Title: Benefits of e-cigarettes in smoking reduction and in pulmonary health among Chronic Smokers Undergoing a Lung Cancer Screening Program at 6 Months

Running head: Benefits of e-Cigarettes at 6 months

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ABSTRACT

Introduction: Electronic cigarettes (e-cigarettes) might be a valid and safe device to support smoking cessation. However, the available evidence is divergent. The aim of the present work was to assess the effects of an e-cigarette program on pulmonary health (cough, breath shortness, catarrh) and to evaluate the effectiveness of e-cigarettes in reducing tobacco consumption.

Methods: The study is a double-blind randomized controlled trial. Two hundred and ten smokers were randomized into three groups: nicotine e-cigarette (8mg/mL nicotine concentration), nicotine-free e-cigarettes (placebo), and control with 1:1:1 ratio. All participants received a 3 months cessation program that included a cognitive-behavioral intervention aimed at supporting people in changing their behavior and improving motivation to quit.

Results: Pulmonary health, assessed with self-reported measures, clinical evaluations and the Leicester Cough Questionnaire, improved in participants who stopped smoking compared to their own baseline. No differences in pulmonary health were found between groups. Statistical tests showed a significant effect of Group ($F(2, 118) = 4.005$, $p < .020$) on daily cigarette consumption: after 6 months participants in the nicotine e-cigarette group smoked fewer cigarettes than any other group. Moreover, participants in this group showed the lowest level of exhaled carbon monoxide (CO) ($M=12.012$, $S.D.=8.130$), and the lowest level of dependence ($M=3.12$, $S.D.=2.29$) compared to the nicotine-free e-cigarette and control conditions.

Conclusions: After 6 months about 20% of the entire sample stopped smoking. Participants who used e-cigarettes with nicotine smoked fewer tobacco cigarettes than any other group after 6 months ($p < .020$). Our data add to the efficacy and safety of e-cigarettes in helping smokers reducing tobacco consumption and improving pulmonary health status.

Keywords: e-cigarettes; smoking cessation; nicotine-free e-cigarettes; pulmonary health; clinical trial

Introduction

Electronic cigarettes (e-cigarettes) are an increasingly popular alternative to tobacco cigarettes among smokers worldwide (Diez, Cristello, Dillon, De La Rosa, & Trucco, 2019). The National Cancer Institute Dictionary of Cancer Terms defined the e-cigarette as a battery-powered electronic delivery that does not contain tobacco and that does not require combustion. The e-cigarette is composed of a battery, a heating element and a tank that contains a solution of nicotine, flavorings and other chemical products, such as propylene glycol (King, Gammon, Marynak, & Rogers, 2018; NCI, 2016; Polosa et al., 2011).

Unlike conventional nicotine replacement therapies, e-cigarettes simulate the visual, sensory, and behavioral aspects of smoking (Corbin L & Spearing E, 2015). Studies confirmed that e-cigarettes deliver sufficient levels of nicotine to convey both physiological and behavioral effects (Polosa, Caponnetto, Maglia, Morjaria, & Russo, 2014; Strongin, 2019). A number of studies addressed the question if e-cigarettes might be considered an effective device to be used in smoking cessation programs (Caponnetto et al., 2013; Hajek et al., 2019; Hartmann-Boyce, McRobbie, Begh, Stead, & Hajek, 2016). However, data are not convergent and the debate is open, also considering possible dangerous side effects. For example, Ghosh and colleagues reported that the e-cigarettes may have biological effects on the lungs and that these effects seem to be linked to the propylene glycol/vegetable glycerine included in juices. Alterations of lungs might also favour chronic diseases (Ghosh et al., 2018). Moreover, (Bullen, Howe, & Laugesen, 2014) reported serious side effects in 27 out of 241 participants who consumed a 16 mg/mL e-liquid, and 5 out of 57 of participants who used nicotine-free e-cigarettes at 6 months. Conversely, a Cochrane review (Hartmann-Boyce et al., 2016) found no serious side effects considering short to midterm outcomes, since most side-effects reported (95.6%) by the reviewed studies were not directly connected to the use of e-cigarettes.

