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Behavioral interventions for tobacco use in HIV-infected smokers: systematic review and pairwise, network meta-analysis of randomized trials

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Abstract

Smoking among persons living with HIV infection (PLWH) is estimated to be 2-3 times greater than that in the general population. Data suggest that cigarette smoking is more common among PLWH because of several factors, including lower socioeconomic status, previous, or concurrent illicit drug and alcohol use, younger age, lower education level, and concomitant depressive symptoms. Cigarette smoking among PLWH has been associated with a higher risk of certain cancers and infections as well as lowered response to antiretroviral therapy. Randomized controlled trials on behavioral interventions for tobacco use among smokers with HIV were searched in the PubMed, Cochrane Library, EMBASE, and Web of Science databases. The retrieval period was from the inception of databases to November 2023. Network meta-analysis (NMA) was performed using the Stata 18.0 software with 19 studies (3190 subjects), of which 15 reported 7-day point prevalence abstinence and seven of which reported continuous abstinence. The NMA results showed that compared with general advice plus self-help brochure, text messaging (relative risk [RR] = 4.60, 95% confidence interval [CI], 1.12-18.81) and cell phone counseling (RR = 3.29, 95% CI, 1.71-6.32) were the most effective for 7-day point prevalence abstinence among smokers with HIV infection. Moreover, the meta-analysis showed that compared with smoking counseling and self-help brochures, continuous abstinence was statistically significantly enhanced after behavioral interventions (RR = 2.52, 95% CI, 1.51-4.20). The study revealed very low-to-high-quality evidence that text messaging, telephone counseling, and smoking cessation websites were effective for smokers with HIV infection.

Keywords

HIV. Tobacco use. Smoking cessation.

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Introduction

Among people living with HIV (PLWH) infection, the smoking prevalence is > 40%[1], which is at least 2 times higher than that in the general population[2-4]. The negative impact of smoking among PLWH includes HIV-related complications (e.g., increased viral load and pneumonia)[5,6], HIV-unrelated medical illnesses (e.g., malignancies and bone disease)[7,8], and increased mortality[9,10]. Women living with HIV/acquired immune deficiency syndrome (AIDS) also face other consequences of smoking, such as pre-eclampsia, low birth weight, or fetal death[11-13].

Although pharmacological interventions can help with long-term smoking cessation, caution should be used in PLWH because HIV drugs may interact with other medications and some side effects may be aggravated[14]. Indeed, varenicline has a number of side effects, including insomnia, abnormal dreams, depression, agitation, behavioral changes, suicidal ideation, and suicide[15,16]. Behavioral interventions among this group of patients include cognitive behavioral therapy, mindfulness meditation, narrative therapy, psychological counseling, positive motivation, and other psychological therapies[17]. The already existing literature has highlighted the value of clinical smoking cessation in practice. Keith et al. analyzed eight studies and indicated that behavioral interventions are effective[18]. A meta-analysis by Uthman et al. compared mobile health interventions with face-to-face interventions and revealed that mHealth-delivered interventions increased smoking cessation in the short term[19]. However, such traditional systematic reviews are conducted by comparing two interventions, which limits comparisons between multiple behavioral interventions and prevents the selection of the best option.

A network meta-analysis (NMA) collectively analyzes direct and indirect comparative evidence from randomized controlled trials (RCTs) to develop a network map that simultaneously compares all interventions in the same analysis and estimates their relative ranking for a given outcome[20-22]. Therefore, the present NMA study aimed to assess the impact of different behavioral interventions on smoking cessation in patients with HIV and analyze existing RCTs through a systematic approach to assess whether these interventions can offer an effective way to increase the odds of quitting smoking.

Methods

Protocol and registration

This NMA was conducted in accordance with the preferred reporting items for systematic reviews and meta-analysis guidelines. The present study protocol has been registered on PROSPERO, with the registration number CRD42023464819.

Search strategy

The PubMed (1980-11/2023), Cochrane Library (1980-11/2023), EMBASE (1980-11/2023), and Web of Science (1980-11/2023) databases were searched using the following search terms: HIV, AIDS, smoke, cigarette, cessation, reduction, and clinical trial. Search filters were used to restrict studies to RCTs on humans and published in English. Meanwhile, the reference lists of included articles were evaluated for possibly relevant studies. The search strategy is summarized in Supplementary Table S1.

