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Cohort study of electronic cigarette use: safety and effectiveness after 4 years of follow-up

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Abstract. – OBJECTIVE: More than a decade after e-cigarette (e-cig) market launch, limited information are available on their safety after 24 months of use. In 2013, we started the first observational study assessing e-cig long-term effectiveness and safety, directly comparing tobacco smokers and e-cig users. Here we report the results after four years of follow-up.

PATIENTS AND METHODS: Adults (30-75 years) were included if: smokers of ≥1 tobacco cigarette/day (tobacco smokers); users of any type of e-cig inhaling ≥50 puffs weekly (e-cig users); users of both tobacco and e-cig (dual users). Data were collected by phone and/or internet, and carbon monoxide levels tested in 50% of those declaring tobacco abstinence. Main outcomes were: possibly smoking-related diseases (PSRD; validated through hospital discharge data or visit in 62.6% of the sample); 4-year tobacco abstinence; number of tobacco cigarettes/day.

RESULTS: Data were available for 228 e-cig users (all ex-smokers), 471 tobacco smokers, 216 dual users. A PSRD was observed in 73 subjects (8.0%). No differences emerged across groups in PSRD rates, with negligible variations in self-reported health. Of e-cig users, 63.6% remained tobacco abstinent; dual users and tobacco smokers showed non-significantly different rates of tobacco (33.8% vs. 26.8%) and all-product (20.2% vs. 19.4%) cessation, and a similar decrease in cigarettes/day. Almost 40% of the sample switched at least once (tobacco smokers: 17.2%; dual users: 81.9%).

CONCLUSIONS: After four years, a scarce, non-significant harm reduction was observed among e-cig or dual users. Given the long-lasting health effects of tobacco smoking, the benefits of e-cig use may start being detectable at the next follow-up (six years). The complete switch to e-cig may help tobacco quitters remain abstinent, but e-cig use in addition to tobacco did not increase the likelihood of smoking cessation or reduction.

Key Words
Electronic cigarettes, Electronic nicotine delivery devices, Smoking cessation, Harm reduction, Tobacco smoking.

Introduction

More than a decade after their launch on the market, e-cigarettes (e-cig) are still at the centre of a vast debate[1-3]. Although their use increased in the last few years, with tens of millions of regular vapers in EU and USA[4-6], and in spite of the universal consensus on the need for additional safety data to support public health policies[2,7-18], the available evidence on e-cig efficacy and safety is still inconclusive[19,20]. The information available on long-term e-cig safety is limited to nine healthy vapers, non-former smokers, who were followed for 3.5 years[21], and scarce data are available on

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e-cig patterns of use over time[19,22]. Moreover, although a recent, large trial reported a marginal efficacy of e-cigarettes as smoking cessation aids among a general population of unselected smokers[23], the few other available randomized trials[24-27] and the observational studies[7-13,18,28-31] reported conflicting results[10,19]. In 2013, we started the only observational longitudinal study aimed at evaluating e-cigarette long-term effectiveness and safety through a direct comparison between the users of tobacco and electronic cigarettes, collecting health outcomes for more than 24 months[32]. The results of the 12- and 24-month follow-ups have been published previously[33,34]; here we report the main findings of the 4-year follow-up.