With regard to the efficacy issue, a meta-analysis of eight studies comparing the efficacy of the e-cigarettes (both with and without nicotine) with no concomitant interventions failed to show a benefit in smoking cessation (El Dib et al., 2017). Instead, in our previous work, we reported short-term (3 months) results that showed e-cigarettes to be helpful in reducing tobacco consumption, when combined with low-intensity counseling in a sample of motivated smokers (Masiero et al., 2018).

This low uniformity of data about the effectiveness of e-cigarettes may depend on many factors (El Dib et al., 2017). In particular, the samples considered are heterogeneous for age, history of smoking and motivation to stop. For example, some studies pointed to smokers who had a low motivation to quit (Caponnetto et al., 2013) while others included only high motivated smokers. This way, data may diverge due to the role of motivation in smoking cessation (Williams et al., 2006). Another important issue has been raised by a survey (Farsalinos, Poulas, Voudris, & Le Houezec, 2016), which

found a link between the regular use of e-cigarettes and chronic smoking so that smokers who have never used e-cigarettes were more likely to succeed in a quitting attempt. Thus, it seems that e-cigarettes might sustain smoking when used ad libitum, instead of promoting a positive change. However, we still need sound data to assess e-cigarettes efficacy in tobacco cessation and to suggest best practices (Van der Aalst, De Koning, Van den Bergh, Willemsen, & Van Klaveren, 2012), also taking into consideration specific settings. In particular, cancer screening programs are now considered positive contexts to provide anti-smoking advice and promote smoking interruption (Van der Aalst et al., 2012). Accruing evidence (Tammemägi, Berg, Riley, Cunningham, & Taylor, 2014; Taylor et al., 2007, 2017) confirmed the pivotal role of the screening as a "teachable moment", that is a context where participants are motivated to change their maladaptive behaviors such as smoking. Some authors suggested (for example, Lawson & Flocke, 2009) that people enrolled in a screening program are more receptive to the clinical suggestions, since they are more aware of the risks their behaviors imply.

For instance, results from the NELSON trial, a program that assessed the effectiveness of a lung cancer computed tomography (CT) screening, showed a positive association between the number of the follow-up recommendations and the abstinence rate (AalstVan Der, R.J. Van Klaveren, Van Den Bergh, Willemsen, & De Koning, 2011). More recently, the SCALE trial outcomes stressed that the screening may be effective to promote smoking cessation for two main reasons: first, it may increase the interaction with health professionals providing continued opportunity to receive clinical advice to quit smoking; second, positive and negative scan results may improve the importance of the smoking interruption increasing the attention on harms and benefits (Joseph et al., 2018). Even only minimal advice permits to scale-up the awareness about the health benefits of the interruption (Lucchiari, Masiero, Botturi, & Pravettoni, 2016; Masiero, Riva, Fioretti, & Pravettoni, 2016). Furthermore, Glasgow and colleagues suggested that the clinical setting and the time spent in hospital may provide to the health professionals an opportunity to offer anti-smoking interventions (Glasgow, Stevens, Vogt, Mullooly, & Lichtenstein, 1991), as well as minimal advice to sustain motivation to give-up or more structured intervention based on psychological counseling and/or pharmacotherapy.

According to this, (Lucchiari, Masiero, Veronesi, et al., 2016) our primary outcome was to assess the effects of an e-cigarette program on pulmonary health. We argued that the reduction of cigarette tobacco consumption due to e-cigarette use instead of tobacco consumption would lead to a significant decrease of cough, breath shortness, and to increase the cough related quality of life at 6 months. Secondary, we aimed to evaluate the impact of e-cigarettes (with or without nicotine) use on smoked daily cigarettes. We expected that the use of e-cigarette with nicotine e-liquid (8 mg/mL) would be more effective in reducing smoking than nicotine-free devices (Lucchiari, Masiero,

Veronesi, et al., 2016). In addition, the study was conducted on a specific population of smokers enrolled in a screening program for early detection of lung cancer named COSMOS II (Continuous Observation of SMOking Subjects) (Veronesi et al., 2008, 2012). This provided the opportunity to assess the effectiveness of e-cigarettes in a clinically controlled setting and in a sample of motivated smokers. Coherently, we argued that the adopted setting is crucial for a successful outcome since it takes advantage of a so-called "teachable moment" (Taylor et al., 2017).