Inclusion and exclusion criteria

The relevant literature was systematically reviewed according to the following inclusion and exclusion criteria. Studies that analyzed PLWH of any age with self-reported cigarette use who received behavioral therapy interventions related to smoking cessation were included in the study. Behavioral interventions administered in several ways, such as cognitive behavioral therapy, health counseling, and personal support, were considered. In terms of comparison, studies in which PLWH in the control group received brief counseling or self-help control conditions were included. In addition, with regard to outcomes, studies that considered 7-day point prevalence according to carbon monoxide levels (no combustible tobacco use for 7 days before the assessment) as the primary outcome and continuous abstinence (no combustible tobacco use from the target quitting date until the assessment) as the secondary outcome were included in the study[23]. Finally, only randomized or quasi-RCTs were included. The exclusion criteria were studies that included participants with other serious complications or those who received pharmacological intervention concurrently; duplicate publications, reviews, or protocols; or studies with incomplete data.

Study selection

Two researchers independently reviewed all study titles and abstracts for the abovementioned eligibility criteria. On meeting the eligibility criteria, the full article was accessed and reviewed. Any disagreement was resolved by discussion with a third party for consensus.

Data extraction

Detailed information from each included study was extracted by two researchers independently. The data included basic information (first author's name and year of publication); participant characteristics (sample size, sex, age, and duration of treatment); intervention and comparison details; and definition of abstinence (e.g., sustained or point prevalence and biochemical validation) at each point.

Risk of bias assessment

Study quality was assessed by referring to the Cochrane risk-of-bias (RoB) tool. The tool contained the seven items of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias[24]. Each article was evaluated according to these items. Articles with complete information were considered "low risk," those with missing information were determined as "unclear risk," and those with a significant bias were regarded as "high risk."

Certainty assessment

Confidence in the evidence of NMA was evaluated using an adapted version of the grading recommendations assessment, development, and evaluation (GRADE) methodology through the web-based application confidence in Network Meta-Analysis (CINeMA) (https://cinema.ispm.unibe.ch/)[25]. Using the netmeta package of the R software, CINeMA calculates the contribution matrix of NMA. This tool considers the following six aspects: intrastudy bias (bias risk), interstudy bias (publication bias or report bias), indirectness, inaccuracy, heterogeneity, and inconsistency. Based on the severity of bias, each area was categorized into no concern (no downgrade), some concern (one-level downgrade), and major concern (two-level downgrade). Finally, evidence for each pair of comparisons was determined as high, moderate, low, or very low[26].

Confidence in the evidence of meta-analysis was evaluated using GRADE (https://www.gradepro.org/). Because the included studies were all RCTs, the evidence quality level was high, but they were analyzed for downgrading owing to the risk of bias, inconsistency, incoherence, inaccuracy, and publication bias of studies analyzed in those RCTs. The final quality of evidence was divided into four levels high, moderate, low, and very low[27].

Statistical analysis

The Stata 18.0 software was used to perform NMA. Dichotomous data were evaluated using relative risk (RR) and 95% confidence interval (CI). The global, loop, and local inconsistencies were estimated using the "network meta i," "ifplot," and "node-splitting" procedures, respectively. The comparison network was obtained using the "network map" procedure. The league tables of the relative effects of interventions were used to visualize the comparisons of network estimations. For all outcomes, the effect of each intervention was ranked in terms of the calculated probabilities. The interpretation of the mean extent of certainty that one treatment was better than another was illustrated as the surface under the cumulative ranking curve (SUCRA) plots. SUCRA values were expressed as a percentage ranging from 0% to 100%. A SUCRA value near 100% indicated that the treatment effect was better, suggesting that the lower the value, the less effective was the treatment. The Review Manager software was used to perform meta-analysis. Dichotomous data were evaluated using RR and 95% CI, and a random-effects model was applied to analyses considering the high heterogeneity. The results are displayed using a forest plot. Statistical heterogeneity between studies was assessed using I^2 and Cochrane Q-test. According to the Cochrane Handbook, the I^2 statistics of 0-40%, 30-60%, 50-90%, and > 75% indicated low, moderate, substantial, and high heterogeneity, respectively[24]. Finally, funnel plots and Egger's test were used to evaluate publication bias when the number of studies was > 10.

