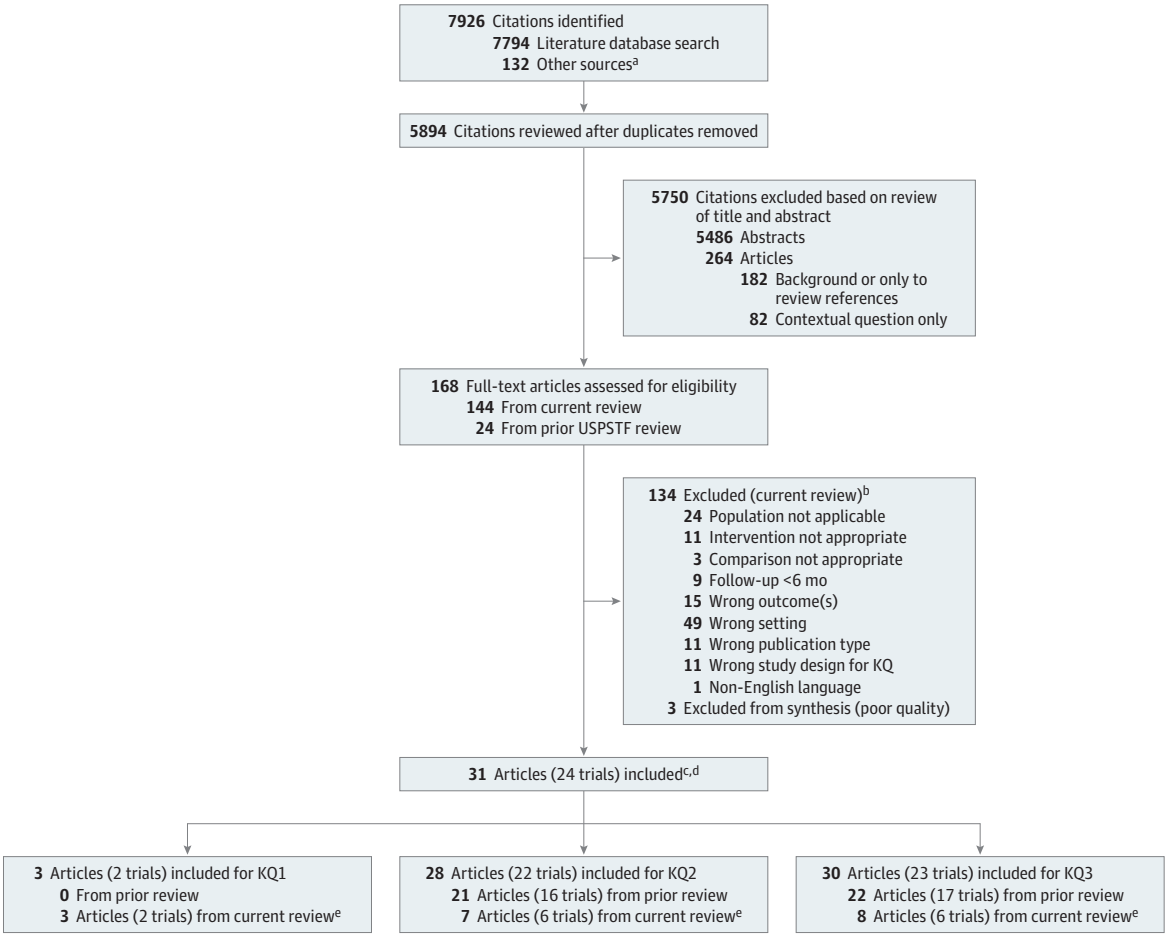
Key Question 1. Do primary care interventions to prevent tobacco and nicotine use or improve tobacco or nicotine cessation rates in children and adolescents improve health outcomes (respiratory, dental, cardiovascular, and oral health) and reduce the likelihood of tobacco and nicotine use in adulthood?

Two new trials were identified that reported the effects of tobacco prevention and cessation interventions in children and adolescents on health outcomes or adult smoking status.[18,19,43] The previous USPSTF review[16,17] included no studies. One long-term follow-up (n = 1020)[45] of a previously included trial (n = 2586)[38] found no effect of brief dentist counseling against smoking vs usual care on the likelihood of adult smoking (odds ratio [OR], 0.78 [95% CI, 0.56-1.09), although the estimate was imprecise.[45] One new trial (n = 1645) that enrolled pregnant teens in the UK found no effect of an intensive program of nurse home visitation in addition to usual care vs usual care alone on smoking status (56% in both groups) or mental health outcomes 2 years' postpartum.[44] However, the extent to which smoking was addressed by the intervention was not well defined.

