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Electronic Nicotine Delivery Systems for smoking cessation

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Abstract

Background: Electronic nicotine delivery systems (ENDS) are used by some tobacco smokers to assist with quitting. Evidence regarding the efficacy and safety of ENDS use for tobacco smoking cessation are needed.

Methods: In this open-label, controlled trial, we randomized adult smokers of at least 5 tobacco cigarettes/day and willing to set a quit date to an intervention involving provision of free ENDS and e-liquids in addition to standard-of-care smoking cessation counseling (SOC) including the optional use of nicotine replacement therapy (NRT), or to control. The control group received SOC and a voucher for the optional purchase of NRT. The primary outcome was biochemically validated, continuous self-reported tobacco cigarette smoking abstinence at 6-months. Secondary outcomes included participant-reported abstinence from tobacco and from any nicotine (including smoking, e-cigarettes, and nicotine-replacement therapy) at 6 months, respiratory symptoms, and serious adverse events.

Results: We randomized 1246 participants. Validated continuous abstinence rate from tobacco smoking was 28.9% in the intervention group and 16.3% in the control group (RR:1.77;95% confidence interval: 1.43 to 2.20). Abstinence from tobacco smoking in the 7 days prior to the 6-months visit was 59.6% in the intervention group vs 38.5% in the control group, but abstinence from nicotine use (through tobacco smoking, ENDS or NRT use) was 20.1% in the intervention group and 33.7% in the control group. SAEs occurred in 25 (4%) and 31 (5%) of the intervention and control group participants, respectively; AEs in 272 (43.7%) and 229 (36.7%).

Conclusion: The addition of ENDS to SOC counseling increased abstinence from tobacco among smokers more than SOC alone.

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Background

Electronic nicotine delivery systems (ENDS, also called electronic cigarettes) are electrically-driven devices that reproduce many attractive features of tobacco cigarettes; as such, they are a potential smoking cessation aid.[1] But the attributes that make ENDS attractive for cessation may also encourage prolonged use,[1,2] making rigorous evaluation of their efficacy and safety and toxicological profile an urgent requirement.

One sufficiently powered randomized trial and a systematic review of randomized controlled trials (RCT) showed ENDS were more effective for tobacco smoking cessation compared to nicotine replacement therapy (NRT),[1,3] but there is limited evidence on the efficacy of ENDS compared to standards of care (SOC) smoking cessation counseling and on ENDS safety measured as adverse events (AE) and serious adverse events (SAE).[1] Few earlier trials systematically collected data on safety outcomes defined *a priori* and confirmed them by reviewing medical charts.[1,3] When smokers quit, smoking-associated respiratory symptoms like cough and phlegm production are likely to diminish,[4] but it is unclear if quitting with ENDS also relieves these respiratory symptoms.

ENDS deliver lower levels of toxic compounds than conventional tobacco cigarettes,[5 6-9] but few RCT verified whether ENDS for smoking cessation is associated with reduction in exposure to nicotine and other tobacco- and smoke-related toxicants, though these substances can be measured with urinary exposure biomarkers.[9,10 11]

We thus conducted the Efficacy, Safety and Toxicology of ENDS (ESTxENDS) RCT to compare 6-month efficacy of provision of ENDS plus SOC to SOC alone on tobacco smoking abstinence. As secondary outcomes, we also explored the safety of ENDS.

Methods

DESIGN AND OVERSIGHT

We conducted a two-group, open-label, randomized controlled trial at five study sites across Switzerland. We recruited participants from July 2018 to June 2021 via free and paid ads in the lay press and on social media, advertising in healthcare facilities and on public transport. Smokers were invited to participate if they were over 18, had smoked at least 5 cigarettes per day for at least 12 months, and were willing to quit smoking within 3 months. We excluded pregnant or breast-feeding women and people who had used NRT or another smoking cessation drug in the last 3 months, or regularly used ENDS or tobacco heating systems in the last 3 months (Table S1 in Supplementary Appendix).