Results

Study selection

The initial search of the four major databases yielded 4445 studies, with no additional eligible studies identified through the secondary search of references in relevant articles or systematic reviews (Fig. 1). After removing 1221 duplicates, 3100 studies were rejected through the initial review of titles and abstracts. The remaining 124

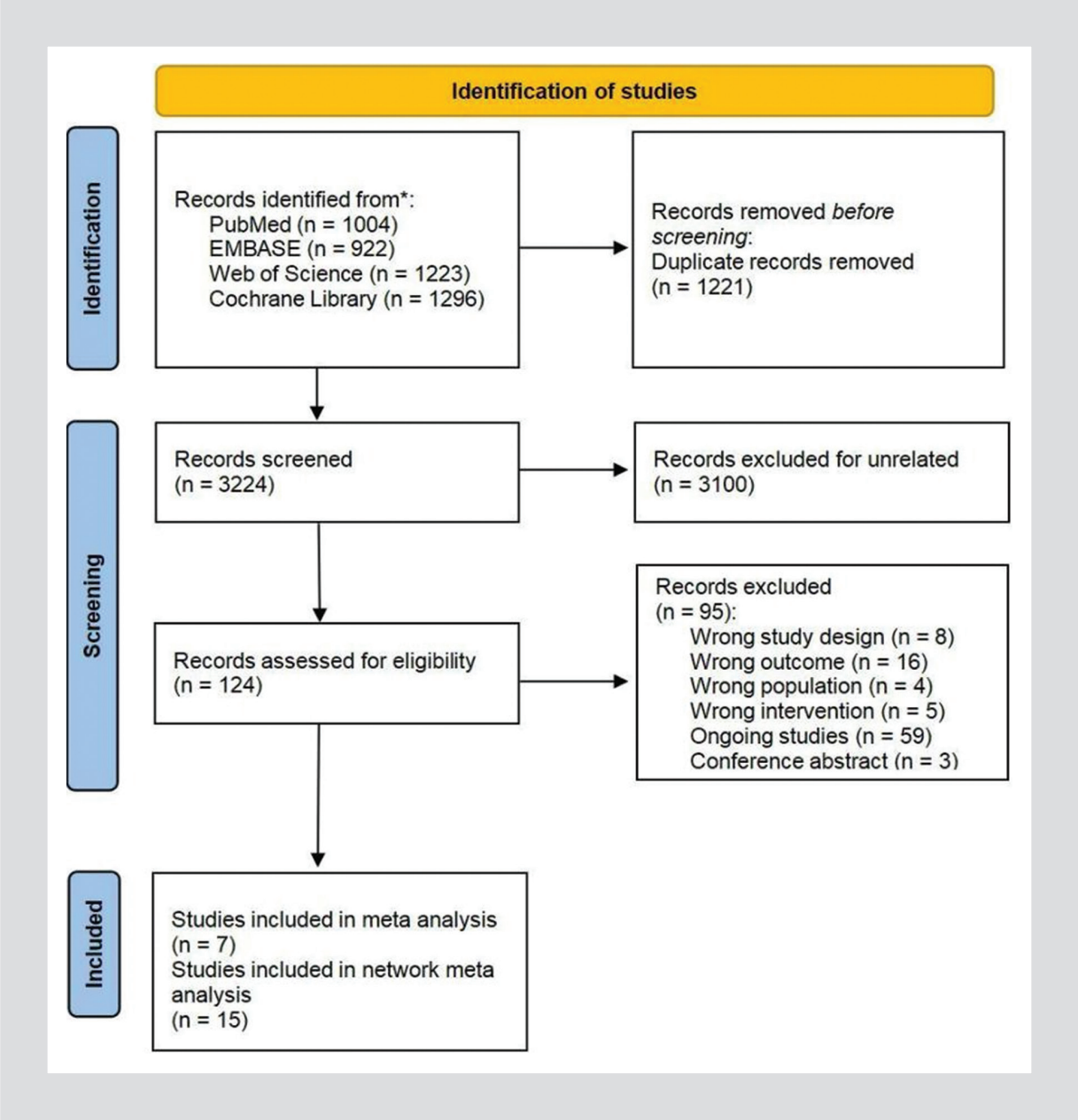

Figure 1. *Preferred reporting items for systematic reviews and meta-analyses flowchart of literature selection.*

full-text articles were reviewed for eligibility, resulting in the exclusion of 105. Finally, 19 studies were identified, of which 15 reported 7-day point prevalence abstinence and seven reported continuous abstinence. The screening process is detailed in figure 1 and the list of excluded studies is listed in Supplementary Table S2.