Key Question 2. Do primary care interventions prevent tobacco and nicotine use or improve tobacco and nicotine cessation rates in children and adolescents?

The prior USPSTF review[16,17] included 15 trials (n = 33 113) on the effects of behavioral or pharmacological interventions on smoking behavior; 6 new trials (n = 7043) were identified for this update.[19,26,31,32,46,47] Across all 21 trials, 9 evaluated prevention of tobacco initiation, 7 (4 behavioral interventions and 3 pharmacotherapy trials) evaluated cessation of current tobacco use, and 5 reported results by smoking status and are included as both prevention and cessation trials. Prevention trials in nonsmokers and cessation trials in smokers were analyzed separately. Trials that included both smokers and nonsmokers but provided results by baseline smoking status appear in more than 1 analysis.

Figure 2. Literature Search Flow Diagram: Primary Care–Relevant Interventions for Tobacco and Nicotine Use Prevention and Cessation in Children and Adolescents



KQ indicates key question; USPSTF, US Preventive Services Task Force.

[a] Other sources include reference lists of relevant articles, systematic reviews, reviewer suggestions.

[b] See the full report at https://www.uspreventiveservicestaskforce.org/uspstf/document/UpdateSummaryFinal/tobacco-and-nicotine-use-prevention-in-children-and-adolescents-primary-care-interventions for the list of excluded studies and list of exclusion criteria.

[c] Studies that provided data and contributed to the body of evidence were considered included.

[d] Studies may contribute data to more than 1 key question.

[e] One new publication[18] is an update of a previously included trial.[19]

Prevention of Tobacco Initiation

Fourteen trials (n = 23 364) evaluated effects of behavioral interventions on the prevention of smoking initiation (eTable 2 and eTable 3 in the Supplement). The mean age of participants ranged from 7 to 17 years. One trial enrolled only female participants,[19] and the proportion of female participants in other trials ranged from 48.6% to 59.2%. One trial enrolled primarily people of color (92.1%),[19] and the proportion of nonwhite participants in other trials ranged from 1.7% to 50.8%. Eight trials targeted the youth to receive the intervention,[19,20,26,28,33,34,40,43] 2 targeted the parent,[23,47] and 4 targeted both.[18,27,30,32] The duration of the interventions ranged from 7 weeks[30] to 25 months,[26] with a mean number of 6 contacts, ranging from 3 contacts[33] to 15 contacts.[26] The duration of follow-up ranged from 6 months[20] to 36 months.[32] All trials were conducted in the US[18,19,23,27,30,33,34,40,43] or Europe[20,26,28,32,47]; trial settings were primary care clinics,[19,33,43] dental clinics,[34,40] homes,[18,20,23,26-28,30,32,47] and a school.[30] In addition to cigarette smoking, 1 trial also assessed effects on the proportion who initiated use of chewing tobacco.[23]

Interventions across trials were heterogeneous. Print materials were used most commonly to deliver part or all of the intervention,[18,20,23,27,28,32-34,47] followed by face-to-face encounters.[19,30,33,34,40,43] Several trials also used telephone support or booster calls,[18,27,32,33,40,43,47] and 3 trials were totally[26] or partially[19,33] internet-based or used an interactive computer program. The comparison groups consisted of usual care,[26,27,34,43] attention control,[33] low-intensity smoking intervention,[18,19,30,40,47] no interaction,[28] or were not described.[20,23,32] The primary smoking outcomes were 30-day point prevalence of smoking,[20,27,33,40] taking even 1 puff of a cigarette,[18,23,32,47] and smoking initiation.[19,26,28,30,43]

