Intensive versus short face-to-face smoking cessation interventions: a meta-analysis

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Abstract

Objectives To evaluate the efficacy of intensive smoking cessation interventions (ISCIs) directly compared with shorter interventions (SIs), measured as successful quitting.

Method Medline, Embase, the Cochrane Library and CINAHL were searched on 15 October 2021. Peer-reviewed randomised controlled trials (RCTs) of adult, daily smokers undergoing an ISCI were included. No setting, time or language restrictions were imposed. Risk of bias and quality of evidence was assessed using the Cochrane tool and Grading of Recommendations, Assessment, Development and Evaluation, respectively. Meta-analyses were conducted using a random-effects model.

Results 17 550 unique articles were identified and 17 RCTs evaluating 9812 smokers were included. 14 studies were conducted in Europe or the USA. The quality of the evidence was assessed as low or moderate. Continuous abstinence was significantly higher in ISCIs in the long term (risk ratio 2.60, 95% CI 1.71–3.97). Direction and magnitude were similar in the short term; however, they were not statistically significant (risk ratio 2.49, 95% CI: 0.94–6.56). When measured as point prevalence, successful quitting was still statistically significant in favour of ISCIs, but lower (long term: 1.64, 1.08–2.47; short term: 1.68, 1.10–2.56). Sensitivity analysis confirmed the robustness of the results.

Conclusion ISCIs are highly effective compared to SIs. This important knowledge should be used to avoid additional morbidity and mortality caused by smoking.

Introduction

Tobacco smoking is the deadliest preventable behavioural lifestyle factor worldwide, with over 1 billion current smokers. It caused almost 8 million deaths, one in five deaths among men and 200 million disability-adjusted life-years in 2019 [1]. Smoking cessation interventions (SCIs) have been thoroughly investigated, and more than 1000 systematic reviews have been published on how to assist quitting – ranging from minimal interventions such as brief advice [2] over specific frameworks, techniques and components [3–9] to programmes combining more elements [10–13], each with different impacts on successful quitting. Overall, the reviews report that SCI programmes are rather heterogeneous and that evidence-based standardised treatments and guidelines differ among countries. The updated World Health Organization (WHO) recommendations focus on short interventions (SIs), such as brief advice taking a few minutes, national quit-lines and mobile messages, leading to quit rates of 2–5%, as well as nicotine replacement therapy, bupropion and varenicline as standalone SIs, leading to 6%, 7% and 15% quit rates, respectively. With the exception of brief advice, the recommendations are expected to reach only a few percent of the global smoking population [14].
Some countries recommend comprehensive multi-factorial programmes, so-called intensive smoking cessation interventions (ISCIs), as their standard treatment. They were originally described in US clinical practice guidelines for treating tobacco use and dependence [15–17]. A similar programme was developed in Denmark and recommended as the standard treatment by the Danish Health Authorities [18]. Recently, two more national ISCIs were developed and evaluated in real-life settings [19]. Health services in other countries, e.g., the National Health Service in England [20] and the National Board of Health and Welfare in Sweden [21], recommend ISCIs for specific groups considered in high need of successful quitting, all delivered face-to-face by trained staff.

Definitions
Systematic reviews have used different definitions of ISCI [10–13], with a focus on the duration of the intervention [10, 11, 22]. In this systematic review we have used the original US core criteria.

In the US, an ISCI is defined by including 1) individual or group-based education of the smoker involving recognition of dangerous situations, coping skills and basic information, 2) motivational or behavioural counselling, 3) supportive medication and 4) follow-up through at least four in-person sessions, each lasting >10 min [17].

While still fulfilling the core criteria, an ISCI is often tailored individually; so, in addition to the mentioned core criteria, the use of different clinicians is strongly encouraged and self-help material, telephone counselling or web-based cessation aids can be used as supplements. The similar Danish ISCI [23, 24] is known as the Gold Standard Programme (GSP) and has been successfully evaluated in randomised studies [25, 26], including across vulnerable groups of smokers [27–31]. It has been proven to be effective, with a successful quit rate of 25–33% after national implementation [19].

Justification for conducting this review
As SIs have become the routine recommendation, it would be relevant to compare the effect of an ISCI with using shorter intervention as the control group. We have not been able to identify any previous systematic reviews that aimed to directly compare the effects of ISCIs and SIs.