Study characteristics

As mentioned earlier, 19 studies with 3190 subjects were identified for inclusion in the review. All 19 studies were RCTs in the English language and published between 2006 and 2023. The number of patients in each study ranged from 15 to 512, and their mean age range was 25-70 years. The studies delivered the behavioral interventions in several formats. Three studies used telephone counseling, three employed group therapy, two utilized targeted intervention, and one used text messaging. In addition, one study utilized cognitive behavioral therapy, one utilized warm handoff, one employed a combination of video-call counseling and a film on smoking cessation, and one

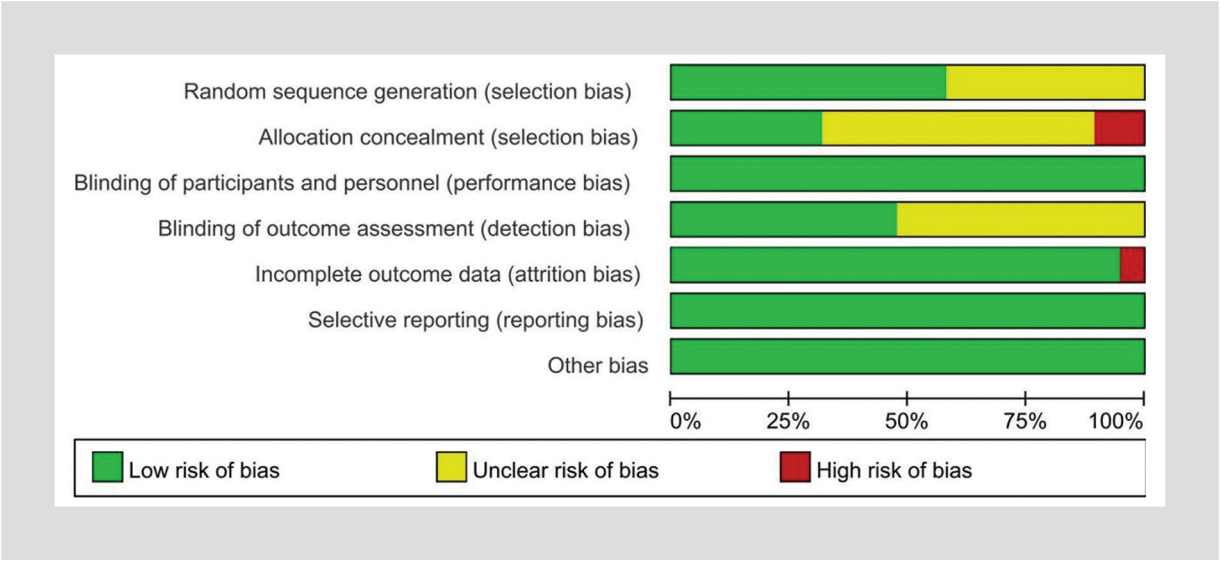

Figure 2. *Risk of bias graph.*

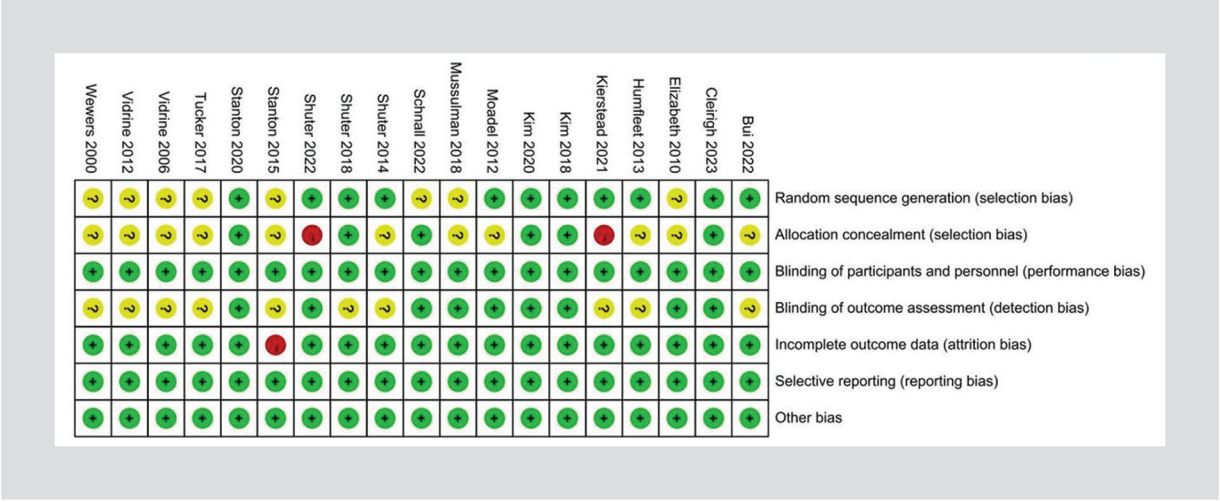

Figure 3. *Risk of bias summary.*

used a combination of cognitive behavioral therapy and text messaging. Finally, one study used a combination of smoking counseling and adherence improvement, one utilized a smoking application, four employed a smoking cessation website, and one utilized motivational interviewing. In terms of outcome, 15 studies reported expired carbon monoxide-verified 7-day point prevalence abstinence and seven reported continuous abstinence. The detailed characteristics of the included studies are mentioned in Supplementary Table S3.

Risk of bias within studies

The risk of bias in the 19 included was assessed using the Cochrane RoB tool. The results are detailed in figure 2, which shows the judgments for all domains in the percentage form, and figure 3, which displays the domain-specific risk of bias in all the included studies. The different colors (red, green, and yellow) and symbols ("–," "+," and "?") in the figures denote "high risk," "low risk," and "unclear risk," respectively. Of the 19