The local ethics committee of each participating study site approved the trial (reference number: 2017-02332). Those who collected and analyzed the data were unblinded to group allocation; we blinded laboratory personnel who measured urinary biomarkers of exposure to group allocation. The Data Safety and Adjudication Committee (DSMB) first met in 2020 and reviewed procedures for collecting adverse events (AE) and serious adverse events (SAE). An independent adjudication committee reviewed SAE based on medical records (Supplementary Appendix). Site investigators gathered the data. The second author analyzed the data and attests to the integrity of the analyses and the accuracy and completeness of the data we report. All authors interpreted data, vouched for the manuscript's completeness and accuracy, approved submission, and affirmed the trial adhered to the protocol. The funding bodies had no role in the trial design; the collection, monitoring, analysis, or interpretation of the data; or the writing of the manuscript. There was no industry involvement in the trial.

PROCEDURES

Those interested in participating contacted study nurses at each site, who prescreened volunteers for eligibility, asked eligible participants for their target quit date (TQD), scheduled a baseline visit a week before that date, and sent study material to participants before their visit. At the baseline visit, the nurses confirmed eligibility and collected written consent forms and baseline data. An automated centralized computed randomization system in a protected environment at the Clinical Trials Unit in Bern then generated randomization sequences (1:1 ratio) for participants. Nurses and participants were not blinded; they could see the allocation group on the screen.

Participants were invited to an in-person clinical visit scheduled 6 months after their TQD. If they missed this visit, study nurses collected data via phone, mail, or email. After three unsuccessful contact attempts, study nurses contacted up to two relatives and the participant's general practitioner if the participant had voluntarily provided this information, and then collected available data on smoking status and (S)AE from these sources.

Control group (SOC only)

Study nurses provided SOC smoking cessation counseling based on cognitive behavior therapy, motivational interviewing, and shared decision-making for smoking cessation drug support, including NRT and smoking cessation recommendations adapted to nicotine dependence (Supplementary Appendix).[12,13] Participants were counseled in-person at the baseline visit and by phone at TQD and Weeks 1, 2, 4, and 8 after TQD. Participants allocated to SOC received CHF 50 (50 USD) vouchers at the baseline visit for the purchase of NRT.

Intervention group (ENDS added to SOC)

In addition to SOC, which we adapted to the context of the intervention, participants in the intervention group received two ENDS starter kits (Innokin Endura T20-S) and 5 spare 0.8-ohm coils (enabling fixed wattage of 16-18W with a 1,500 mAh internal Li-Po battery) at the baseline visit, where study nurses showed them how to use ENDS, charge the device, fill it with e-liquid, and change the coil every two weeks. Participants could choose between 6 flavors and 4 nicotine concentrations (24 different e-liquids, in 19.6-, 11-, 6- and 0 mg/ml nicotine concentrations and 6 flavors: 2 tobacco, 1 menthol, 3 fruity). E-liquids contained propylene glycol, vegetable glycerin, medical-quality free-base nicotine, alcohol, and flavoring. All e-liquids had a 76/24 propylene glycol to vegetable glycerin ratio. At the baseline visit, participants could sample 24 ENDS, comprising all the flavors and nicotine combinations, which were presented to them on an e-liquid testing board. They could then choose the e-liquid and nicotine concentration they preferred. Study nurses gave participants no more than 10 e-liquid bottles at the end of this baseline visit and advised them to use only the e-liquids we provided. Participants could use ENDS *ad libitum* and re-order e-liquids whenever and in whatever amount they wanted, in whatever nicotine concentrations or flavors they preferred for 6 months (Supplementary Appendix).