Some years ago, a systematic review reported a significant but marginally increased 6-month quit rate (13% versus 11%) for combined behavioural counselling and supportive medication compared to the control group that only received medication. Behavioural counselling without pharmacology also resulted in a significant difference (11% versus 7%) [11]. Other systematic reviews have reported indirectly compared impacts of several elements of an ISCI [12, 13] and a recent, but still indirect, network meta-analysis evaluated the impact of several specific elements on quit rates, of which behavioural counselling and financial initiatives showed a significant effect when compared to no or alternative interventions (14% and 10% versus 5%) [22].

In theory, a comprehensive programme taking into account more elements, each of which could impact successful quitting, may be followed by a greater effect. On the other hand, indirect comparisons of increasing number and duration of sessions have only have only shown a trend towards an effect [11, 22].

From a user, clinical and healthcare point of view, it is therefore important to gather new knowledge by directly comparing the efficacy of an ISCI against SIs based on the definition above.

The aim was, therefore, to evaluate the long-term continuous abstinence (CA) associated with ISCIs compared directly with SIs in adult daily smokers in a systematic review design; other aims were to evaluate CA in the short term as well as point prevalence abstinence (PP) in both the short and long term. We also sought to investigate the effects of ISCIs in different subgroups.

The main hypothesis was that long-term CA was higher after attending an ISCI than after an SI.

Methods
This systematic review was performed in accordance with a publicly available pre-submitted protocol (PROSPERO 2017; CRD42017059879) and reported in line with the PRISMA guidelines [32].

Eligibility criteria
Randomised controlled trials (RCTs) that were randomised at an individual level and published in peer-reviewed journals were included without time or language restrictions.
Studies were considered if they described the method of inclusion, the interventions, the comparison group, the participants and successful quitting at follow-up.

All participants had to be $\geq 18$ years of age and smoke $\geq 1$ cigarette daily at the time of inclusion. We used the definition of ISCI described above [15, 17] with the following core criteria to identify an intensive intervention: $\geq 4$ scheduled in-person meetings, each $> 10$ min, including patient education (e.g. basic information, recognition of dangerous situations and coping skills). Both individual and group interventions were included without restrictions on pharmacotherapy or setting.

We excluded studies on contingency reinforcement to reward or punish participants financially according to outcome, as this was not part of the original definition.

The ISCIs were evaluated against SIs, defined as interventions delivered in-person and/or by telephone with a maximum of three in-person sessions and 1 h in total.

We excluded studies that did not include an intervention that agreed with the definition of an SI above. This was also the case for studies insufficiently described in relation to being able to determine whether the definitions were met regarding the intervention. In cases of doubt the authors were contacted before excluding a study.

**Search strategy**

The search strategy “(Smok* OR Tobacco) AND (Gold Standard Program* OR GSP OR Intensive OR Patient Education OR Cessation) AND (Random* OR Control*)” was used in combination with the filters: “Randomized controlled trial”, “Controlled Clinical Trials” and “Adult” (online supplement A).

The search was carried out from inception until 15 October 2021 in Medline (via PubMed), Embase (via Ovid), CINAHL (via EBSCO) and the Cochrane Central Register of Controlled Trials (CENTRAL). Manual and reference searches were added (figure 1).

**Definition of outcome**

All outcomes in this study were successful quitting measured as CA or PP in the long or short term. The efficacy was estimated as the proportion of successful quitters according to the intention-to-treat principles [33, 34], i.e. the number of randomised patients was the denominator.

The primary outcome was measured as CA after 6 or 12 months (long term), respectively. Secondary outcomes were CA at the end of the intervention (short term) and PP, also in the short and long term. The outcome measures for successful quitting were used as defined by Hughes *et al.* [35].

**Study selection and extraction of information**

All identified papers were uploaded to the Covidence software [36] to combine searches and remove duplicates. Thereafter, the procedure outlined in Covidence was followed to identify relevant studies, assess quality (risk of bias) and extract data.

All stages of the screening were conducted independently by two authors and, in the case of disagreement, a third author made the final decision. Potentially relevant studies identified in the title and abstract screening by authors H.T., M.R., S.V.L. or B.P. were forwarded for full-text screening by M.R., B.P. or S.V.L.

Data extraction was also conducted independently by two in three authors (M.R./S.V.L./B.P.), and disagreements were resolved through discussion and consensus.

The extraction forms in Covidence were used for each study: study details (e.g., country, setting and sponsorship), publication year, corresponding author, design, inclusion and exclusion criteria, interventions, and participants. We also extracted: baseline characteristics (age, sex, and tobacco consumption), meeting adherence, attrition and successful quitters at the end of intervention and 6- and 12-months post intervention. Successful quitting was collected as self-reported CA and PP with or without validation.