studies, 11 studies reported specific methods for random sequence generation, whereas six studies had a low bias in allocation concealment and two had a high bias. Because it is difficult to keep participants blinded to treatment in behavioral intervention trials, downgrading was considered. One study had high bias because of incomplete outcome data. All RCTs were reported without selectivity and without any other bias.

Certainty of evidence

The certainty of evidence for the outcome of 7-day point prevalence is detailed in Supplementary Table S4. In the analysis of outcomes, 76% of confidence in the evidence was rated low and 23% was rated very low, with only 1% rated as moderate-to-high, primarily because of within-study bias, imprecision, or heterogeneity. Imprecision extended the 95 % CI of most comparisons beyond the area of equivalence, indicating insufficient data to confirm definitive effects. Meanwhile, owing to the absence of closed loops in the analysis, the incoherence of all comparisons was rated as a major concern. Finally, the certainty of evidence for the outcome of continuous abstinence was low.

NMA results of 7-day point prevalence abstinence

Network diagrams

An NMA was performed for 15 studies (Fig. 4). In the figure, the nodes correspond to each intervention included within the network and the interventions with direct comparisons are connected with a line. The thickness of the lines indicates the number of trials evaluating the comparison.

NMA results

The study results revealed that the 7-day prevalence abstinence rate improved the confidence of the participants to quit smoking. For presenting the results, league tables were used to summarize comparisons between pairwise interventions by outcome. At the same time, color shading was used to represent the CINeMA classification results in the league table to increase the visibility and convenience of viewing the strength of evidence. In the analysis, 15 RCTs that assessed the 7-day point prevalence abstinence rate (3055 patients) were included. Supplementary Table S5 shows the NMA of the smoking cessation effect of each