Materials and Methods

Study design and participants

The study is a double-blind randomized controlled trial (Clinicaltrials.gov NCT02422914). It was approved by the ethical committees of the European Institute of Oncology (IEO) and the University of Milan. Participants were enrolled at the IEO within the COSMOS II (Continuous Observation of SMOking Subjects) screening program. COSMOS II allows assessing early detection of lung cancer by a low-dose computed tomography (CT) scan and blood tests. The inclusion criteria of the COSMOS II program include being 55 years old or more, having smoked an average of 10 cigarettes or more a day for at least the past 10 years (Veronesi et al., 2012). All participants received full details about the study by a trained psychologist and signed the informed consent. The study was conducted in accordance with the principles stated in the Declaration of Helsinki (59th WMA General Assembly, Seoul, 2008). The research protocol with full methods details are reported elsewhere (Lucchiari, Masiero, Veronesi, et al., 2016).

Procedure

The first randomization was on 30 September 2015, and the last follow-up was on 31 January 2016. A randomization list using a permuted block design (40 blocks of 6 subjects randomly assigned to 1 of the 3 treatment arms) had been previously prepared by independent personnel. According to this randomization, three groups have been identified (Lucchiari, Masiero, Veronesi, et al., 2016; Masiero et al., 2018): Nicotine e-cigarette group (E-cigarette and Support, n=70): each participant received an e-cigarette kit and 12 10-mL liquid cartridges (8 mg/mL nicotine concentration). During the first week, participants could use the e-cigarette ad libitum. At the end of the first week, they were solicited to use only the e-cigarette for the next 11 weeks. Nicotine-free cigarette group (Placebo and Support, n=70): the same program of nicotine e-cigarette group but with nicotine-free e-cigarettes. This was a double-blind placebo condition. The control group (Support-Only, n=70): each participant received only support following the same protocol of other groups.

All participants independent of the group received low-intensity counseling (support) delivered by phone at weeks 1, 4, 8 and 12. The low-intensity counseling is a cognitive/behavioral intervention aimed at supporting people in changing their behavior. It promotes awareness about personal smoking and supports motivation to quit. This intervention is routinely provided in screening programs (Lucchiari, Masiero, Botturi, & Pravettoni, 2016).

After the end of the trial, participants enrolled in the nicotine e-cigarette group and nicotine-free cigarette group were asked to return all the liquid cartridges, which were delivered at the beginning of the study. Participants then were free to continue to use e-cigarettes on their own and/or tobacco cigarettes. During follow-up at 6 and 12 months, the smoking behaviour was assessed as well as pulmonary health.

Instruments

Expired carbon monoxide (*CO*): it was assessed using the Micro+™ Smokerlyzer® (Bedfont Scientific Ltd), which has less than 5% H2 cross-sensitivity. A value from 1 to 5 particles per million (ppm) is normally considered within the normal limits for non-smokers (Lucchiari, Masiero, Veronesi, et al., 2016; Masiero et al., 2018).

Abstinence: continuous smoking abstinence (self-reported complete abstinence over the previous month). Self-report abstinence was tested for confirmation with the CO value. Only participants who declared to be abstinent and with a CO level lower or equal than 7 ppm were considered abstinent for subsequent analyses.

Fagerstrom Test for Nicotine Dependence (FTND): A 6-item self-report questionnaire assessing nicotine dependence. The Italian version was proved to be valid and reliable (Fekketich, Fossati, & Apolone, 2009).