Patients and Methods

Patients

A detailed description of the study methodology has been reported[32,34], and it is also available on Clinicaltrials.gov (NCT01785537). Briefly, we recruited adults (30-75 years) who were: (a) smokers of ≥ 1 tobacco (only) cigarette daily for ≥ 6 months (tobacco smokers); (b) users of any type of e-cig for ≥ 6 months (e-cig users); (c) users of both tobacco and e-cig for ≥ 6 months (dual users). Potential participants were recruited via general practitioners, e-cig shops, internet advertisements, and social networks. Data were collected through a structured questionnaire, administered through a phone interview and/or by internet. Two investigators (MEF and LM) tested carbon monoxide levels in expired breath (Smokerlyzer® piCO+ ™, Bedfont Scientific Ltd.) in a random sample of 50% of the subjects declaring tobacco smoking abstinence. The follow-up will continue up to 72 months. Effectiveness outcomes were: (a) the rate of quitting of all products (either tobacco and/or e-cig, for >30 days); (b) the rate of abstinence/cessation from tobacco smoking at 48 months; and (c) the change in the daily number of tobacco cigarettes. Health outcomes were: (a) the rate of possibly smoking-related diseases; and (b) the change in self-reported health (assessed through the final item of the Italian version of the EuroQol EQ-D5L[35,36]). The following diseases occurred during the 4-year follow-up were considered as "possibly smoking-related diseases" (PSRD): chronic obstructive pulmonary disease (COPD), myocardial infarction and/or angina, congestive heart failure, transitory cerebrovascular ischemia or stroke, any cancer. Additional information was requested on allergies and/or mouth irritation, which were considered separately from other safety outcomes. Health data were both self-reported and obtained from direct visits (for the residents in Sicily - 16.0% of the sample) or hospital discharge abstracts (for the residents in the Abruzzo Region - 46.6%). The last data collection was performed for all participants after 48±3 months since enrollment.

Data Analysis

In long, "real-life" studies, both the exposure – smoking status – and the main effectiveness outcome – quitting – change over time in a considerable proportion of participants[37,38]. As a consequence, the analyses based upon baseline status, which are similar to an Intention-to-treat approach (ITT, typically the best approach for randomized trials with stable final outcomes and group switching rate rarely exceeding 10%), should be complemented with analyses based upon "real-life" group assignments. Therefore, since this is an observational analysis aimed at providing real-life information after 4 years, we did not follow a strict ITT approach and did not include in the analyses the participants who did not provide any data at any follow-up assessment. Instead, three approaches were used for the analyses, with a decreasing similarity with ITT:

A1 The exposure group (e-cig, dual user or tobacco only smoker) was assigned based upon the baseline smoking/vaping status (regardless of switching), and the analyses included all subjects that provided some data at the first follow-up visit (12 months – n=959). This analytical approach was used for the evaluation of both categorical outcomes of effectiveness (quit all products and quit tobacco).

A2 The exposure group was assigned based upon the baseline smoking/vaping status (regardless of switching), and the analyses included only those who were followed up to 48 months (n=915). Notably, no PSRD were observed in previous 12- and 24-month assessments among the 44 subjects that were lost to follow-up at 24 or 48 months. This second analytical approach was used for the evaluation of all outcomes.

A3 The exposure group was assigned based upon the baseline smoking/vaping status, and the analyses included only those subjects who were followed up to 48 months and never switched smoking/vaping status during the follow-up ("quitting" was not considered a switch). This analytical approach was used for the evaluation of both the continuous outcome of the effectiveness and the safety outcomes. Multivariate ran-

dom-effect linear and logistic regressions[39,40], with geographical region as the cluster unit, were used to investigate potential predictors of continuous and categorical outcomes, respectively. Multivariate models were set three times, one for each of the above three analytical approaches. The models predicting effectiveness outcomes were adjusted for the following baseline characteristics, all included *a priori* into the model regardless of significance: age, gender, BMI, marital status, educational level, occupation, alcohol use, hypertension, hypercholesterolemia, diabetes mellitus, self-rated health, smoking/vaping amount, and years of tobacco smoking. To reduce overfitting, the models predicting health outcomes were adjusted only for age, gender, self-rated health, years of tobacco smoking, and hypertension (all of which showed a *p*-value <0.2). Missing data were very few for all variables (<1%); no missing data imputation technique was thus adopted. A two-tailed *p*-value of 0.05 was considered significant for all analyses, which were performed using Stata 13.1 (Stata Corp., College Station, TX, USA, 2014).