Two in three authors (M.R./S.V.L./B.P.) independently assessed the risk of bias using the Cochrane Collaboration tool [33], and disagreements were resolved through discussion and consensus. We assessed the following domains: random sequence generation, allocation concealment, blinding of outcome

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assessors, incomplete outcome data, selective reporting and other sources of bias. As blinding of participants or intervention staff is hardly possible, all studies were granted a high risk of bias.

Furthermore, GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was used by two assessors (M.R. and S.V.L.) to assess the quality of the body of evidence.

**Data synthesis and statistical analysis**

Meta-analyses were performed in Review Manager 5.3, using a random-effect model (DerSimonian and Laird inverse variance method) to estimate the pooled treatment effect on successful quitting, reported as risk ratio ± confidence interval (CI), with a two-sided p-value. This model was chosen to allow for between-study variance because we expected the included populations and settings to differ. Analyses were only conducted for studies with comparable outcomes, and results were presented using forest plots.

The efficacy was summarised by estimating risk ratios and 95% CIs. Before the meta-analyses, studies testing more than two interventions were collapsed into two arms (ISCI and SI). Arms not fulfilling any of the definitions for ISCI or SI were excluded from the analysis. If results were reported as percentages, the total number of successful quitters was calculated using the percentage and the number of patients included.

To explore statistical heterogeneity, we performed several sensitivity analyses by excluding: 1) studies with a high risk of bias (≥2 assessments showing a high risk of bias), 2) studies with high attrition (≥50%) and

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**FIGURE 1 PRISMA flowchart of the literature search and study selection. ITT: intention to treat; RCT: randomised controlled trial.**

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3) we decided to analyse studies with low compliance post hoc (≤50%). Studies without information on the factor under investigation were excluded.

The possibility of reporting bias was evaluated by drawing funnel plots and testing the presence of small-study effects using the Egger test [37] in STATA.IC version 17 for any outcome including at least 10 studies.

Results

The searches yielded 26 100 publications. After removing duplicates and screening titles/abstracts, 573 studies remained for full-text assessment. Of those, 556 studies were excluded, leaving 17 studies [25, 26, 38–62] for inclusion (figure 1).

Study characteristics

The study characteristics are summarized in table 1. All 17 studies included in the qualitative synthesis were also included in the meta-analysis. The 17 RCTs were published during 1994–2020 and included 9812 smokers; 6130 smokers were randomised to ISCIs and 3682 to the comparison condition SIs. We excluded 188 smokers from two studies [38, 43] because the intervention did not fulfil the criteria for ISCIs or SIs.

The majority of the studies was conducted in Europe (n=8) [25, 26, 40–42, 58, 61, 62] or in the USA (n=6) [38, 39, 44, 45, 48, 60]. Three studies were conducted in Syria [57], Qatar [59] and Iran [43], respectively. One study only included women [40] and one only men [43]; overall, 58% of the participants were men.

At baseline, the mean level of daily cigarette smoking ranged from 10.0 to 35.7 cigarettes per day [40, 58], and nicotine dependence 2.5–7.3 [38, 40] on the Fagerström test for nicotine dependence (FTND). Only two studies reported an FTND score below 5.0 [40, 43].

The studies included citizens (8), surgical patients (2), lung patients (2), cardiac patients (2), people with a psychotic disorder (2) and nurses (1).

Only two studies [40, 44] specifically mentioned that they did not request participants to be motivated to quit.

For eight studies, we used more information than originally published. Supplementary references are added in table 1.

One study [44] reported prolonged abstinence (PA) in the past year, allowing a 2-week grace period. As the intervention lasted 6 months, the 12 months PA was reported after 18 months. We treated this outcome as CA, even though it included a possible grace period. One study [26] included smokers who had quit ≤3 days before randomisation.

Interventions and measurements

All included studies fulfilled the core criteria defining an ISCI, but the interventions varied regarding minutes per session from 13 to 180, number of sessions from 4 to 20, and the calendar time interval from 4 weeks to 6 months. Furthermore, the use of pharmacotherapy differed as 11 studies used pharmacotherapy as part of the intervention, whereas one study did not allow either group to use pharmacotherapy [42]. The date of quitting was reported in six studies. In ALTERMANN et al. [48], GILBODY et al. [61] and GILBODY et al. [62] the quit day was planned in agreement with the smoker during the first meeting. In the remaining seven studies, the quit day was neither described, reported nor commented upon [39–41, 44, 56, 57].