Table 1. Results of Prevention Intervention Trials

Source	Quality	Person targeted	Role of primary care	Mode of intervention	Time point analyzed, mo	% Initiating smoking at follow-up		RR (95% CI)
						Intervention	Control	
Ausems et al,[20] 2002	Fair	Youth	None	Print	6	10.4[a]	18.0	NR[a]
Bauman et al,[23] 2000	Fair	Parent	None	Telephone, print	7	17.0	21.0	0.81 (0.61-1.07)
Cremers et al,[26] 2015	Fair	Youth	None	Computer	12	Group 1: 0.59 Group 2: 1.06	1.02	NR[b]
Curry et al,[27] 2003	Fair	Both	Recruitment only	Telephone, print	20	2.4[c]	2.3[c]	1.04 (0.68-1.58)
Fidler and Lambert,[28] 2001	Fair	Youth	Recruitment only	Print	12	5.1	7.8	0.65 (0.47-0.90)
Haggerty et al,[30] 2007	Fair	Both	None	Face-to-face	12	11.8[d]	9.0[d]	1.31 (0.52-3.28)
Hiemstra et al,[32] 2014	Fair	Both	Recruitment only	Print	12	10.8	12.0	NR[e]
Hollis et al,[33] 2005	Good	Youth	Conducted in primary care, clinician/clinic staff delivered part	Face-to-face, computer	12	9.3	12.1	0.76 (0.59-0.99)
Hovell et al,[34] 1996	Good	Youth	Conducted in dental care, clinician/clinic staff delivered most	Face-to-face, print	24	12.0[f]	12.6[f]	0.95 (0.84-1.07)
Jackson and Dickinson,[18] 2006	Fair	Both	None	Print	36	11.9	19.3	0.62 (0.44-0.87)
Lando et al,[40] 2007	Fair	Youth	Conducted in dental care, clinician/clinic staff delivered part	Face-to-face, telephone	12	9.7	16.7	0.58 (0.25-1.37)
Pbert et al,[43] 2008	Fair	Youth	Conducted in primary care, clinician/clinic staff delivered part	Face-to-face, telephone	12	3.2	4.5	0.69 (0.30-1.58)
Redding et al,[19] 2015	Fair	Youth	Conducted in family planning clinics, primary care not involved	Face-to-face, computer	18	8.5	7.3	NR[g]
Schuck et al,[47] 2015	Fair	Parent	None	Telephone, print	12	20.1	14.7	NR[h]

Abbreviations: NR, not reported; RR, relative risk.

[a] The number of baseline nonsmokers and the number of children initiating smoking at follow-up were not reported. The percentages of children initiating smoking at follow-up (as reported in the article) were 10.4% (95% CI, 6.9%-14.0%) in the intervention group and 18.1% (95% CI, 12.5%-23.7%) in the control group.

[b] Adjusted odds ratio (age, sex, ethnicity, socioeconomic status, among others) for prompt-reinforced intervention, 0.53 (95% CI, 0.12-2.47); for no prompt-reinforced intervention, 1.01 (95% CI, 0.24-4.21).

[c] Among the assessment cohort (n = 492), 2.5% of the intervention group and 0% of the control group reported smoking in the past 30 days at baseline. Authors do not report whether baseline smokers were included in the follow-up.

[d] At baseline, 22.0% of the intervention group and 21.7% of the control group reported smoking; these individuals were excluded from the analysis at follow-up.

[e] Intention-to-treat adjusted odds ratio (adjusted for parental smoking), 1.01 (95% CI, 0.82-1.24); adjusted for asthma, 0.91 (95% CI, 0.32-2.60); adjusted for socioeconomic status, 1.06 (95% CI, 0.71-1.59).

[f] Baseline smokers were excluded from the analysis (specific numbers not reported).

[g] Generalized estimating equation analysis indicated no significant differences between groups.

[h] Odds ratio, 0.70 (95% CI, 0.41-1.20).

Behavioral interventions were associated with statistically significantly reduced smoking initiation compared with controls at 7 to 36 months' follow-up (13 trials, n = 21 700; 7.4% vs 9.2%; RR, 0.82 [95% CI, 0.73-0.92]; I^2 = 15%) (**Table 1** and **Figure 3**).[18,19,23,26-28,30,32-34,40,43,47] One prevention trial (n = 3349) that could not be pooled because of confounding with a school-based social influence program 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' follow-up (10.4% vs 18.1%, $P < .05$).[20] One trial found no significant differences between the intervention and control groups in initiation of chewing tobacco use, but very few adolescents began chewing tobacco during the study period (approximately 3% in both groups).[23]

Exploratory meta-regression and stratified analysis found an interaction between the use of a single mode of delivering the intervention (eg, face-to-face counseling) and between fewer contacts and stronger effects on smoking initiation (RR for initiation of smoking, 0.66 [95% CI, 0.53-0.82] in trials using a single mode of intervention [5 trials, n = 6239] vs 0.90 [95% CI, 0.82-0.99] in trials using multiple methods [8 trials, n = 15 461] [P = .04] and 0.74 [95% CI, 0.64-0.86] for trials with ≤6 contacts [8 trials, n = 11 210] vs 0.92 [95% CI, 0.83-1.03] for trials with >6 contacts [5 trials, n = 10 490] [P = .03]). There were no effects of other study-level characteristics (ie, study location, trial duration, target of the intervention, role of primary care, and definition of smoking outcome) on tobacco use.