Results

The flow of the participants is shown in the **Additional Figure 1:** 959 of the 1355 enrolled subjects provided data at least once (70.8%) and formed the sample of the analytical approach A1. After 4 years, data were available for 228 subjects that were e-cigarette only users at baseline, 471 tobacco only smokers, and 216 dual users, for a total of 915 subjects (48.4 years on average, 56.3% males). The latter sample, who completed the 48-month follow-up, was used for the analytical approaches A2 and A3.

Health Outcomes

A PSRD was observed in 73 subjects (8.0%), with no significant differences across baseline groups: 7.9% PSRD were observed among baseline e-cig users, 6.8% among tobacco smokers, and 10.7% among dual users (Table I, analytical approach A2). The results were similar when the analyses were restricted to the non-switchers (Table I, A3). No significant differences were also observed when only cancers (n=33 overall), or mouth irritation (n=41) were considered, both

Table I. Rates of possibly smoking-related diseasesψ during the follow-up.

	E-cig. % (n/N)	Tobacco cig. % (n/N)	Dual use % (n/N)
Any possibly smoking-related disease			
A2. Analyses by baseline status, including only the participants with 4-year follow-up data	7.9 (18/228)	6.8 (32/471)	10.7 (23/216)
A3. Analyses restricted to non switchers only, with all data at 48 months	8.1 (10/123)	7.1 (29/409)	7.7 (3/39)
Analyses further restricted to the participants with a visit or hospital discharge data available			
A2.	8.2 (17/208)	10.5 (21/200)	12.8 (21/164)
A3.	7.8 (9/115)	12.3 (19/154)	10.7 (3/28)
Cancer only			
A2.	4.4 (10/228)	3.4 (16/471)	3.2 (7/216)
A3.	4.9 (6/123)	3.4 (14/409)	2.6 (1/39)
Analyses further restricted to the participants with a visit or hospital discharge data available			
A2.	4.3 (9/208)	6.0 (12/200	3.7 (6/164)
A3.	4.3 (5/115)	7.1 (11/154)	3.6 (1/28)
Mouth irritation			
A2.	6.1 (14/228)	4.5 (21/471)	2.8 (6/216)
A3.	6.5 (8/123)	3.7 (15/409)	0.0 (0/39)
Self-rated health - Mean difference baseline-4 years	Mean (SD)	Mean (SD)	Mean (SD)
A2.	-0.3 (1.5)	-0.2 (1.4)	0.0 (1.6)
A3.	-0.3 (1.5)	-0.1 (1.3)	+0.2 (1.4)

ψChronic obstructive pulmonary disease (COPD), myocardial infarction and/or angina, congestive heart failure, transitory cerebrovascular ischemia or stroke, any cancer.
All p-values for the comparisons between groups were not significant: they were thus not shown.

in the complete and restricted sample. Also, a very small variation in self-reported health was observed over time and across groups (Table I). When the analyses were repeated including only the 297 participants who did not switch smoking/vaping group, and that were visited or had their outcomes confirmed through a linkage with hospital discharge abstracts, the rates of PSRD or cancer were lower among e-cig or dual users, as compared with tobacco smokers, but the differences were still non significant (Table I). Multivariate analyses were in line with univariate results (Table II), with the exception of a significantly lower decrease – although clinically negligible – in self-reported health among e-cig users, as compared to tobacco smokers (Table II).