Eight studies [25, 26, 39, 41, 42, 44, 57, 59] measured successful quitting as CA, while all but two studies [25, 26] reported PP; eight studies [25, 38, 39, 43, 44, 48, 59, 60] reported successful quitting in the short and long term; of these, two reported both CA and PP [39, 59], one CA only [25], four PP only [38, 43, 48, 60] and one PP in the short term and CA in the long term [44].

Based on this, 32 datasets were extracted for meta-analyses. The study by WILLIAMS et al. [44] comprised four meetings in 6 months, thus the 6-month outcome could be short- or long-term follow-up. A 12-month PA was reported after 18 months. We had pre-defined the 6-month follow-up as short term (end of intervention) and therefore used the follow-up at 18 months as the long-term outcome.

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<table>
<thead>
<tr>
<th>Study/country</th>
<th>N/arms</th>
<th>Men (%)</th>
<th>Mean age (years)</th>
<th>FTND/cigs per day</th>
<th>Motivation</th>
<th>Participants/setting</th>
<th>Outcome</th>
<th>Compliance (%)</th>
<th>FU rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alterman et al. [48]</td>
<td>240/3</td>
<td>50.8</td>
<td>40.2</td>
<td>6.9/26.9</td>
<td>At least one previous failed attempt at cessation</td>
<td>Citizens</td>
<td>PP^a, end, 6 months, 12 months CO ≤ 9 ppm</td>
<td>NI</td>
<td>End: 84% 6 months: 85% 12 months: 92%</td>
</tr>
<tr>
<td>Anthonsen et al. [56] / USA [45–47]</td>
<td>5.887/3</td>
<td>62.9</td>
<td>48.5</td>
<td>NI/31.3</td>
<td>Agree to enter an SCI</td>
<td>Citizens with mild to moderate COPD</td>
<td>PP: 12 months CO ≤ 10 ppm COT salivary ≤ 22 ng·mL^{-1}</td>
<td>NI</td>
<td>End: NI 6 months: NI 12 months: 95%</td>
</tr>
<tr>
<td>Assar et al. [57]</td>
<td>50/2</td>
<td>86</td>
<td>34.8</td>
<td>5.0/NI</td>
<td>Desire to quit smoking</td>
<td>Citizens/cessation clinic at hospital</td>
<td>CA: End PP^c; End CO ≤ 10 ppm</td>
<td>40</td>
<td>End: 64% 6 months: NI 12 months: NI</td>
</tr>
<tr>
<td>Brunner Frandsen et al. [58] / Denmark</td>
<td>94/2</td>
<td>58.5</td>
<td>NI</td>
<td>NI/35.7</td>
<td>NI</td>
<td>Ischaemic stroke or transient ischaemic attack/hospital</td>
<td>PP^d: 6 months CO &lt; 8 ppm</td>
<td>88</td>
<td>End: NI 6 months: 42% 12 months: NI</td>
</tr>
<tr>
<td>El Hajj et al. [59]</td>
<td>314/2</td>
<td>97.7</td>
<td>NI^a</td>
<td>5.2/22.5</td>
<td>Motivation to quit</td>
<td>Citizens/ pharmacies</td>
<td>CA: End, 6 months, 12 months PP: End, 6 months, 12 months PP^b: End, 6, 12 CO ≤ 6 ppm</td>
<td>36</td>
<td>End: 63% 6 months: 63% 12 months: 55%</td>
</tr>
<tr>
<td>Gifford et al. [60]</td>
<td>303/2</td>
<td>41.3</td>
<td>45.99</td>
<td>NI/24</td>
<td>At least one quit attempt in past 2 years with ≥24 h of abstinence</td>
<td>Citizens</td>
<td>PP^d: End, 6 months, 12 months CO ≤ 10 ppm</td>
<td>59</td>
<td>End: 70% 6 months: 51% 12 months: 45%</td>
</tr>
<tr>
<td>Gilbody et al. [61]</td>
<td>97/2</td>
<td>59.8</td>
<td>47.2</td>
<td>6.1/24.8</td>
<td>Interest in cutting down or quitting smoking</td>
<td>Severe mental illness/ mental health sites</td>
<td>PP^d: 1 month, 6 months PP^d 12 months CO &lt; 10 ppm</td>
<td>NI</td>
<td>1 month: 86% 6 months: 71% 12 months: 70%</td>
</tr>
<tr>
<td>Gilbody et al. [62]</td>
<td>526/2</td>
<td>58.7</td>
<td>46.0</td>
<td>NI/24.0</td>
<td>Interest in cutting down or quitting smoking</td>