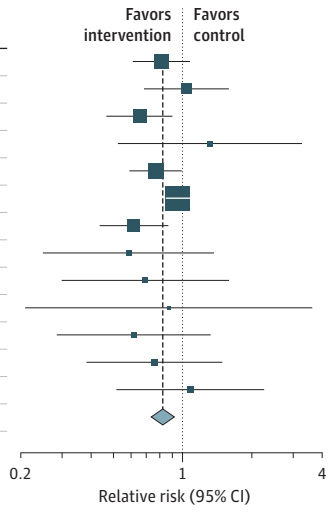
Tobacco Cessation—Behavioral Intervention Trials

Nine trials (n = 2516) assessed behavioral interventions for the cessation of tobacco use (eTable 3 and eTable 4 in the Supplement). The mean age of participants ranged from 14 to 18 years. One trial enrolled only female participants,[19] and the proportion of female participants in other trials ranged from 47.5% to 61.0%. One trial enrolled primarily people of color (92.1%),[19] and the proportion nonwhite in other trials ranged from 7.4% to 45.0%. Seven trials targeted the youth,[19,24,31,33,40,42,43] 1 targeted the parent,[21] and

Figure 3. Meta-analysis of Smoking Prevention Interventions to Reduce Smoking Initiation

Source	No. smoking at follow-up/ total participants (%)		Relative risk (95% CI)
	Intervention	Control	
Bauman et al,[21] 2001	68/400 (17.0)	90/428 (21.0)	0.81 (0.61-1.07)
Cremers et al,[24] 2015	5/1158 (0.4)	3/604 (0.5)	0.87 (0.21-3.63)
Curry et al,[25] 2003	42/1749 (2.4)	42/1814 (2.3)	1.04 (0.68-1.58)
Fidler and Lambert,[26] 2001	54/1068 (5.1)	89/1144 (7.8)	0.65 (0.47-0.90)
Haggerty et al,[28] 2007	10/85 (11.8)	7/78 (9.0)	1.31 (0.52-3.28)
Hiemstra et al,[30] 2014	10/630 (1.6)	18/696 (2.6)	0.61 (0.29-1.32)
Hollis et al,[31] 2005	89/962 (9.2)	118/973 (12.1)	0.76 (0.59-0.99)
Hovell et al,[32] 1996[a]	440/3668 (12.0)	493/3913 (12.6)	0.95 (0.84-1.07)
Jackson and Dickinson,[35] 2006	44/371 (11.8)	78/405 (19.2)	0.62 (0.44-0.87)
Lando et al,[39] 2007	7/72 (9.7)	14/84 (16.7)	0.58 (0.25-1.37)
Pbert et al,[42] 2008	9/254 (3.5)	13/253 (5.1)	0.69 (0.30-1.58)
Redding et al,[43] 2015	15/210 (7.1)	16/169 (9.5)	0.75 (0.38-1.48)
Schuck et al,[47] 2015	14/256 (5.5)	13/256 (5.1)	1.08 (0.52-2.25)
Total	807/10883 (7.4)	994/10817 (9.2)	0.82 (0.73-0.92)

Heterogeneity: $I^2 = 14.9\%$, $P = .30$



Box sizes represent weights of studies in the analysis and are from random-effects analysis.

[a] This study reports on any tobacco use at follow-up, not just smoking.

1 targeted both.[25] The duration of the intervention ranged from 1 week[24] to 12 months,[33] and the duration of the trials ranged from 6 months[24,25,31] to 24 months,[33] with a median of 4 contacts and a range of 2 contacts[24] to 66 contacts (all text messages, including 11 assessment messages).[31] All trials were conducted in the US,[19,21,24,25,33,40,42,43] except for 1 trial conducted in Switzerland.[31] Trials were conducted in primary care clinics,[19,33,43] a school health clinic,[42] a dental clinic,[40] and homes.[21,31] In 2 trials[24,25] the location was not specified.