Outcomes of Effectiveness

After 4 years, 63.6% of the 228 baseline e-cig users were still abstinent from tobacco smoking; 26.8% of the 471 baseline tobacco smokers and 33.8% of the 216 baseline dual users achieved tobacco abstinence ($p<0.05$ for all differences across groups; Table III, analytical approach A2). The proportion of subjects who achieved complete abstinence (were not using either tobacco cigarettes or e-cigarettes) did not significantly differ by baseline group: 23.7%, 20.2% and 19.4% among e-cig users, tobacco smokers and dual users, respectively (all $p>0.05$; Table III, A2). The results of both outcomes were similar when the 12-month larger sample was used (Table III, A1). During the follow-up, both baseline dual users and tobacco smokers showed a significant decrease in the mean number of tobacco cigarettes smoked per day, but the reduction was only marginally higher among dual users (-4.9 *vs*. -4.3, respectively; Table III, A2). When the analyses were restricted to those who did not switch (Table III, A3), a large and significantly higher decrease in the number of tobacco cigarettes smoked per day was observed among dual users (*vs*. tobacco smokers; $p<0.001$). All univariate results were confirmed by the multivariate analyses (after adjusting for age, gender, BMI, marital status, educational level, occupation, alcohol use, hypertension, hypercholesterolemia, diabetes, self-rated health, smoking amount and years of tobacco smoking), with one important exception: as compared to tobacco smokers, dual users did not

Table II. Multivariate analyses on possibly smoking-related diseases and self-reported health.

Outcomes	Adjusted OR (95% CI)	p^A
Possibly smoking-related disease		
A2. Analyses by baseline status, including only the participants with 4-year follow-up data		
- Tobacco smokers (ref. cat.)	1 (--)	--
- E-cig. users	1.01 (0.52-1.98)	0.9
- Dual users	1.57 (0.84-2.96)	0.16
A3. Analyses restricted to non switchers only, with all data at 48 months		
- Tobacco smokers (ref. cat.)	1 (--)	--
- E-cig. users	0.95 (0.41-2.22)	0.9
- Dual users	1.31 (0.34-5.04)	0.7
Self-rated health score Difference baseline-4 years	**Adj. coefficient (95% CI)**	**p^B**
A2. Analyses by baseline status, including only the participants with 4-year follow-up data		
- Tobacco smokers (ref. cat.)	0 (--)	--
- E-cig. users	-0.28 (-0.48; -0.08)	0.007
- Dual users	0.18 (-0.02; 0.39)	0.08
A3. Analyses restricted to non switchers only, with all data at 48 months		
- Tobacco smokers (ref. cat.)	0 (--)	--
- E-cig. users	-0.34 (-0.65; -0.04)	0.028
- Dual users	0.45 (-0.13; 1.04)	0.13

[A]Multivariate random-effect logistic regression, with geographical region as the cluster unit, adjusted for baseline age, gender, self-rated health, years of tobacco smoking and hypertension.
[B]Multivariate random-effect linear regression, with geographical region as the cluster unit, adjusted for baseline age, gender, BMI, marital status, educational level, occupation, alcohol use, hypertension, hypercholesterolemia, diabetes, self-rated health, smoking/vaping amount, and years of tobacco smoking.

Table III. Cigarette use after four years of follow-up.

	E-cig. % (n/N)	Tobacco cig. % (n/N)	Dual use % (n/N)	p *
Quitting any product (tobacco and/or e-cigarettes)				
A1. Analyses by baseline status, including the larger 12-month sample	24.1 (57/236)	20.0 (98/491)	18.5 (43/232)	
A2. Analyses by baseline status, including only the participants with 4-year follow-up data	23.7 (54/228)	20.2 (95/471)	19.4 (42/216)	
Continuous tobacco abstinence from baseline or cessation from tobacco during follow-up				
A1. Analyses by baseline status, including the larger 12-month sample	64.0 (151/236)	26.3 (129/491)	32.3 (75/232)	<0.001[A]; <0.001[B]; 0.03[C]
A2. Analyses by baseline status, including only the participants with 4-year follow-up data	63.6 (145/228)	26.8 (126/471)	33.8 (73/216)	<0.001[A]; <0.001[B]; 0.03[C]
Number of tobacco cigarettes per day - Mean difference 4y-baseline	Mean (SD)	Mean (SD)	Mean (SD)	
A2. Analyses by baseline status, including only the participants with 4-year follow-up data	–	-4.3 (8.5)	-4.9 (11.2)	
A3. Analyses restricted to non switchers only, with all data at 48 months	–	-3.3 (7.9)	-10.2 (11.7)	<0.001[C]

**p*-values that were significant at univariate analyses (using chi-squared test for categorical variables; *t*-test for continuous ones). If not reported, *p*-values are >0.05.
[A]E-cig. only vs. tobacco cig. only.
[B]E-cig. only vs. dual use.
[C]Tobacco cig. only vs. dual use.

show a significantly higher probability of tobacco smoking cessation ($p \leq 0.10$; Table IV).