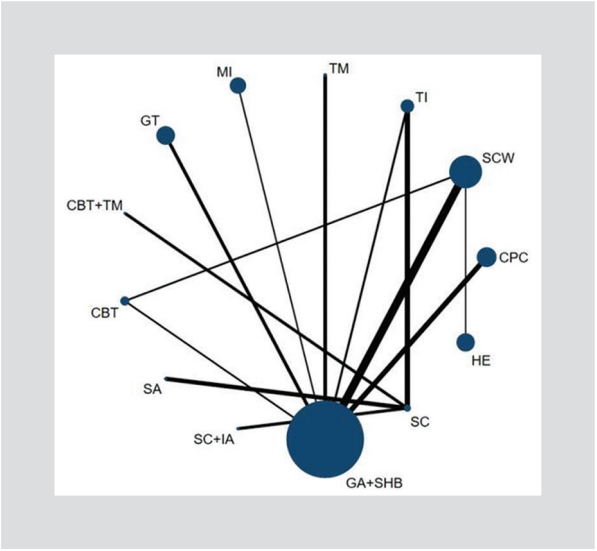

Figure 4. *The network diagram for all interventions. CPC: cell phone counseling; SCW: smoking cessation website; TI: targeted intervention; TM: text message; MI: motivational interviewing; GT: group therapy; CBT + TM: cognitive behavioral therapy + text message; CBT: cognitive behavioral therapy; SA: smoking app; SC + IA: smoking counseling + improving adherence; GA + SHB: general advice + self-help brochure; SC: smoking counseling; HE: health education.*

intervention. The results showed that compared with general advice plus self-help brochure, text messaging was associated with the highest cessation rate (RR = 4.60, 95% CI, 1.12-18.81; low certainty), followed by cell phone counseling (RR = 3.29, 95% CI, 1.71-6.32; high certainty). By contrast, the difference between general advice plus self-help brochures and other methods, including smoking cessation websites, targeted intervention, motivational interviewing, group therapy, cognitive behavioral therapy plus text messaging, cognitive behavioral therapy, smoking application, smoking counseling plus adherence improvement, or health education, was not significant. Meanwhile, compared with smoking counseling, text messaging was associated with the highest cessation rate (RR = 44.56, 95% CI, 3.36-590.09; low certainty), followed by cell phone counseling (RR = 31.88, 95% CI, 3.32-306.01; low certainty), smoking cessation website (RR = 13.61, 95% CI, 1.46-126.92; low certainty), group therapy (RR = 11.73, 95% CI, 1.29-106.33; low certainty), cognitive behavioral therapy (RR = 10.74, 95% CI, 1.11-103.84; low certainty), general advice plus self-help brochure (RR = 9.69, 95% CI, 1.06-1.80; low certainty), and targeted intervention (RR = 9.32, 95% CI, 1.27-68.39; low certainty). By contrast, the difference between smoking counseling and other