As in the prevention trials, the interventions were heterogeneous. Face-to-face counseling was used most often,[19,24,25,33,40,42,43] followed by telephone counseling.[24,25,33,40,43] One trial sent text messages to participants.[31] Four trials made use of print materials,[21,24,25,33] and 2 trials used a computer to deliver part of the intervention.[19,33] Smoking outcomes included 30-day point prevalence of smoking,[21,24,33,40,42] 7-day point prevalence of smoking,[24,25,31] or was not reported.[19,43]

There was no statistically significant difference between behavioral interventions vs controls in likelihood of continued smoking at 6 to 12 months' follow-up (9 trials, n = 2516; 80.6% vs 84.1%; RR, 0.97 [95% CI, 0.93-1.01]; I^2 = 29%) (eFigure and eTable 5 in the Supplement).[19,21,24,25,31,33,40,42,43] Exploratory meta-regression found no interactions between mode of intervention delivery, number of contacts, study location, trial duration, target of the intervention, role of primary care, or definition of smoking outcome and effects on smoking cessation. Results were similar with stratified analyses.

Tobacco Cessation—Medication Intervention Trials

The prior USPSTF report included 2 fair-quality trials (n = 211 and n = 312) of bupropion sustained release (SR)[39,41] for smoking cessation. One new, good-quality trial (n = 257) evaluated NRT for smoking cessation in children aged 12 to 18 years[46] (eTable 3 and eTable 4 in the Supplement). All 3 medication trials recruited from schools, used placebo as a control, included a 6-month follow-up assessment, and enrolled adolescents who were motivated to quit smoking[46] or who had at least 1[39] or 2 previous quit attempts.[41]

The new trial (n = 257) randomized adolescents (mean age, 16.7 years; 52.9% female) who smoked at least 7 cigarettes per day to receive an NRT patch vs a placebo patch for 6 or 9 weeks depending on the number of cigarettes smoked at baseline. The initial NRT dose was 14 or 21 mg/d, depending on baseline tobacco use, and tapered down.[46] All participants also received a 75-minute behavioral intervention that included an information meeting on smoking cessation and NRT instruction. There was no effect of NRT on smoking cessation (defined as 30-day point prevalence abstinence) after 6 or 12 months, but estimates were imprecise (8.1% vs 5.7% at 6 months; adjusted OR, 2.09 [95% CI, 0.20-22] and 8.1% vs 8.2% at 12 months; adjusted OR, 1.13 [95% CI, 0.17-7.44]) (eTable 5 in the Supplement).[46]

One trial (n = 312; mean age, 16.0 years; 45.8% female; 26.0% nonwhite) included in the prior USPSTF report found no significant differences between bupropion SR (300 mg or 150 mg) vs placebo in self-reported abstinence at 26 weeks in 14- to 17-year-olds who smoked 6 or more cigarettes per day (17% and 6% vs 10%).[41] The other bupropion trial (n = 211; mean age, 17.3 years; 31.3% female; 49.8% nonwhite) from the prior USPSTF report found no significant difference at week 26 between bupropion SR (150 mg) vs placebo in quit rates among adolescents aged 15 to 18 years who smoked at least 10 cigarettes per day (24% vs 28%).[39] However, adherence to medication use in this trial was low. At week 5, only 39 of 103 participants (38%) had evidence of bupropion in their urine, and only 22% reported taking all bupropion pills.

Harms of Primary Care Interventions

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?

Adverse events were not well reported in trials of behavioral interventions, but no serious adverse events were indicated.

Four medication trials reported harms—3 bupropion trials[29,39,41] included in the prior USPSTF review[16,17] and 1 new trial of NRT.[46] Serious adverse events in these trials were uncommon; study withdrawals due to adverse events were not reported or were not different between study drug and placebo; and adverse events experienced by those in the placebo groups were not always reported.

In the NRT trial, no serious adverse events were reported.[46] NRT was associated with increased risk of headache, cough, abnormal dreams, muscle pain, and patch-related adverse events vs placebo ($P < .05$); placebo was associated with more sleeplessness ($P < .01$).