<td>Severe mental illness/ mental health sites</td>
<td>PP^d, 6 months, 12 months CO &lt; 10 ppm</td>
<td>6.4±3.5 Median: 6</td>
<td>6 months: 89% 12 months: 88%</td>
</tr>
<tr>
<td>Jorenby et al. [38]</td>
<td>504/6</td>
<td>46.6</td>
<td>44.2</td>
<td>7.3/27.8</td>
<td>NI</td>
<td>Citizens</td>
<td>PP^e: End, 6 months CO &lt; 10 ppm</td>
<td>NI</td>
<td>End: 79% 6 months: 86% 12 months: NI</td>
</tr>
<tr>
<td>Kehlet et al. [26]</td>
<td>32/2</td>
<td>78.6</td>
<td>65/61^f</td>
<td>NI/14 (22)^f</td>
<td>NI</td>
<td>Vascular surgery/hospital</td>
<td>CA: End</td>
<td>73</td>
<td>End: 88% 6 months: NI 12 months: NI</td>
</tr>
<tr>
<td>Mohiuddin et al. [39] / USA</td>
<td>209/2</td>
<td>62.7</td>
<td>65/61^f</td>
<td>&gt;7/24.1</td>
<td>NI</td>
<td>Acute cardiovascular disease/hospital</td>
<td>CA: End, 6 months</td>
<td>8.3±5.4</td>
<td>End: 96% 6 months: 96% 12 months: 96%</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
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<th>Outcome</th>
<th>Compliance (%)</th>
<th>FU rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUIKA et al. [40]/Spain</td>
<td>30/2</td>
<td>0</td>
<td>40.2</td>
<td>2.5/10.0</td>
<td>Thinking about quitting was irrelevant</td>
<td>Nurses/teaching hospital</td>
<td>PP: End CO &lt;8 ppm COT urine: 500 ng·mL⁻¹ (COT if reporting abstinence for at least 1 week)</td>
<td>100</td>
<td>End: 100% 6 months: NI 12 months: NI</td>
</tr>
<tr>
<td>MØLLER et al. [25]/Denmark [51]</td>
<td>120/2</td>
<td>42.6</td>
<td>64/66f</td>
<td>NI/15 (3–30)##</td>
<td>NI</td>
<td>Elective hip or knee allograft/hospital</td>
<td>CA: End, 12 months</td>
<td>NI</td>
<td>End: 90% 6 months: NI 12 months: 84%</td>
</tr>
<tr>
<td>NØHLERT et al. [41]/Sweden [52]</td>
<td>300/2</td>
<td>21.8</td>
<td>48.6</td>
<td>NI/NI</td>
<td>NI</td>
<td>Citizens/dentist clinic</td>
<td>CA: 12 months PP: 12 months</td>
<td>68</td>
<td>End: NI 6 months: NI 12 months: 85%</td>
</tr>
<tr>
<td>ROMAND et al. [42]/France [53]</td>
<td>228/2</td>
<td>46.5</td>
<td>43/43f</td>
<td>NI*/20 (1–30)##</td>
<td>Willing to make an attempt at quitting</td>
<td>Citizens</td>
<td>CA*: 12 months PP: 6 months, 12 months CO &lt;10 ppm</td>
<td>53</td>
<td>End: NI 6 months: 50% 12 months: 84%</td>
</tr>
<tr>
<td>SHARIPOUR et al. [43]/Iran [54]</td>
<td>60/3</td>
<td>100</td>
<td>53.6</td>
<td>4/23 (5–60)##</td>
<td>NI</td>
<td>COPD/hospital</td>
<td>PP: End, 6 months</td>
<td>95</td>
<td>End: 95% 6 months: 95%</td>
</tr>
<tr>
<td>WILLIAMS et al. [44]/USA [55]</td>
<td>1006/2</td>
<td>36.1</td>
<td>45.5</td>
<td>5.0/20.5</td>
<td>None needed</td>
<td>Citizens</td>
<td>PP: End PA**: 12 months</td>
<td>NI</td>
<td>End: 70% 12 months: 63%</td>
</tr>
</tbody>
</table>

##: not clear if the reported outcome is PP or CA. *: available as categories. #: self-reported outcome despite a CO threshold. #: not defined. f: median (control/intensive smoking cessation intervention). ##: median (range). **: included in the CA analyses. CA: continuous abstinence; cigs: cigarettes; COPD: chronic obstructive pulmonary disease; COT: cotinine; FTND: Fagerström test for nicotine dependence; FU: follow-up; GC/MS: gas chromatography–mass spectroscopy; NI: no information; PA: prolonged abstinence; PP: point prevalence; PP/PP30: 7-day/30-day point prevalence; SCI: smoking cessation intervention.