MEASURES

At baseline and 6-month follow-up visit, participants completed questionnaires and a battery of clinical tests. Data comprised demographic variables, smoking history, smoking status, expired carbon monoxide (CO) level, (S)AE (in-person and at each phone contact), withdrawal symptoms, and respiratory symptoms (COPD (chronic obstructive pulmonary disease) Assessment Test [CAT]) (Supplementary Appendix for details of trial measures).[14-16] The CAT score is computed by adding up points from a 8-item questionnaire each ranging from 0 to 5 (40 points max.); higher CAT-score indicates more symptoms. Participants were told to collect their first morning urine and bring the filled bags to their examination.

Primary outcome was 6-month continuous tobacco smoking abstinence (self-reported no cigarette smoking from TQD, biochemically validated by urinary levels of anabasine <3 ng/ml).[17-19] If anabasine data was unavailable, we validated abstinence by exhaled carbon monoxide(CO) of ≤9 ppm. We classed participants who withdrew or were lost to follow-up or who lacked biochemical validation as non-abstinent in the primary analysis.[18]

Secondary tobacco smoking abstinence outcomes included 6-month sustained abstinence (allowing up to 5 cigarettes or a "grace period" of 2 weeks after TQD),[18] and 7-day point prevalence abstinence at 6-months, with and without biochemical validation.

The Supplementary Appendix describes secondary outcomes, including (S)AE, antibiotic use and respiratory and withdrawal symptoms.

STATISTICAL ANALYSIS

We calculated that a sample of 1114 participants would give the trial 90% power (at a 2-sided alpha level of 0.05) if the percentages of 6-month abstinence were 19% in the intervention group and 12% in the control group (relative risk [RR]:1.6, 7% absolute difference in abstinence). We assumed 5% loss to follow-up and that 5% of participants in the control group would choose to purchase e-cigarettes on their own, despite the recommendation not to do so (and thus crossover from the control group to the intervention group would occur), so we increased our sample size by 5% (59 smokers), aiming to recruit 1173 smokers.

Primary and secondary abstinence outcomes were analyzed by log-binomial regression to compute risk ratios of smoking status onto the trial group at 6 months. In sensitivity analyses, we further adjusted models for baseline covariates and computed inverse probability of censoring weights (IPCW) in the multivariable regression models to assess the effect of missing data on the outcome. Variables included in the multivariable adjusted model and IPCW models were pre-specified before beginning the analyses. We also conducted a tipping point analysis to assess the effect of missing primary outcome on the main efficacy results.[20] We estimated between-group differences in the percentage of participants who had SAE or AE, and those who reported antibiotic use. Confidence interval widths for secondary outcomes and exploratory outcomes were not adjusted for multiplicity and may not be used in place of hypothesis testing. We also present data on self-reported exposure to ENDS and tobacco smoking in the last 7-days prior to 6-months visit and on NRT within the 24 hours prior to the 6-month visit. We classed participants into following exposure groups: "tobacco abstainers" reported no tobacco cigarettes, regardless of ENDS use; "tobacco and ENDS abstainers" reported no tobacco cigarettes or ENDS; "nicotine abstainers" reported no tobacco cigarettes, ENDS, or NRT; "exclusive ENDS users" reported no tobacco cigarettes but used ENDS; "dual users" reported both tobacco cigarettes and ENDS; "exclusive smokers" reported tobacco cigarettes but not ENDS. We used Stata software, version 17 (StataCorp) for all analyses except the tipping point analyses, for which we used R version 4.3.1 (package TippingPoint 1.2.0).

Results

Characteristics of participants at baseline

We screened 2027 smokers and included 1246 in the primary analyses (622 in the intervention group; 624 in the control group; Figure 1, Tables S1 and S2 in the Supplementary Appendix). Most were middle-aged smokers; 47% identified as women (Table 1, Table S4 and Table S5). Mean time (SD) from baseline visit to target quit date (TQD) was 6.0 (3.6) days in the intervention group and 6.0 (3.9) days in the control group.