In 1 bupropion trial there was 1 suicide attempt in a participant randomized to bupropion.[41] A separate publication of this trial found no increases in body mass index, either among those who achieved smoking abstinence or those who did not.[51] In another trial, bupropion was associated with abnormal dreams vs placebo, but the estimate was imprecise (12.3% vs 0%; RR, 15.92 [95% CI, 0.95-268]).[29]

Discussion

The findings in this evidence report are summarized in **Table 2** and are consistent with those from the prior USPSTF review. Behavioral interventions may reduce the likelihood of smoking initiation in nonsmoking children and adolescents. Most studies were conducted in the US; the remainder were conducted in Western Europe and are likely applicable to US settings. Additionally, trials were required to be conducted in primary care settings or to be referable from primary care. However, trials enrolled mostly white children and adolescents, making it unclear if there are differences based on race or ethnic background in the effects of various interventions.

In children and adolescents who do not smoke conventional cigarettes, behavioral interventions were effective at decreasing smoking initiation by approximately 18% based on a meta-analysis of 13 trials (n = 21 700); owing to the sizable number of participants included in these trials and size of the treatment effect, these findings are not likely to change significantly with the addition of future studies. No prevention trials that enrolled young adults were identified. Meta-regression and stratification of study-level variables found interactions between the use of a single modality for delivering the intervention (eg, use of only print materials, use of only face-to-face counseling) and between having 6 or fewer contacts with adolescents/parents and prevention of smoking initiation. These results were unexpected in suggesting that less intensive interventions may be more effective in this population. However, there were relatively few trials, and these findings need to be interpreted with caution.

Among children and adolescents who smoke cigarettes, behavioral interventions were not found to be effective for smoking cessation, but confidence that additional trials would not alter this finding is low. Fewer children and adolescents in studies smoked, so numbers of participants eligible for cessation interventions were substantially fewer than numbers of participants eligible for prevention interventions; future cessation trials, when added to the current meta-analysis, may alter the findings. Examination of study-level characteristics found no variables or group of variables that predicted the magnitude of the treatment effect in cessation trials.

Adverse events were not well reported in trials of behavioral interventions but indicated no serious adverse events.

In the few smoking cessation drug trials meeting inclusion criteria for this review, neither bupropion SR nor NRT demonstrated an effect on smoking cessation in adolescents; additional trials of these medications may strengthen or change these findings. Although bupropion and NRT were both associated with increased risk of abnormal dreams, serious adverse events in drug trials were uncommon. Bupropion has a US Food and Drug Administration boxed warning regarding increased risk of suicidal thinking and behavior in children taking antidepressants.[52] In the bupropion trials included in this review, 1 child in a bupropion group attempted suicide (0.3%), while there were no reports of suicidality in control groups.[41] However, the trials were not powered to assess suicidal risk.

Another pharmacotherapy for smoking cessation is varenicline, which is not recommended for patients 16 years or younger because of lack of efficacy in younger children.[53] One varenicline randomized trial (n = 157) included adolescents and young adults aged 14 to 21 years but was excluded because the mean age was 19.1 years and results were not reported separately for those younger than 18 years.[54] That trial found no significant difference between varenicline vs placebo in self-reported 7-day smoking abstinence at the end of 12 weeks of treatment (n = 90; 31% vs 27%; RR, 1.17 [95% CI, 0.63-2.20]). At 6-month follow-up, the difference between varenicline and placebo on 7-day abstinence had widened (n = 83; 36% vs 17% [estimated from graph]; point estimate and 95% CI not reported). Attrition was high (47%); in addition, it is unclear why varenicline would show a delayed effect. Results of this trial were similar to those from an unpublished varenicline trial in adolescents (NCT01312909).[55] There was no significant difference between varenicline and placebo on 4-week continuous abstinence rate (week 9 through week 12) (OR, 1.18 [95% CI, 0.59-2.37] for high-dose varenicline; OR, 1.73 [95% CI, 0.88-3.39] for low-dose varenicline), but in participants who received low-dose varenicline (0.5 mg), continuous abstinence rates from week 9 through weeks 24 and 52 were significantly improved with varenicline (OR, 2.26 [1.07-4.79] for weeks 9 through 24; OR, 2.79 [95% CI, 1.19-6.55] for weeks 9 through 52). Attrition in this trial was 40%.

Searches yielded no trials for the prevention or cessation of e-cigarette use. Children and adolescents are a vulnerable population whose bodies and brains are still developing. Most smokers initiate smoking in adolescence.[56] Methods to reduce exposure to nicotine and known and unknown toxins and carcinogens found in cigarettes, cigars, e-cigarettes, and other tobacco products may have consequences for short-term health (eg, nicotine addiction, harm to the developing brain, nicotine toxicity, burns from vaping device explosions) and long-term mental health (eg, problems with learning, attention, mood) and physical health (eg, lung cancer, mouth and throat cancer, myocardial infarction, stroke).