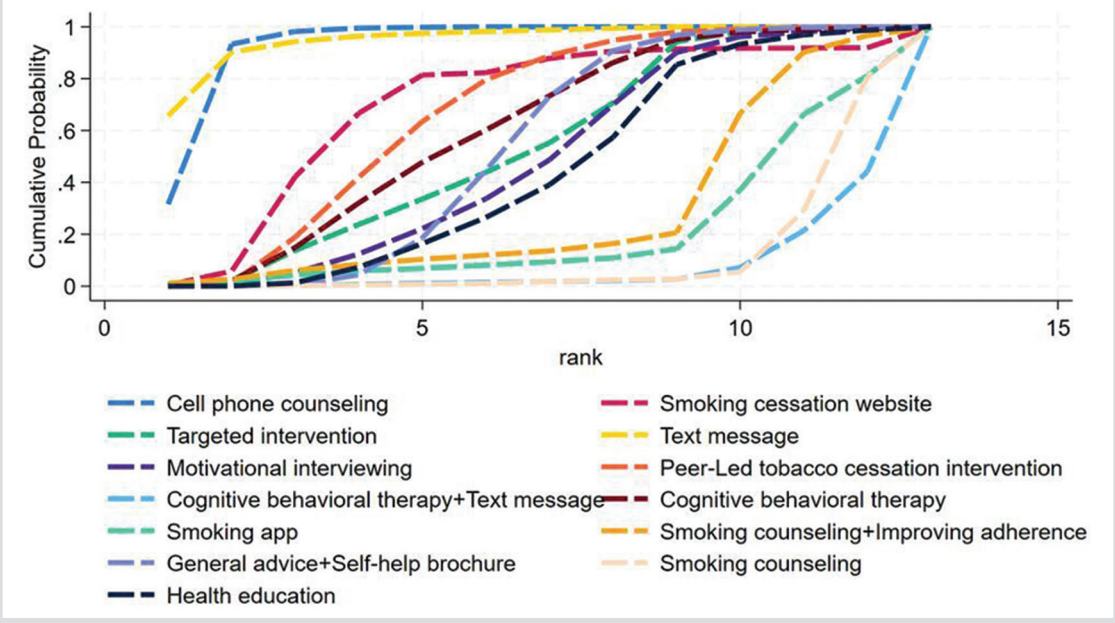

Figure 5. *The surface under the cumulative ranking curve plot.*

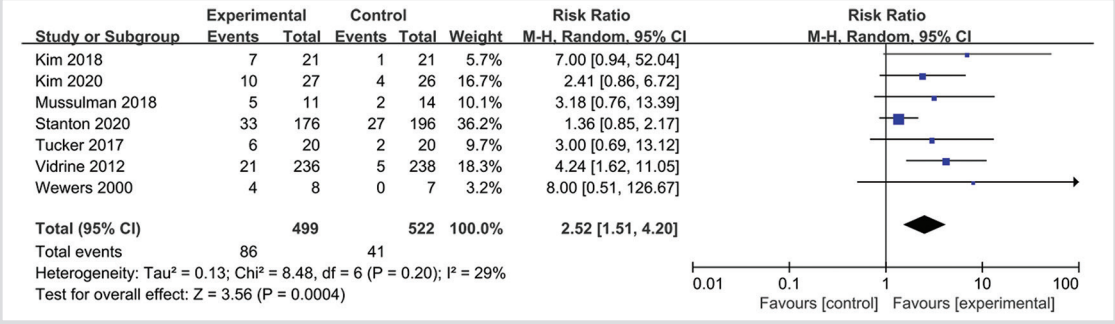

Figure 6. *Forrest plot of continuous tobacco abstinence.*

methods, such as motivational interviewing, cognitive behavioral therapy plus text messaging, smoking application, smoking counseling plus adherence improvement, or health education, was not significant.

Probability ranking

Figure 5 depicts the proportion of area under the cumulative ranking curve for all interventions. The SUCRA ranking probability results showed that the top three most effective smoking cessation methods were text messaging (94.8%), cell phone counseling (93.7%), and smoking cessation website (73.6%). The efficacy of the other interventions, in descending order, was group therapy (65.1%), cognitive behavioral therapy (59.5%), targeted intervention (52.8%), general advice plus self-help brochure (52.5%), motivational interviewing (48.2%), health education (43.7%),

smoking counseling plus adherence improvement (28.3%), smoking application (20.5%), smoking counseling (10.0%), and cognitive behavioral therapy plus text messaging (7.0%). The probability ranking for the outcome of 7-day point prevalence is detailed in Supplementary Table S6.

Meta-analysis results of continuous abstinence

Seven studies (n = 1438) reported the outcome of continuous abstinence (Fig. 6). The results showed that compared with smoking counseling and self-help brochures, the smoking cessation effect was significantly enhanced after behavioral interventions (RR = 2.52, 95% CI, 1.51-4.20), with mild heterogeneity (I^2 = 29%). The certainty of evidence for the outcome of continuous abstinence was low.

Publication bias

More than 10 studies analyzed the outcome of 7-day point prevalence abstinence. Thus, a funnel plot was drawn to assess publication bias. The funnel plot in seven indicates a roughly symmetrical distribution of research points on both sides of the central axis, suggesting a low likelihood of publication bias. Meanwhile, as only seven studies (< 10) reported the outcome of continuous smoking cessation rates, publication bias was not assessed for this group.

Discussion

This NMA study aimed to investigate the impact of multiple behavioral interventions on smoking cessation among patients with HIV. According to the CINeMA approach, an overwhelming majority of relevant published research was of low or very low quality, suggesting that the study findings should be interpreted with caution.