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In 12 studies [38–40, 42, 48, 56–62], successful quitting was validated by carbon monoxide (CO) and/or cotinine measurements. Combined CO and cotinine was used in three studies [40, 48, 56], while nine studies [38, 39, 42, 57–62] used CO only. On a participant level this equates to smoking status being validated in 85% of the participants.

Assessment of risk of bias
As it is hardly possible to blind participants and interventions staff, all studies were assigned a high risk of bias in this regard.

One study [56] was assessed as having a low risk of bias in all other categories, the rest had a moderate risk of bias (online supplement B).

Five studies were considered at high risk of bias due to high attrition. Two studies [26, 59] were graded at a high risk of bias in other areas because the distribution of ISCI and SI was rather uneven despite parallel allocation to the arms and a block-randomisation design.

We appraised the quality of the evidence according to the GRADE assessment. The CA outcomes were rated as moderate regardless of the time interval, as was PP in the long term. PP in the short term was ranked low (online supplement C).

Successful quitting

CA
Six studies reported long-term CA [25, 39, 41, 42, 44, 59] and included 2177 smokers; and 164/1319 (12.4%) versus 50/858 (5.8%) were successful quitters after ISCI and SI, respectively. One study [57] found SI to be more effective than ISCI, in both the short and long term. Long-term follow-up showed a statistically significant association (risk ratio 2.60, 95% CI 1.71–3.97; p<0.001) (figure 2a). This resulted in an additional 152 (100–231) in 1000 smokers being continuously abstinent in the long term after an ISCI (online supplement C).

The five studies [25, 26, 39, 57, 59] reporting short-term outcomes included 725 smokers, of which 140 in 372 (37.6%) were abstinent in the ISCI group, and 45 in 353 (12.7%) in the SI group; however, without being statistically significant (risk ratio 2.49, 95% CI 0.94–6.56; p=0.07) (figure 2b).

PP
In the long term, 12 studies [38, 39, 41–43, 48, 56, 58–62] reported on 8574 smokers, resulting in 1687 of 5305 (31.8%) and 380 of 3269 (11.6%) abstaining following ISCI or SI, respectively (risk ratio 1.64, 95% CI 1.08–2.47; p=0.02) (figure 2c).

The nine studies [38–40, 43, 44, 48, 57, 59, 60] reporting short-term outcomes included 2528 smokers, with 405 of 1507 (26.9%) being abstinent in the ISCI group and 213 in 1021 (20.9%) in the SI group (risk ratio 1.68, 95% CI 1.10–2.56; p=0.02) (figure 2d).

When comparing the same studies measured as CA and PP in both the short and long term, only one study [39] in the long term was more in favour of ISCI when measured as PP, and no studies in the short term.

Exploration of heterogeneity
Only in long-term CA could the heterogeneity be considered moderate (I²=41%). The remaining three meta-analyses revealed substantial heterogeneity (I²=83–90%). Three sensitivity analyses were conducted to explore the variance (i.e. heterogeneity); one sensitivity analysis excluding studies rated a high risk of bias for at least two domains, one excluded studies with high attrition (at least 50%) and one excluded studies with a low degree of participant compliance (less than 50%) measured as meeting adherence.

While a high risk of bias explained a substantial part of the variance for the outcome of CA, this was not the case for the PP outcomes (table 2). High attrition did not explain any of the heterogeneity, mainly due to the fact that PP in the long term was the only outcome that covered studies with high attrition and this result was only affected slightly, lowering the I² from 90% to 88% (table 2).

In contrast, excluding studies with low compliance was the factor that reduced the between-study variance the most for all outcomes. In the CA analyses, heterogeneity was lowered to 24% and 14% in the short and long term, respectively. In the PP analyses, I² was reduced from 90% to 46% in the long term.
Meta-analysis of all studies reporting continuous abstinence and/or point prevalence divided into short- and long-term follow-up.

Risk of bias legend: A) random sequence generation (selection bias); B) allocation concealment (selection bias), C) blinding of participants and personnel (performance bias), D) blinding of outcome assessment (detection bias), E) incomplete outcome data (attrition bias), F) selective reporting (reporting bias), G) other bias. CI: confidence interval; M-H: Mantel–Haenszel.