Motivational questionnaire: A 4-item self-report questionnaire assessing the motivation to quit smoking (Marino, 2002). The total score enables classification of smokers into 1 of 4 motivational categories: 4-6 = low (not yet seriously considering giving up smoking); 7-10 = middle (the person evaluated both the benefits of quitting and the risks of smoking); 11-14 = high (there are moments in which the person is determined to quit smoking); 15-19 = very high (the person is ready to give up smoking).

Hospital Anxiety and Depression Scale (HADS): A 14-item self-report questionnaire assessing anxiety and depression (Zigmond & Snaith, 1983). The Italian version (Costantini et al., 1999) has

proved validity and feasibility similar to the original version (Bjelland, Dahl, Haug, & Neckelmann, 2002).

Leicester Cough Questionnaire (LCQ): A 19-item self-report questionnaire to assess the impact of an acute and chronic cough on quality of life, is composed of two subscales: physical and psychological. The overall score ranges from 3 to 21, with higher scores indicating a better quality of life (Birring et al., 2003). Berkhof and colleagues (2012) reported a Cronbach's α ranging from .74 to .80 (Berkhof et al., 2012).

Respiratory Symptoms: Self-reported measures were used to assess respiratory symptoms such as dry cough, catarrh, and breathlessness. In addition, during the visit at month 6, the self-report items were discussed with the researcher in charge in order to further investigate and eventually confirm the self-assessment.

Side effects: Self-reported measures were used to assess side effects. Participants were asked to complete a checklist of symptoms likely to be related to e-cigarette (Burning throat, Cough, Nausea, Headache and so on).

E-cigarettes use: an ad-hoc self-report questionnaire was used to collect qualitative data about e-cigarettes acceptability and to offer participants the opportunity to report their experience about the use of the device.

Additional information on the trial is published elsewhere (Lucchiari, Masiero, Veronesi, et al., 2016; Masiero et al., 2018).

Statistical analysis

The primary aim of the clinical trial was to assess a change in pulmonary health due to smoking reduction, while the secondary aim was to assess the efficacy of e-cigarettes to reduce smoking. Using a two-sided *Z* test, a sample of 70 participants in either the Nicotine e-cigarette group or Nicotine-free e-cigarette group and 70 in control group will reach 80% power, at .05 significance level, to detect a 20% reduction in the frequency of respiratory symptoms from the baseline in either of the e-cigarette groups (Nicotine e-cigarette group and Nicotine-free e-cigarette group) compared to a 5% reduction in the control group (Lucchiari, Masiero, Veronesi, et al., 2016).

The Chi-squared test was used to assess differences in frequencies of respiratory symptoms, participants who stopped smoking, and any other categorical variable. We identified two main groups: Abstinence and Reduction. The Abstinence group involved participants who stopped smoking tobacco cigarettes. Continuous smoking abstinence (defined as the self-reported abstinence over the previous month and confirmed at 6 months by expired CO) was considered. The reduction group involved participants that showed at least a 20% decrease of daily tobacco smoking compared with the baseline independent of the study group and it did not include participants who were abstinent at the evaluation point. For this group an Intention-to-treat analysis (ITT) was used. ANCOVA tests were used to evaluate significant changes from baseline to 6-month in cigarette consumption and other continues variables (CO, Dependence Level, LCQ, HADS). All the analyses were performed with the SPSS package (version 23.0, IBM, USA, 2014).

Results

Sample characteristics

Two hundred and ten smokers (132 men and 78 women) with a mean age of 62.8 (S.D. = 4.58) accepted to participate. Overall, the age of the first cigarette was 17.40 years (S.D. = 3.68) and the number of the daily cigarette smoked was 19.38 (S.D. = 7.84). The mean value of the CO assessed for ppm was 14.84 (S.D. = 6.09; min. 3 ppm and max. 33 ppm). No significant differences between groups on smoking behaviour, psychological wellbeing (HAD scale) and LCQ scores were present at baseline. Due to missing data, at the 6-month the sample was of 155 participants. In particular, 52 in Nicotine e-cigarette group (19 women and 33 men), 51 in Nicotine-free e-cigarette group (21 women and 31 men) and 52 in Control group (13 women and 38 men). Further characteristics of the actual participants at month 6 are shown in table 1.