Switching Smoking/Vaping Status, and Pathway of Use Through the Follow-Up

We defined "switchers" those who changed their exposure status (e.g., from e-cig only to dual use) at least once during the follow-up. Quitting all products was not considered switching, as this is an outcome of effectiveness. The smoking/vaping pathways of all participants throughout the follow-up, including switching category (yes or no), are reported in the **additional Figure 2**. A large number of participants switched during the 4-year follow-up (37.7% of the overall sample), with wide differences across groups: 17.2% of tobacco smokers; 46.1% of e-cig users; and 81.9% of dual users. Such a pattern implies that, on one side, the analyses restricted to those who never switched were based upon a limited number of e-cig users (n=123) and dual users (n=39), and the results are complex to interpret (Tables III and IV, analytical approach A3). On the other side, some interesting data can be obtained from the analysis of participants' pathways: e.g., the most common switching patterns or the rate of quitting failures. Of the 324 subjects who switched smoking/vaping group at the 12- or 24-month assessments, 29.9% (n=91) switched group again during the follow-up. Among the 63 baseline tobacco smokers who changed status, 47 initially switched to e-cig use only. Of them, 30 were able to remain abstinent from tobacco, while 17 switched back to tobacco or dual use. Among the 105 baseline e-cig users who changed status, 72 initially switched to tobacco smoking only. After this switch, only 10 subjects made a further attempt to cease tobacco. Among the 177 baseline dual users who changed status, 141 initially switched to tobacco smoking only (114 of them switched after 12 months of follow-up). After this switch, only a minority (n=23) made a further attempt to stop smoking. As regards the rate of quitting (of all products) failures, the proportion of subjects that were able to maintain abstinence after a quit attempt at the 12- or 24-month follow-up assessments were:

– 67.6% (71/105) among those who quit from tobacco smoking only;
– 94.1% (16/17) among those who quit from e-cig use only;
– 61.8% (21/34) among those who quit from dual use.

Overall, 496 subjects used e-cig at least once during the follow-up (including both e-cig users and dual users at baseline, and those who were tobacco smokers at baseline and then switched to e-cig or dual use during the follow-up). Of them, 99 (20.0%) were able to quit the use of all products. A similar quitting rate (21.7%) was observed among the 419 subjects who never used e-cig during the follow-up. Thus, even when the switching pattern was kept into account, the use of e-cig, either alone or in combination with tobacco cigarettes, did not seem to substantially enhance the propensity to quit.

Table IV. Multivariate analyses predicting tobacco and/or e-cig use abstinence and/or cessation, and the difference in the daily number of tobacco cigarettes smoked between year 4 and baseline.