According to the results of the outcome of 7-day point prevalence tobacco abstinence, the top three best smoking cessation effects were text messaging, telephone counseling, and a smoking cessation website. Of note, all these were electronic health interventions administered through mobile devices. Li et al. conducted a systematic review and meta-analysis of studies that employed e-health as a smoking cessation support tool for healthy people, and the results showed that e-health interventions for smoking cessation were effective for smokers from different countries. Indeed, compared with traditional in-person methods, the smoking cessation rate increased by 1.86-fold[28]. Meanwhile, Zhou et al. aimed to determine the efficacy of mobile phone-based interventions compared with usual practice or assessment-only controls on smoking cessation in young people. Their meta-analysis provided evidence that text messaging-based smoking cessation interventions were effective in this study group[29]. Finally, Uthman et al. also noted that among people with HIV, interventions delivered through mobile health may better improve smoking cessation rates in the short term[19]. This finding may be attributed to the nature of electronic products. More importantly, e-health interventions are simpler, more convenient, and easier to disseminate than in-person methods[30]. Thus, these methods offer possibilities for addressing this global issue in public health-challenged areas or environments with unequal medical resources.

Because the secondary outcome of continuous tobacco abstinence was analyzed in 8 of the 19 included studies, a network diagram could not be drawn. Therefore, a meta-analysis was performed for continuous abstinence, which showed that behavioral interventions among smokers with HIV infection had a significant effect on continuous abstinence. However, behavioral interventions led to slightly lower rates of sustained smoking cessation than point-based smoking cessation. Of note, there is a lack of long-term clinical follow-up studies to demonstrate that the effects of smoking cessation can persist for a long period, and more RCTs are needed to validate the evidence in terms of sustained smoking cessation rates.

The quality of included studies in a meta-analysis has an important impact on the level of evidence, and high-quality study designs are more likely to produce reliable evidence[31-33]. For smoking cessation outcomes, the CINeMA evaluation results indicated that the overall quality of the evidence was rated very low-to-high due to low methodological quality, imprecise effect sizes, heterogeneity among studies, and incoherence (differences between direct and indirect evidence). The underlying heterogeneity of the included RCTs may be a key contributor to the inconsistencies, which were reflected in trial conditions (e.g., intervention dose and duration of treatment) and population differences (duration of disease and duration of smoking). At the same time, most RCTs need to be methodologically well designed to provide more details on determining whether the design of random sequences and assignment concealment is standardized as well as details on how to implement the design. Meanwhile,

the sample sizes among the included RCTs were different, which may have produced wider CIs for the combined effect sizes in the case of small sample sizes and resulted in imprecise effect sizes. The study results showed that indirectness and inconsistency may affect NMA stability[34]. These potential factors warrant further attention in future clinical trials and public health practice.

Researchers should consider the influence of more factors on the effect of smoking cessation when conducting similar studies to improve the quality of evidence. The basic characteristics of the population, daily smoking frequency, and smoking duration should be considered the most important factors during participant recruitment to avoid differences between the populations and reduce heterogeneity. Finally, studies focusing on the effect of long-term smoking cessation (> 6 months) in patients with HIV are lacking, and researchers should consider including the sustained smoking cessation rate as an outcome in similar studies in the future.

The strengths of this systematic review include the use of NMA to produce reliable estimates of 7-day prevalence abstinence in smokers with HIV. Moreover, the CINeMA approach was employed to assess the certainty of the evidence, which was highlighted in the result tables.

The study also had some limitations. First, only 19 RCTs were included in this analysis, which may have reduced the statistical power of direct evidence, as the number of studies is proportional to the level of evidence in meta-analysis. Second, only PLWH with self-reported cigarette use were included, and population differences (sex, education level, daily smoking frequency, and smoking duration) and changes in intervention conditions (intensity of intervention and duration of intervention) may have produced certain heterogeneity in the results. Third, as it is difficult to blind the implementers of interventions in non-pharmacological trials, the study may have suffered from low methodological quality and a high risk of bias.

Conclusion

NMA was performed to explore the impact of different behavioral interventions on smoking cessation in patients with HIV. The results revealed very low-to-high-quality evidence that text messaging, telephone counseling, and smoking cessation websites were effective for smokers with HIV. However, owing to the lack of indirect evidence for continuous abstinence, more research focusing on the outcome of continuous abstinence is required to validate the current study results.

Supplementary data

Supplementary data are available at DOI: 10.24875/AIDSRev.24000008. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

Authors' contribution

Xinyu Huang and Junjie Ren contributed to the research design and data analysis, drafted the protocol, and wrote the paper. Xu Hui, Liying Zhou, and Liping Guo participated in data collection and management. Kehu Yang and Li Xu made critical revisions to the paper. All authors reviewed and approved the final version of the manuscript.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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