Missing data at T1 (month 1) was 26 (12.4), at T2 (month 3) 38 (18.1%) and at T3 (month 6) 55 (26%).

Table 1 here

Figure 1. Insert here

Primary outcome assessment: improving in pulmonary health

Participants who stopped smoking reported a significant improvement in pulmonary health. In particular, independent of the study group only 9% of former smokers reported cough versus about 57% of current smokers. Similarly, about 6% of former smokers had a pulmonary disease (bronchitis) during the 6 months before the evaluation time, versus about 18% of current smokers (Table 2). To evaluate changes in cough-related quality of life (LCQ) and general psychological well-being (HADS) we run two ANCOVA tests with baseline value as covariate and the smoking status at 6-month as fixed factor. We found that former smokers had a significant improvement with respect to baseline in anxiety HADS subscale ($F(1, 141) = 7.457$, $p = .007$) and the general LCQ score ($F(1, 141) = 12.555$, $p = .001$). In particular, former smokers showed a significant improvement of cough-related quality of life at 6 months compared to baseline (Figure 2). Abstinent smokers also showed a significant weight increase ($F(1, 141) = 22.958$, $p < .001$). The positive effect of quitting on cough-related quality of life and psychological well-being was equally present in all groups considered. We also ran an analysis considering Group as independent variable to test if pulmonary health was affected by the treatment. We failed to find any differences.

Figure 2 Insert here

Table 2. Insert here

Secondary outcome assessment: reduction of tobacco smoking

The number of participants who stopped smoking after 6 months by groups is reported in table 3. Nicotine e-cigarette group and nicotine-free e-cigarette group include more abstinent smokers than control; however, we failed to find significant differences between groups ($p = .691$). Most participants who had stopped smoking at 3-month remained abstinent at 6. In particular, 1 in Nicotine e-cigarette group, 2 in Nicotine-free e-cigarette group and 1 in Control group relapsed.

Table 3. Insert Here

Focusing on smoking reduction, we ran three ANCOVA tests using the corresponding baseline value as a covariate and the group as a fixed factor. In the first, we compared the number of daily cigarettes

smoked by groups. Results showed that participants who used e-cigarettes with nicotine smoked fewer tobacco cigarettes than any other group ($F(2, 118) = 4.005$, $p < .020$). Indeed, smokers in the nicotine e-cigarette group smoked a mean of 11.007 (S.D.= 6.51), while smokers in nicotine-free e-cigarette group and control groups smoked respectively 14.026 (S.D.=7.92) and 13.454 (S.D.= 6.49) daily cigarettes.

The second ANCOVA was on exhaled CO. We found significant differences between groups ($F(2, 117) = 4.233$, $p < .025$). Participants in nicotine e-cigarette group had a mean exhaled CO of 12.01 (S.D. = 8.13), while higher levels in nicotine-free e-cigarette group (M = 15.28, S.D. = 11.43) and control group (M = 16.52; S.D. = 10.24) were recorded.

Finally, we tested whether there were differences between groups on the level of nicotine dependence as measured by the FTND. Also in this case, the ANCOVA test revealed significant differences ($F(2, 117) = 3.561$, $p < .032$). Smokers in nicotine e-cigarette group had a lower level of dependence (M = 3.12, S.D = 2.29) with respect to smokers in nicotine-free e-cigarette group (M = 4.32, S.D. = 2.03) and control group (M = 3.59, S.D. = 2.32).

The only side effect possibly related to the use of e-cigarettes recorded is burning throat, which frequency increases from 3 to 6 months (see table 4).