Tobacco smoking Abstinence Rates at 6-months follow-up

Data on smoking status and SAE at 6-months were available from 90.8% of included patients (63.9% obtained at the follow-up visit; 23.4% self-reported over the phone, e-mail, or mailed questionnaire; 2.8%

from relatives; and 0.2% from the general practitioner; Figure 1 and Table S3). The primary endpoint, continuous validated 6-month tobacco smoking abstinence, occurred in 28.9% (180/622) of the intervention group and 16.3% (102/624) in the control group (crude RR: 1.77 (95% confidence interval[CI]:1.43 to 2.20) (Table 2 and Table S6). Absolute difference in 6-month abstinence rate between the groups was 12.6% (95%CI:8.0% to 17.2%). Secondary outcomes, including sustained abstinence without biochemical validation, allowing either a 2 week grace period or up 5 total cigarettes, and 7-day point prevalence with and without validation were generally consistent. Sensitivity analyses returned similar results (Table S6 and Figure S3).

Adherence to recommended smoking cessation drug therapy and ENDS during the trial

90% of in the intervention group and 86% of the control group participated in the phone follow-up one week after TQD. In the intervention group, 95.9% reported using ENDS, 6.8% NRT, and 0.5% other smoking cessation drug therapy (varenicline or bupropion) (Table S8). Participants who reported having used ENDS said they used a median of 10 ml of e-liquids throughout the week; with median e-liquids concentration of 11 mg nicotine/ml (Table S9). In the control group, 3.9% reported using ENDS, 63.6% NRT, and 4.1% other smoking cessation drug therapy.

Self-reported use of tobacco cigarettes, ENDS and NRT at 6-month follow-up

At 6-month follow-up, 85% (1056/1246) of trial participants reported on their use of tobacco cigarettes and ENDS in the 7 days before the visit and on their use of NRT in the last 24 hours (Table 3). 59.6% (329/552) of the intervention group and 38.5% (194/504) in the control group were “tobacco abstainers” (i.e. reported no tobacco cigarettes in the last 7 days) (Table 3). By contrast, 20.1% of the intervention group and 33.7% of the control group were “nicotine abstainers” (abstaining from tobacco cigarettes, ENDS with nicotine and NRT).

Safety evaluation

In the control group, 1 of 624 died during the trial. Between baseline and 6-month follow-up, 25 (4.0%) participants in the intervention group had an SAE, as did 31 (5.0%) participants in the control group (RR of participants with SAE: 0.81, 95%CI:0.48 to 1.35; unadjusted p-value 0.49) (Tables S10 and S11). 272 (43.7%) participants in the intervention group reported 425 AEs; 229 (36.7%) participants in the control group reported 366 AEs (RR of participants with AE:1.19; 95%CI:1.04 to 1.37; unadjusted p-value 0.01) (Table S12 and S13). Symptomatic and confirmed COVID-19 was reported by 18 intervention and 8 control group participants, including 1 participant who was hospitalized in the control group. Between baseline and 6-month follow-up, 54 (8.7%) participants in the intervention group reported 61 episodes of antibiotic use; 43 (6.9%) of those in the control group reported 56 episodes of antibiotic use (RR of participants with antibiotic use: 1.26; 95%CI:0.86 to 1.85; Table S14).

Respiratory symptoms

At 6-month follow-up, 81% of the intervention group and 66% of the control group provided data on respiratory symptoms (Table S18). Mean total CAT-Score was 4.8 (SD 3.9) in the intervention group and 5.7 (SD 4.5) in the control group (multivariable adjusted mean difference in total score: -0.66 (95%CI: -1.13 to -0.18) (Table S19). Proportions of participants in the intervention group vs the control group 41% vs. 34% for no coughing, 62% vs 51% for no phlegm, 73% vs 72% for no chest tightness, 34% vs 30% for not feeling breathless, 95% vs 93% for no limitation in home activities, 96% vs 95% for confidence leaving home, 92% vs 90% for sound sleep, and 40% vs 39% for having lots of energy (Table S18).