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**FIGURE 2** a-d) Meta-analysis of all studies reporting continuous abstinence and/or point prevalence divided into short- and long-term follow-up. Risk of bias legend: A) random sequence generation (selection bias); B) allocation concealment (selection bias), C) blinding of participants and personnel (performance bias), D) blinding of outcome assessment (detection bias), E) incomplete outcome data (attrition bias), F) selective reporting (reporting bias), G) other bias. CI: confidence interval; M-H: Mantel–Haenszel.
However, in the short term, it was only reduced to 76%, which is still considered a substantial amount of heterogeneity.

None of the sensitivity analyses altered the direction of the results which point towards robust results. Regarding the efficacy of ISCIs compared to SIs, the summary effect remained the same or increased for all outcomes.

Due to extensive differences in the included populations, as well as in the reporting and timing of outcomes, we did not consider it appropriate to perform subgroup analyses.

**Assessment of reporting bias**

We found few studies that met our criteria and only the PP long-term outcome included ≥10 studies. Based on the funnel plot (figure 3) and the Egger test results (p=0.008) we cannot exclude the possibility of reporting bias, though an asymmetric funnel plot can be caused by several other causes, such as e.g. selection bias, true heterogeneity and methodological flaws [37, 63]. Likewise, there is a possibility of reporting bias in any of the other three outcomes assessed.

**Discussion**

In this study, we systematically reviewed the efficacy of ISCIs compared directly with SI. 17 studies were identified and we confirmed our main hypothesis by finding a significant effect in favour of ISCIs when measured as CA in the long term. The tendency was the same in the short term though not statistically

![SE(log[risk ratio])](https://doi.org/10.1183/16000617.0063-2022)
significant. In addition, the efficacy was statistically significant, though less distinct, in the ISCI when measured as PP in both the short term and the long term.

The subject of ISCIs has been touched upon in other systematic reviews, mainly during the last decade; however, they used indirect comparison methods and were limited to specific subpopulations or formats of intervention. This is exemplified by a systematic review investigating the long-term efficacy of interventions for pre-operative smoking cessation, which reported that the sub-analysis of intensive interventions had higher efficacy than the sub-analysis for brief interventions; the crude quit rates being 29.8% versus 10.5% (risk ratio 2.96, 95% CI 1.57–5.55) and 17.5% versus 16.0% (risk ratio 1.09, 95% CI 0.68–1.75), respectively [12].

Another review of hospitalised patients reported the quit rates after categorising the studies into four groups of intensity based on number and duration of contacts and follow-up. The sub-analysis of patients receiving the most intensive interventions initiated in the hospital and extending for at least 1 month after discharge had a significantly higher crude quit rate and risk ratio for remaining abstinent in the longer term when compared to their control groups, 29.3% versus 20.6% (risk ratio 1.37, 95% CI 1.27–1.48), while the other categories did not reach statistical significance, e.g. the shortest intervention showed 10.0% versus 8.8% (risk ratio 1.14, 95% CI 0.82–1.59). These results also show the challenges caused by the accumulated control groups in a meta-network-analysis, as the results from the control groups differed in each of the four categories: 8.8%, 17.4%, 13.4% and 20.6% [13].

A more recent comprehensive systematic review focused on two of the core criteria in ISCIs, the contact time and number of sessions [11]. They were categorised into five and four groups, respectively. The separate sub-analyses identified that the crude quit rates in the intervention groups as well as the risk ratio increased with higher numbers of sessions and longer duration of contact; ranging from 8.4% to 14.6–35.0% for both outcomes versus 8.0% to 9.1% and 8.0% to 9.5% in the control groups. Furthermore, this demonstrates the overlap per se by the two criteria of intensity.

Our study was the first to use the definition of ISCI proposed in the US clinical practice guidelines for treating tobacco use and dependence [15–17]. Moreover, the above-mentioned studies were limited to specific sub-populations or formats of intervention (e.g., individual interventions).

This study has bias and limitations; one of which concerns compliance. Among the 17 included studies, meeting adherence was not reported in any way in six studies [25, 38, 44, 48, 56, 61]. Additionally, compliance was generally low, with only four studies reporting that ≥75% smokers were compliant. Compliance has shown to be of the greatest importance to benefit most from the intensive Danish GSP [64]: participants doubled their CA for each of the five meetings they attended. Therefore, we assumed that low compliance to the ISCI could influence the summary effect in a negative way.

Another challenge of this study is that although the ISCIs fulfil the pre-defined core criteria [17], they may differ in other ways by adding different extra elements to the programme and by using different measures of successful quitting [35, 65, 66] and follow-ups.