Outcomes	Adjusted OR (95% CI)	p^A
Quitting any product (tobacco and/or e-cigarettes)		
A1. Analyses by baseline status, including the larger 12-month sample		
- Tobacco only smokers (ref. cat.)	1 (--)	--
- E-cig. only users	1.25 (0.85-1.85)	0.3
- Dual users	0.98 (0.64-1.48)	0.9
A2. Analyses by baseline status, including only the participants with 4-year follow-up data		
- Tobacco only smokers (ref. cat.)	1 (--)	--
- E-cig. only users	1.22 (0.82-1.82)	0.3
- Dual users	1.03 (0.67-1.57)	0.9
Continuous tobacco abstinence from baseline or cessation from tobacco during follow-up		
A1. Analyses by baseline status, including the larger 12-month sample		
- Tobacco only smokers (ref. cat.)	1 (--)	--
- E-cig. only users	5.20 (3.66-7.38)	<0.001
- Dual users	1.35 (0.94-1.92)	0.10
A2. Analyses by baseline status, including only the participants with 4-year follow-up data		
- Tobacco only smokers (ref. cat.)	1 (--)	--
- E-cig. only user	5.00 (3.51-7.13)	<0.001
- Dual users	1.41 (0.98-2.02)	0.066
Number of tobacco cig. per day - Difference 4y-baseline	**Adj. coefficient (95% CI)**	**p^b**
Number of tobacco cig. per day - Difference 4y-baseline	Adj. coefficient (95% CI)	p B
A2. Analyses by baseline status, including only the participants with 4-year follow-up data		
- Tobacco only smokers (ref. cat.)	0 (--)	--
- Dual users	0.38 (-0.97; 1.73)	0.6
A3. Analyses restricted to non switchers only, with all data at 48 months		
- Tobacco only smokers (ref. cat.)	0 (--)	--
- Dual users	6.80 (4.27; 9.34)	<0.001

[A]Multivariate random-effect logistic regression, with geographical region as the cluster unit, adjusted for baseline age, gender, BMI, marital status, educational level, occupation, alcohol use, hypertension, hypercholesterolemia, diabetes, self-rated health, smoking/vaping amount, and years of tobacco smoking.
[B]Multivariate random-effect linear regression, with geographical region as the cluster unit, adjusted for baseline age, gender, BMI, marital status, educational level, occupation, alcohol use, hypertension, hypercholesterolemia, diabetes, self-rated health, smoking/vaping amount, and years of tobacco smoking.

Discussion

In this study, we have reported the results of the fourth year of follow-up of an observational cohort study evaluating the long-term safety and effectiveness of e-cigarettes. We were able to describe "real-world" vaping and smoking pathways over time, and to update previously published data[33,34]. The main findings can be summarized as follows. First, we did not observe a significantly lower rate of possibly smoking-related diseases (including cancers) among e-cig users, as compared with dual users or tobacco smokers. This finding was consistent across all analytical approaches and data sources. Moreover, e-cig use did not substantially improve self-reported health. On one side, these findings are in line with those from several other studies with shorter follow-up (≤2 years)[4,24-27,41-44], as well as with the only study providing long-term safety data (although limited to a sample of nine naive e-cig users)[21]: no serious adverse events and no higher risk were reported for e-cig when compared to traditional tobacco smoking. On the other side, the current results are not supporting the hypothesis and preliminary lab data suggesting a substantial harm reduction from e-cig exclusive use[22,45-47]. The interpretation, however, must be cautious, since the excess risk of tobacco smoking may take five to ten years to substantially decrease[48]. Consequently, although this is the longest follow-up to date, it is still insufficiently long to detect a significant harm reduction from e-cig among former smokers, as were all the participants of the study. Therefore, at this stage, the absence of a noticeable risk decrease was expected, and we presume that, if differences are to emerge, they will begin to be detectable at the last assessment, which has been rescheduled from 60 to 72 months. Second, although the complete switch to e-cig did seem to help tobacco quitters to remain abstinent from smoking, with rates of relapse lower than 40% after four years, the use of e-cig in addition to tobacco smoking (dual use) did not improve smoking cessation nor reduction: (a) baseline dual and tobacco smokers showed comparable quitting rates (of both tobacco and/or e-cig); (b) almost 80% of dual users relapsed to tobacco smoking alone at some point during the follow-up; (c) differently from the previous 24-month assessment[34], the reduction of tobacco cigarettes smoked per day was non significantly different between dual users and tobacco only smokers. Expectedly, given the heterogeneous evidence available[10,19], the present findings on e-cig effectiveness are comparable to some previous studies, reporting similar tobacco abstinence rates between dual users and tobacco smokers[28,31,41,49-52], but different from other studies, which reported lower tobacco abstinence rates among e-cig users[23-26,42,53,54], or showed encouraging results for dual use (higher quitting rates and lower relapsing rates as compared to traditional smoking[6,29]). Among the suggested potential explanations[34], the enrolment of less motivated subjects[23,25,42,54], or previous bans against e-cigarette sales[53] may have contributed to the low quitting rates reported in some published studies. Instead, at least two factors have been advocated to explain the combined scenario of high quit rates and low relapse rates reported in some of the most recent surveys[6,29]: first, the free choice of e-cig in real-world studies may contribute to quitting success[55]; second, newer-generation e-cig may reduce nicotine withdrawal symptoms, thus improving sustained nicotine abstinence[56,57]. Real-life data on the pathways of use of e-cig or dual users are strongly needed[19,22,58], as they are limited to two dedicated studies with one year of follow-up[28,51]. In this study, during the four years of follow-up, less than one fifth of the tobacco smokers made an attempt to use e-cig (either alone or in combination). In contrast, the vast majority of dual users and almost half of e-cig users changed their status at least once (and almost one third of both changed status twice). When they switched status, most dual users and e-cig users relapsed to tobacco smoking alone, mainly within the first 12 months, and only a minority made a further attempt to stop smoking. Notably, however, once an attempt to quit was made, it was successful – in the following 2 to 3 years of follow-up – in more than 60% of the cases. Taken together, these findings add to the existing evidence[10,59,60] on the dramatic reluctance of tobacco smokers to change their habit over and beyond quitting, and confirm that the most complex step, the one requiring the main efforts, remains the first attempt to quit[61,62].