We present results for withdrawal symptoms in the Supplementary Appendix.

Discussion

Tobacco smoking abstinence rate increased when ENDS were added to SOC counseling that allowed NRT, but many who abstained from smoking tobacco continued using ENDS. The intervention increased adverse events but not serious adverse events.

Relative difference in tobacco smoking abstinence between randomized groups aligns with findings of previous trials, but because tobacco smoking abstinence was high in both groups, absolute difference in tobacco smoking abstinence was higher in our trial.[1,21,22] Rate of tobacco smoking abstinence was high in the intervention group, but so was ongoing use of ENDS with nicotine. ENDS plus SOC may be a viable option for smokers who want to abstain from tobacco smoking without necessarily abstaining from nicotine, but may be less appropriate for smokers who want to abstain from both tobacco and nicotine. ESTxENDS plans 12-, 24- and 60- month follow-up visits to gather data on longer-term use patterns for tobacco and nicotine containing products.

ESTxENDS was not powered to detect significant differences in SAE, but our results align with those of another large RCT (which failed to meet recruitment targets).[23] This trial also applied rigorous, pre-defined methods to systematically collect SAE and AE.[23] Our results should be pooled with those of other RCTs that test ENDS for smoking cessation to better detect differences in SAE and AE.[1] Self-reported respiratory- and withdrawal symptoms align with previous findings.[1,4]

The trial had seven main limitations. First, group allocation was unblinded, creating the risk that participants in the control group were disappointed with their group allocation. We mitigated their potential disappointment by giving participants in the control group a voucher at baseline, although we did not assess how they interpreted this voucher nor did we ask participants in either arm how confident they were in the efficacy of the treatment. We assessed group allocation preference shortly before randomizing: the coefficient of the interaction term of allocation preference on the effect of group allocation on the primary outcome was 1.01(95%CI:0.93 to 1.10). Second, we provided free ENDS and e-liquids to the intervention group, but did not provide free NRT to the control group, as was done in previous trials.[2] Participants in the control group could use their voucher to purchase NRT. We did not intend to contrast a recommendation to use ENDS with a recommendation to use NRT; instead, we added free ENDS and e-liquids to SOC and compared that to SOC, which ordinarily recommends NRT and further smoking cessation drugs. Third, we provided participants with free e-liquids for 6-months before collecting outcomes for an "end of treatment" assessment. Our current results do not predict whether the primary outcome will be sustained over subsequent visits, so we plan to continue follow-up at 12-, 24- and 60-months. Fourth, attrition was more prevalent in the biochemically validated analyses than in participant self-reports; attrition was more prevalent in the control than the intervention group. The results of the tipping point analyses suggest that our main conclusions would likely remain unchanged if we had had a complete dataset on the primary outcome. However, our primary analyses might have overestimated the RR difference between randomized groups because we followed guidelines for reporting smoking cessation trials: we categorized participants with missing outcomes as non-abstinent from smoking.[18] Fifth, we tested the intervention in an ambulatory healthcare setting in Switzerland, so readers should be cautious in assuming results will be similar in other settings. Seventh, we did not adjust confidence interval widths for multiplicity for our secondary outcomes, so these intervals should not replace hypothesis testing.

In conclusion, the addition of ENDS to SOC counseling increased abstinence from tobacco among smokers more than SOC alone.

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and LungeZürich. The funding bodies had no role in the trial design; the collection, monitoring, analysis, or interpretation of the data; or the writing of the manuscript. There was no industry involvement in the trial.