Table 4. Insert here

Discussion

In this study, we tested if the use of e-cigarettes in well-motivated smokers coming from a lung cancer screening population could be effective in improving pulmonary health. We presented here outcomes at six months. First, we did not record any severe adverse events linked to the use of e-cigarettes, and the few side effects reported were well tolerated. However, burning throat increased from month 3 to month 6 in participants who used nicotine e-cigarettes. We argue, that it could be linked to the device and/or to the specific e-liquid used, different from the one provided during the study. Though some studies reported severe adverse events linked to the use of e-cigarettes, in our study we showed the safety of their use in a clinical controlled trial, where participants had the possibility to report any possible issues and a researcher was always available to support them. However, this aspect needs further investigation, indeed, recently the e-cigarette has been associated with respiratory disorders such as asthma and chronic obstructive pulmonary disease (Wills, Pagano, Williams, & Tam, 2019). Otherwise, a recent narrative review suggested treating with caution results about health risks related to long-term vaping (Polosa, O'Leary, Tashkin, Emma, & Caruso, 2019). We believe that more studies should be performed to better understand the real impact of the e-cigarette and e-liquids used both in habitual smokers, as well as never smokers in order to provide guidelines for using e-cigarette as a safe device to quit smoking.

At the same time, we found a positive effect of our program on the pulmonary health of participants, who independent of the study group reported a meaningful improvement in all the investigated areas. This improvement was linked to the smoking status at month 6 (current smokers or formers smokers). Coherently with other studies (Walele et al., 2018), we found a positive association between the use of e-cigarettes and tobacco smoking reduction. After 6 months from the beginning of the study, about 20% of the evaluated participants stopped smoking (about 15% of the original sample included in the ITT analysis). Furthermore, about 95% of the evaluated participants reduced the number of daily cigarettes. However, we did not find any difference between groups with regard to pulmonary health, cough-related quality of life, and mood, since the found differences were related only to the smoking status.

The use of nicotine e-liquids during the program seems to play an important role. Indeed, participants who used nicotine significantly reduced their daily tobacco cigarettes and the nicotine dependence more than any other participants did. Moreover, the use of nicotine-free e-cigarettes seems to have a positive effect only at the short-term (Masiero et al., 2018), while in mid- and probably long-term an inverse trend may be observed. Participants who used the latter not only did not report a higher reduction rate with respect to control participants (who received only low-intensity counseling), but

they also reported a higher level of dependence. We argue that this latter datum may suggest that the mismatch between the expectation raised by the use of an e-cigarette and the null physiological effect due to the absence of nicotine-delivering may have induced a reinforcing effect to smoke desire due to the behavioral pattern associated with using a cigarette-like device. The present study has also some limitations mainly due to the sample characteristics. First, outcomes were powered on group differences, rather than on differences between abstinent and not abstinent smokers. Thus, inferences about the effectiveness of e-cigarettes on quitting must be considered in light of the study design and its statistical power. Second, our sample includes only people older than 55-year-old with a long history of smoking who decided to take part in a screening program and with a high motivation to stop smoking. However, even if the present study targeted a particular smokers group, we feel that our results are not only interesting for this population, but they also support the idea that future research in different samples may prove the profitability of e-cigarettes use.

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Protocol

Clinicaltrials.gov NCT02422914; https://clinicaltrials.gov/ct2/show/NCT02422914

Conflicts of interest

The authors declare no conflicts of interest.

Authors' Contributions

CL, MM, GP, PM, and GV conceived and designed the study. CL coordinated the study, CL and GP acquired legal authorizations, and MM, KM, and SS managed participants. Statistical analyses were provided by CL, while data management was provided by RB. E-cigarettes and liquids were managed by JC and EOS. Drafting and writing of the manuscript were handled by MM, KM, CL, and GP. All authors have read and approved the final manuscript.