Intuitively, one would expect the PP to be higher than the CA, as it is easier to remain abstinent for the very short period used in PP. When looking at the separate sub-analyses, this also seems to be the case for the long-term crude quit rates; 12.4% and 5.8% for CA, and 31.8% and 11.6% for PP, but not for the weighted risk ratio.

Overall, the included studies had a moderate risk of bias. In general, it is not possible to blind neither participants nor the healthcare personnel when evaluating behavioural interventions such as smoking cessation; thus, all studies were assessed as having a high risk of bias in this respect. The main purposes of the included studies also varied. While some studies were consistent with the aim of this review, others aimed to investigate more main outcomes (e.g., post-operative complications [25, 26] or annual decline in lung function [56]) and a multiple risk behaviour change intervention [44].

Finally, this review mainly included studies from North America and Western Europe, and only three from Syria [57], Qatar [59] and Iran [43]. The results should therefore be considered carefully before generalising them to other parts of the world.

Among the strengths of our review were the inclusion of only RCTs randomised on an individual level and the conduction of an extensive literature search, resulting in more than 17,550 potentially relevant
publications. Surprisingly, only 17 studies met the inclusion criteria with a clear definition [15, 17] without meeting the exclusion criteria. This indicates that the research area of directly comparing ISCIs with SIs may not yet have been fully investigated. We also ran sensitivity analyses confirming the robustness of the results.

The perspectives of improved SCI outcomes are tremendous.

The health consequences of smoking have long been established [67], as have the health benefits of smoking cessation [68, 69]. SCIs are a pivotal means of tobacco control. It is essential to offer the most effective SCIs available to limit the development and aggravation of noncommunicable diseases and other negative impacts of smoking, such as post-operative complications [70].

Based on our findings, twice as many smokers allocated to an ISCI – directly compared with SIs – remained continuously abstinent in the long term. This is not only a statistically significant result but a result of great importance for individual smokers and their families. Given that most smokers want to quit [71–73], the widespread frequency of smoking and the related human and economic consequences, it is important to be able to offer the most effective smoking cessation programmes. The results are also relevant for healthcare providers and society at large as the health of the population would improve and healthcare costs would be reduced [74]. Offering ISCIs would also be relevant for countries and regions aiming to become smoke-free in the near future [75].

The results may also be relevant for future research, as they further indicate a need for a comparison of cost effectiveness between ISCIs and shorter SCIs to decide on the “best buy” considering different healthcare systems and patient groups. The cost analyses should include the training of staff and the greater time and resource consumption of ISCI sessions. To address the limitations mentioned above, new studies on ISCIs conducted outside of North America and Western Europe are required to increase the generalisation. It would also be relevant to evaluate contingency management as integrated in an ISCI and to further investigate the effect among more vulnerable groups of smokers than included in this review.

<table>
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<tr>
<th>Points for clinical practice and questions for future research</th>
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<tr>
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<tr>
<td>• This direct comparison shows that ISCIs more than double the 6-months CA compared to SIs.</td>
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<td>• Based on that, ISCIs should be offered to all smokers in need of the most effective intervention.</td>
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<td><strong>Questions for future research</strong></td>
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<tr>
<td>• What is the efficacy in high-quality randomised trials when directly comparing ISCIs and SIs in terms of CA over years?</td>
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<tr>
<td>• What is the efficacy in high-quality randomised trials outside Western Europe and North America?</td>
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<tr>
<td>• What is the cost-effectiveness of ISCIs compared to SIs when including the impact of long-term CA on costs and quality of life?</td>
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</table>

**Conclusion**

This review provides a comprehensive overview of the efficacy of ISCIs and successful smoking cessation, revealing a doubled CA rate among smokers randomised to ISCIs compared to SIs. This knowledge plays a role in implementing tobacco control and preventing morbidity and mortality.

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Availability of data: Templates, code, and data used in this review will be available from the corresponding author upon reasonable request.

Authors contributions: M. Rasmussen, B. Pedersen, S.V. Lauridsen and H. Tønnesen screened the literature, M. Rasmussen and S.V. Lauridsen made the data extraction, the assessment of risk of bias and GRADE. M. Rasmussen conducted the statistical analyses. B. Pedersen, S.V. Lauridsen and H. Tønnesen helped interpreting the analysis. M. Rasmussen drafted the manuscript. All authors read, critically revised, and approved the final manuscript. M. Rasmussen is the guarantor.
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