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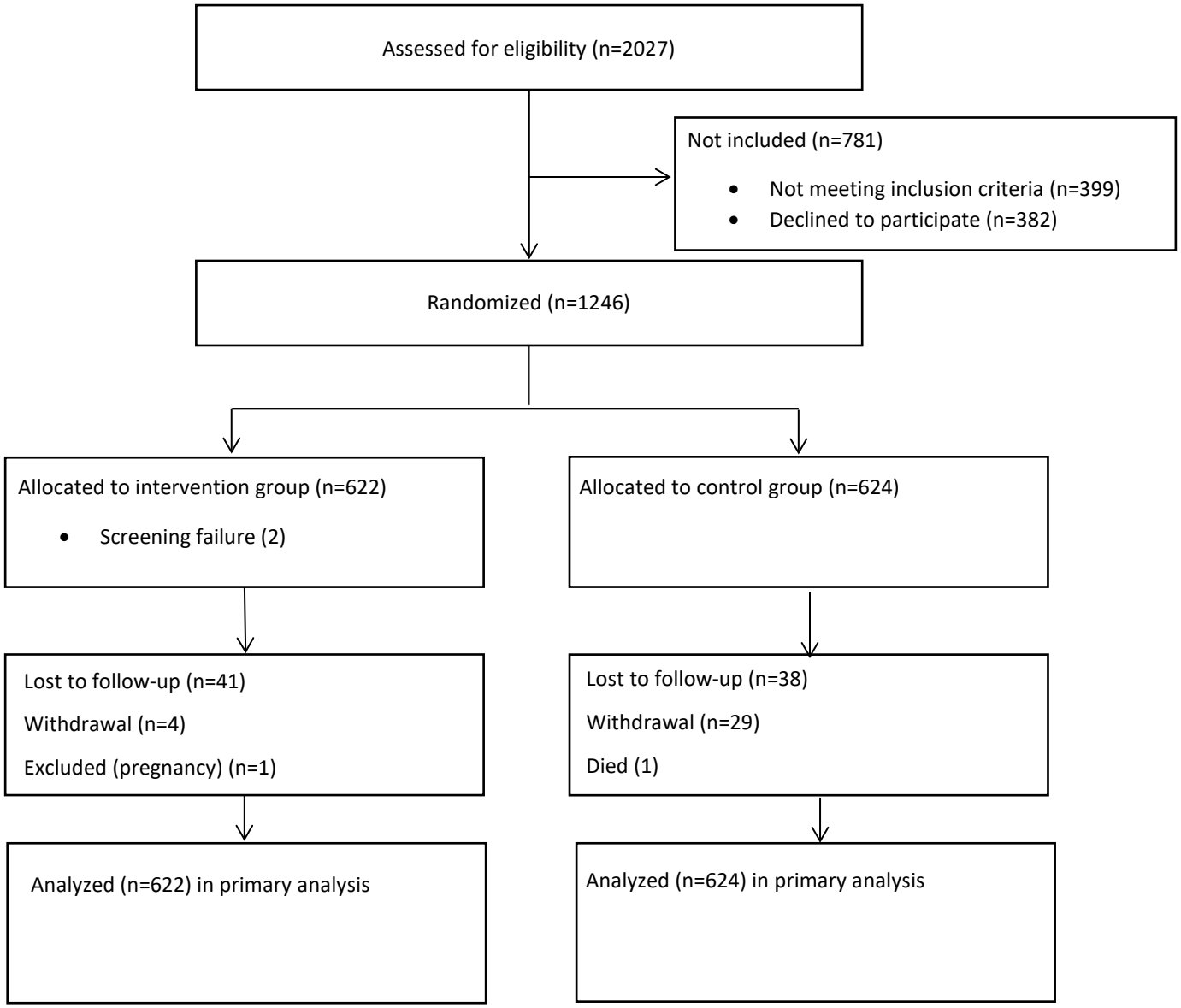
Figure 1. **Enrollment, Allocation and Follow-up.***



* Reasons for not including 781 of the 2027 persons screened are detailed in Table S1 and S2 in the Supplementary Appendix. Two participants mentioned after randomization that they were taking smoking cessation medications (bupropion for depression or bupropion for smoking cessation). One participant in the control group died. Lost to follow-up defined as no data available for smoking status and SAE based on self-report by participants directly or by contacting relatives or the general practitioner (see Table S3 in Supplementary Appendix for way data was obtained).