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477 **Figure 1.** CONSORT diagram for reporting trials

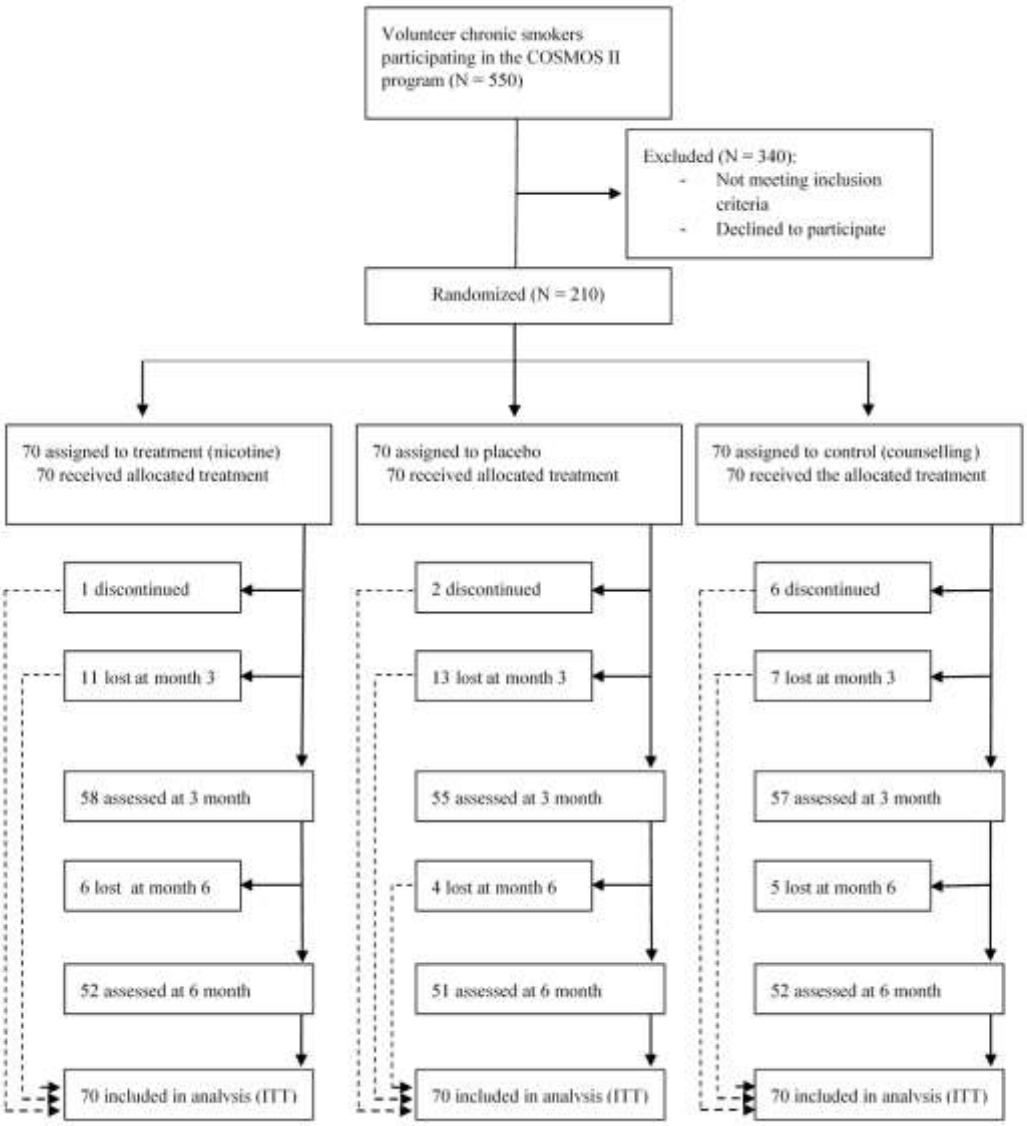

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Table 1 Descriptive statistics for smoking starting age, smoked daily cigarettes, e-CO (ppm value), dependence level, and motivational level.