This study has some limitations. First, although false declarations were sporadic (<10 overall during all assessments), part of the information were self-reported: smoking cessation was confirmed with a test of carbon monoxide levels in only 50% of the quitters, and health data were checked through direct visits or hospital

discharge abstracts for only 62.6% of the participants. Second, we lost 29.2% of the participants at the first follow-up assessment, and although responders and non-responders were similar for most variables[33], and the rate of subsequent losses was very low, we had no 4-year data for almost one third of the initial sample. Third, like previous observational studies, we included all types of e-cig to approach real-life conditions, but different e-cig models with various nicotine doses might lead to diverse results[28]. However, the rates of tobacco abstinence and all-smoking cessation did not differ by nicotine concentration ([33], 4-year data not shown), and observational studies, which imply a free choice of product, may represent a better picture of the real world experiences[63]. Acknowledging these caveats, the present study provides the longest results to date on the comparative effectiveness of electronic and traditional cigarettes, in a sample of unselected users, and describes for the first time the changes in smoking and vaping status over time in a real-life scenario.

Conclusions

After four years of follow-up of a large sample of current or former smokers, the use of e-cig, either alone or in combination with tobacco cigarettes, did not significantly decrease the rate of diseases potentially related to tobacco, and did not substantially improve self-reported health. Given the long-lasting health effects of tobacco smoking, a harm reduction from e-cig use, if obtainable, is expected to be detectable at the next follow-up assessment, which has been rescheduled at 72 months. Concerning e-cig potential effectiveness as a tool for smoking cessation, the complete switch to e-cig did seem to help tobacco quitters to remain abstinent from smoking, but the use of e-cig in addition to tobacco smoking (dual use) did not increase the likelihood of either smoking cessation or reduction. In real-life conditions, the vast majority of dual users and half of e-cig users switched smoking/vaping status during the follow-up, raising important issues for the classification of these subjects, and suggesting that real-life data, with multiple assessments, are required to improve the validity of long-term observational or experimental studies on the effects of electronic and/or tobacco cigarettes, as well as most recent heat-not-burn tobacco products.

Authors' Declaration of Personal Interests

None of the authors declare any potential conflict of interests.

Declaration of Funding Interests

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Ethics Approval

The work was approved by the Chieti-Pescara University Ethics Committee (Record n. 6; 25-03-2013); all participants provided written informed consent.

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