Table 1. **Characteristics of the Participants at baseline**.*

Characteristic	Control group N=624	Intervention group N=622	Total N=1246
Age yr - median (IQR)	39 (30 - 52)	37 (28 - 51)	38 (29 - 51)
Women gender - no. (%)	295 (47.3)	290 (46.6)	585 (47.0)
Employed - no. (%)	465 (74.5)	438 (70.4)	903 (72.5)
Highest educational qualification - no. (%)			
Obligatory school; other; none	45 (7.2)	50 (8.0)	95 (7.6)
Secondary education	277 (44.4)	291 (46.8)	568 (45.6)
Tertiary education	302 (48.4)	281 (45.2)	583 (46.8)
Age started smoking yr - median (IQR) †	16 (15 - 19)	16 (15 - 18)	16 (15 - 19)
Number of cigarettes per day - median (IQR)	15 (10 - 20)	15 (10 - 20)	15 (10 - 20)
Previous quit attempts (at least one) - no. (%)†	530 (84.9)	531 (85.4)	1061 (85.2)
Fagerström Test for Nicotine Dependence †, ‡ - mean (SD)	4.4 (2.3)	4.3 (2.3)	4.3 (2.3)
Expired CO level § - median (IQR) – p.p.m.	20 (12 - 29)	20 (13 - 29)	20 (12 - 29)

* Plus–minus values are means ±SD. There were no significant differences between the trial groups. Abbreviations: IQR: Interquartile range, p.p.m.: parts per million; SD: standard deviation; yr: years

† Missing data on 2 participants

‡ Tobacco dependence was assessed using the Fagerström Test for Nicotine Dependence, which consists of 6 questions ranging from 0 to 1, 0 to 2 or 0 to 3 that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence; Scores range from 0 to 10, with higher scores indicating greater dependence.[24]

§ Missing data on 18 participants

Table 2. Tobacco Smoking Abstinence Rates at 6-months follow-up

Outcome	Control group, N included in analyses=624	Intervention group, N included in analyses=622	Crude relative Risk (95% CI) ‡	Sensitivity analysis, Adjusted relative risk (95% CI) §	Absolute risk reduction (95%CI) ¶
Primary outcome*/#					
Continuous abstinence, validated by anabasine and by CO if anabasine missing, N (%)†	102 (16.3)	180 (28.9)	1.77 (1.43 - 2.20)	1.71 (1.39 - 2.12)	12.6 (8.0 - 17.2)
Secondary outcomes**					
Continuous abstinence, without biochemical validation, N (%)	146 (23.4)	237 (38.1)	1.63 (1.37 - 1.94)	1.57 (1.32 - 1.85)	14.7 (9.6 - 19.8)
Sustained abstinence allowing a 2-week' grace period, validated by anabasine and by CO if anabasine unavailable, N (%)	110 (17.6)	191 (30.7)	1.74 (1.42 - 2.14)	1.70 (1.39 - 2.08)	13.1 (8.4 - 17.8)
Sustained abstinence allowing up to 5 cig in total, validated by anabasine and by CO if anabasine unavailable, N (%)	109 (17.5)	219 (35.2)	2.02 (1.65 - 2.46)	1.96 (1.61 - 2.38)	17.7 (12.9 - 22.5)
7 days point prevalence abstinence, validated by anabasine and by CO if anabasine unavailable, N (%)	133 (21.3)	245 (39.4)	1.85 (1.54 - 2.21)	1.74 (1.47 - 2.07)	18.1 (13.1 - 23.1)
7 days point prevalence abstinence, without biochemical validation, N (%)	200 (32.1)	332 (53.4)	1.67 (1.45 - 1.91)	1.56 (1.37 - 1.77)	21.3 (16.0 - 26.7)

* Tobacco smoking abstinence at 6-months follow up was defined as a self-report of smoking no cigarettes from target quit date (TQD) to 6-months follow-up, validated biochemically by urinary anabasine level of less than 3 ng/ml and if not available, by expired carbon monoxide level of ≤ 9 ppm at 6-months. One participant in control group died and was therefore excluded from the primary analyses.