Variable	**Nicotine e-cigarette group**		**Nicotine-free e-cigarette group**		**Control group**	
	M	SD	M	SD	M	SD
Smoking starting age	17.55	3.77	16.90	3.58	17.76	3.68
Smoked daily cigarettes	19.17	6.14	19.70	8.25	19.27	8.93
e-CO (ppm value)	15.34	5.29	14.58	5.90	14.63	6.99
Dependence Level	4.53	1.77	4.49	1.88	4.09	1.95
Motivational Level	12.66	2.25	13.35	2.79	13.10	2.49

Table 2. Respiratory symptoms at 6 months

		Dry cough (%)	Catarrh (%)	Breathlessness (%)	Bronchitis (%)
Nicotine e-cigarette					
	Former smokers	13.9	7.8	46.1	7.4
	Current smokers	62.6	67.4	86.4	25.3
Nicotine-free e-cigarette					
	Former smokers	6.1	10	69.9	9.6
	Current smokers	46.1	50.1	81.5	18.9
Control					
	Former smokers	8.54	14.3	71.5	3.8
	Current smokers	62.2	58.6	76.3	11.4
All groups					
	Former smokers	9.7	10.1	60.1	6.4
	Current smokers	56.6	57.5	81.4	17.9

488 **Table 3.** Numbers of current smokers and former smokers at month 6 by groups

	Abstinent Smokers	Current Smokers	Tot
Nicotine e-cigarette group	13 (16%)	57 (84%)	70
Nicotine-free e-cigarette group	11 (19%)	59 (81%)	70
Control group	7 (10%)	63 (89%)	70
Tot	31 (10%)	179 (80%)	210

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491 **Table 4.** E-cigarettes Side Effects at months 3 and 6

	Burning throat	**Cough**	**Nausea**	**Headache**	**Insomnia**	**Stomachache**	**Confusion**
3 Month							
Nicotine e-cigarette group	5.7%	10%	1.4%	-	1.4%	-	1.4%
Nicotine-free e-cigarette group	2.9%	2.9%	2.9%	-	-	-	-
6 Month							
Nicotine e-cigarette group	15.9%	5.8%	5.8%	-	1.4%	4.3%	1.4%
Nicotine-free e-cigarette group	5.6%	2.8%	7%	1.4%	-	4.2%	-

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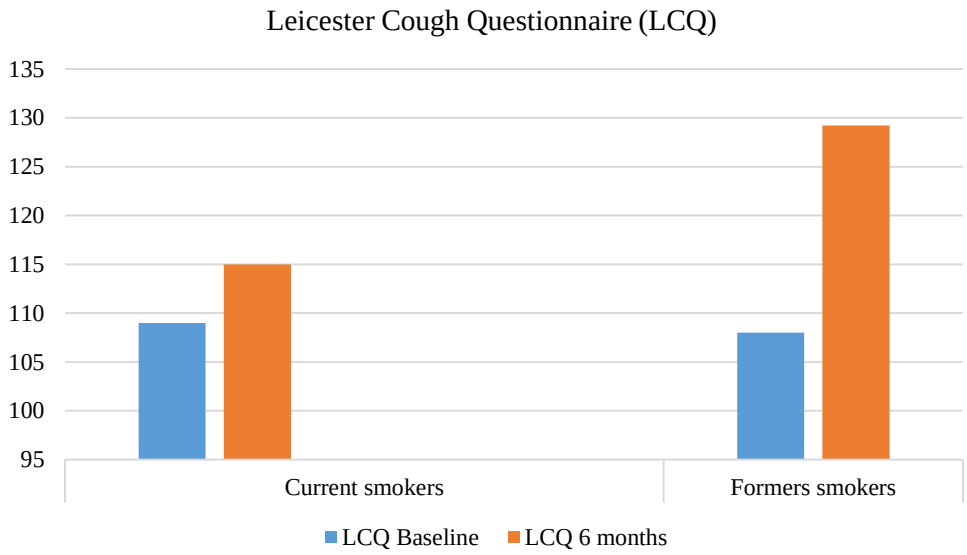
Figure 2 Leicester Cough Questionnaire (LCQ) scores at baseline and at 6 months



In this graph, differences in cough related quality of life as measured by the LCQ are showed. Participants who stopped smoking during the study (former smokers) showed a significant increase in LCQ score with respect to baseline values. Participants who continued smoking, instead, showed a non significant increase.