Research is needed to identify effective behavioral interventions for youth who already smoke cigarettes or who use other

Table 2. Summary of Evidence: Primary Care–Relevant Interventions for Tobacco and Nicotine Use Prevention and Cessation in Children and Adolescents

Intervention	Intervention goal, population	No. of trials (observations)	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1: Benefits of interventions (adolescent health outcomes and adult tobacco and nicotine use)							
Interventions to prevent tobacco and nicotine use or improve cessation	Improve adolescent health outcomes	1 (n = 1092)	Enrolled pregnant adolescents Maternal ED/hospital admission (OR, 1.32 [95% CI, 0.99-1.76]), 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 US services; intensive nurse visits less applicable to primary care practice
	Reduce tobacco product use in adulthood	1 (n = 2178)	Enrolled 12-y-olds and evaluated smoking at age 29 years; prevalence of smoking, 15.3% vs 18.5% (OR, 0.78 [95% CI, 0.56-1.09])	Unknown consistency; imprecise estimate	Only 39% responded to follow-up survey	Insufficient	Finnish trial—applicable to US
KQ2: Benefits of interventions (tobacco and nicotine use and cessation in children and adolescents)							
Behavioral interventions	Prevent smoking initiation in nonsmokers	14 (n = 25 049)	Pooled analysis of 13 trials (n = 21 700); 7.4% vs 9.2% (RR, 0.82 [95% CI, 0.73-0.92]); I^2 = 15%	Consistent; precise	Most trials have moderate risk of bias	Moderate for benefit	Most trials US
	Smoking cessation in baseline smokers	9 (n = 2516)	Pooled analysis of 9 trials; 80.7% vs 84.1% (RR, 0.97 [95% CI, 0.93-1.01]); I^2 = 29%	Consistent; precise	Most trials have moderate risk of bias	Low for no effect	Most trials US
Bupropion	Smoking cessation in baseline smokers	2 (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
NRT	Smoking cessation in baseline smokers	1 (n = 265)	6 mo: 8.1% vs 5.7% (adjusted OR, 2.09 [95% CI, 0.20-22]) 12 mo: 8.1% vs 8.2% (adjusted OR, 1.13 [95% CI, 0.17-7.44])	Unknown consistency, imprecise estimate	None	Insufficient	Netherlands trial—applicable to US
KQ3: Harms of interventions (tobacco and nicotine use and cessation in children and adolescents)							
Behavioral interventions	Baseline smokers and nonsmokers	0	NA	NA	NA	NA	NA
Bupropion	Baseline smokers	3 (n = 657)	No significant difference between bupropion and control in experiencing a serious or severe adverse event (2 trials) 4% withdrew with bupropion because of 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 US
NRT	Baseline smokers	1 (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—applicable to US

Abbreviations: ED, emergency department; NA, not applicable; NRT, nicotine replacement therapy; OR, odds ratio; RR, relative risk.

tobacco products and to understand the effectiveness of pharmacotherapy. Owing to the rapid escalation of e-cigarette use among youth,[4] and since e-cigarette use is associated with the initiation of conventional tobacco products,[7-11] both prevention and cessation trials that target or include e-cigarette use are needed.

Limitations

This review has several limitations. First, inclusion was restricted to English-language articles, although no non–English-language trials that would have met inclusion criteria were identified. Second, moststudies were published more than 10 years ago and

only examined cigarette smoking. Third, the behavioral interventions included for prevention and cessation of tobacco use were quite heterogeneous and not always well described. Fourth, trials used inconsistent definitions of baseline smoking status, initiation, and abstinence. Fifth, meta-regression and stratified analyses were limited by the few number of studies available, which also limited the ability to perform statistical and graphical tests for publication bias.

Conclusions

Behavioral interventions may reduce the likelihood of smoking initiation in children and adolescents. Research is needed to identify effective behavioral interventions for adolescents who smoke or who have used cigarettes or other tobacco products and to understand the effectiveness of pharmacotherapy.

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Concept and design: Patnode, Chou.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Selph, Pappas, Stoner, Chou.
Critical revision of the manuscript for important intellectual content: Patnode, Bailey, Pappas, Chou.
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