† Proportion with 95% Wilson confidence interval: Control group: 0.16 (0.14 - 0.19) and intervention group: 0.29 (0.26 - 0.33)

‡ Relative risk with 95% Koopman confidence interval

§ Multivariable adjusted model with stabilized inverse probability of censoring weights (IPCW, adjusted for study site, age, gender, employment status, education, age started smoking, number of cigarettes per day, participants with previous quit attempts, Fagerström score

¶ Risk reduction with 95% Newcombe-hybrid-score confidence interval

p-value <0.01 for chi2 test between control and intervention group.

** Confidence interval widths for secondary outcomes have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

Table 3. Self-reported use of tobacco cigarettes, ENDS and NRT at 6-months follow-up. *

Self-reported use	Control group		Intervention group		Difference between groups
	N	**%**	**N**	**%**	**%**
N with data on self-reported use†	504	100	552	100	
No tobacco cigarettes ("tobacco abstainers")	**194**	**38.5**	**329**	**59.6**	***+21.1***
No ENDS and no tobacco cigarettes ("tobacco and ENDS Abstainers")	179	35.5	62	11.2	*-24.3*
with NRT	*14*	*2.8*	*1*	*0.2*	*-2.6*
with smoking cessation medication	*1*	*0.2*	*0*	*0*	*-0.2*
ENDS user and no tobacco cigarettes ("exclusive ENDS users")	15	3.0	267	48.4	*+45.5*
without nicotine in ENDS	*5*	*1.0*	*50*	*9.1*	*+8.1*
with nicotine in ENDS	*10*	*2.0*	*217*	*39.3*	*+37.3*
with NRT	*0*	*0.0*	*1*	*0.2*	*+0.2*
with smoking cessation medication	*0*	*0.0*	*0*	*0.0*	*0.0*
No Nicotine ("nicotine abstainers") ‡	**170**	**33.7**	**111**	**20.1**	**-13.6**
Tobacco cigarettes	**310**	**61.5**	**223**	**40.4**	***-21.1***
No ENDS and tobacco cigarettes ("exclusive smokers")	294	58.3	122	22.1	*-36.2*
with NRT	*18*	*3.6*	*4*	*0.7*	*-2.9*
with smoking cessation medication	*2*	*0.4*	*0*	*0*	*-0.4*
ENDS and tobacco cigarettes ("dual users")	16	3.2	101	18.3	**+15.1**
without nicotine in ENDS	*5*	*1.0*	*10*	*1.8*	***+0.8***
with nicotine in ENDS	*11*	*2.2*	*91*	*16.5*	***+14.3***
with NRT	*1*	*0.2*	*4*	*0.7*	***+0.5***
with smoking cessation medication	*0*	*0*	*0*	*0*	***0***

* Categories of exposure based on self-reported use of ENDS and/tobacco cigarettes in the last 7 days and use of NRT within last 24 hours before study visit.

† Data on 1056 out of 1246 participants (84.7%) who provided data on self-reported use of tobacco cigarettes, ENDS use at 6-months follow-up ((504 out of 624 participants in the control group (80.8%) and 552 out of 622 participants in the intervention group (88.7%) (Table S3 in Supplementary Appendix). Proportions in each category of exposure computed on number of participants reporting on use as the denominator. Participants reporting ENDS use with missing information on nicotine use in ENDS (5 in control group and 23 in intervention group) considered using ENDS without nicotine. Abbreviations: ENDS: electronic nicotine delivery systems, NRT: nicotine replacement therapy.

‡ No self-reported exposure to nicotine through tobacco cigarettes, ENDS or NRT.