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Tobacco *vs.* electronic cigarettes: absence of harm reduction after six years of follow-up

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Abstract. – OBJECTIVE: Information on the long-term safety of electronic cigarettes (e-cig) is still limited. We report the results after six years of follow-up of the first observational study assessing e-cig long-term effectiveness and safety.

PATIENTS AND METHODS: Participants were adults who smoked ≥1 tobacco cigarette/day (tobacco smokers); or used any type of e-cig inhaling ≥50 puffs weekly (e-cig users); or used both (dual users). Participants were contacted directly or by phone and/or internet interviews. Hospital discharge abstract data and carbon monoxide level tests were also used.

RESULTS: Data were available for 228 e-cig users (all ex-smokers), 469 tobacco smokers, 215 dual users. A possibly smoking-related disease (PSRD) was recorded in 90 subjects (9.9%); 11 deceased (1.2%). No differences were observed across groups in PSRD rates, with minor changes in self-reported health. Among e-cig users, 64.0% remained tobacco abstinent. Dual users and tobacco smokers did not significantly differ in the rate of cessation of tobacco (38.6% *vs.* 33.9%, respectively) and all products (23.7% *vs.* 26.4%). A comparable decrease in daily cigarettes was also observed. 39.5% of the sample switched at least once (tobacco smokers: 15.1%; dual users: 83.3%).

CONCLUSIONS: After six years, no evidence of harm reduction was found among e-cig or dual users. The complete switch to e-cig might support tobacco quitters remain abstinent, but the use of e-cig in addition to tobacco did not improve smoking cessation or reduction.

Key Words:
Electronic cigarettes, Traditional smoking devices, Heat-not-burn products, Smoking cessation, Harm reduction, Tobacco smoking, Adverse health effects.

Introduction

In spite of the widespread consensus on the necessity for additional data on electronic cigarette (e-cig) long-term effectiveness and safety to support public health policies[1-12], uncertainty remains[13,14]. Despite the alarming emergence of observational evidence of lung injuries[15-17] and altered cardiovascular parameters[18] in the short-term, the available information on long-term safety is limited to a large observational cohort with only self-reported data after 3 years of follow-up[19], and nine healthy vapers, non-former smokers, who were followed for 3.5 years[20].

Concerning effectiveness, numerous studies with short follow-up are available[1,3-8,11,21-30], the results are conflicting[14,22,29,31], and long-term data are still lacking. Finally, scarce longitudinal data are also available on e-cig patterns of use over time[29,32-34].

In 2013, we initiated the first longitudinal cohort study to evaluate the long-term effectiveness and safety of e-cig through a direct comparison with tobacco cigarette smokers[35]. We previously

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published the results of the 12-, 24-, and 48-month follow-up[36-38]; and we are here updating the analyses with the main findings of the 6-year follow-up.

Patients and Methods

The protocol has been registered on Clinicaltrials.gov (NCT01785537), and published[35]. Briefly, participants were adults (30-75 years) who, since ≥6 months: smoked only tobacco cigarettes (≥1 per day – tobacco smokers), or used any type of e-cig (e-cig users), or used both tobacco and e-cig (dual users). The recruitment was based on general practitioners, internet advertisements and social networks, and e-cig shops. Participants' information was collected through a structured questionnaire, administered directly or by phone and/or internet interviews.

The outcomes of effectiveness were: (a) the rate of quitting of all products (either tobacco and/or e-cig, since 30 days or more); (b) the rate of abstinence (for e-cig users) and cessation from tobacco smoking (for the other two groups) at 72 months; and (c) the difference in the number of tobacco cigarettes per day. To check the abstinence from tobacco, we tested carbon monoxide levels in expired breath (Smokerlyzer® piCO+™, Bedfont Scientific Ltd., Station Road, Harrietsham, Maidstone, Kent, UK) in a random sample of 50% of the subjects declaring tobacco smoking abstinence.

The safety (health) outcomes were: (a) the rate of possibly smoking-related diseases (PSRD, including chronic obstructive pulmonary disease, myocardial infarction and/or angina, congestive heart failure, transitory cerebrovascular ischemia or stroke, any cancer); and (b) the variation in self-reported health (assessed via the final item of the Italian version of the EuroQol EQ-D5L[39,40]). Allergies and/or mouth irritation were also evaluated separately from other safety outcomes. Safety data were both self-reported and collected through direct contact (for the Sicilian residents – 16.0% of the sample) or hospital discharge abstracts (for the Abruzzo residents – 46.8%). The last data collection was carried out after 72±3 months since the enrollment.

The Ethics Committee of the University of Chieti-Pescara approved the protocol (Record n. 6; 25-03-2013). A written informed consent was obtained by all participants, and the entire dataset is available upon request from the authors.

Data Analysis

In long, observational studies, a substantial proportion of participants typically change their exposure status during the follow-up[41,42]. As an example, tobacco smokers can switch to e-cig, and vice versa. Real-life studies in this field present some additional complexities, because the outcome of quitting smoking/vaping is not stable, and can also change over time. Consequently, the classical analytical approach, where participants are classified only according to their baseline exposure status (similar to an Intention-to-treat approach - ITT - which is instead the best approach for randomized trials with stable final outcomes and group switching rate infrequently exceeding 10%), must be complemented with additional analyses that take into account switching and "real-life" group assignments. Thus, a stringent ITT approach was not followed, and the participants who did not provide any data at any follow-up assessment were not included in the analyses. We used the following three analytical approaches, with a decreasing similarity with ITT:

(A1) The exposure group was determined according to the baseline smoking/vaping status (regardless of switching), and the analyses included all participants providing data at the first, 12-month follow-up (n=959). This analytical approach was used for the categorical outcomes of effectiveness.

(A2) The exposure group was assigned according to the baseline status (regardless of switching), but only those who were followed up to 72 months were analyzed (n=912). Remarkably, only one PSRD was observed in previous assessments among the 47 participants that were lost during previous follow-ups. This analytical approach was adopted for the assessments of all the outcomes.

(A3) The exposure group was determined according to the baseline status, but only the participants who provided data at 72 months and never switched smoking/vaping status were included in the analyses. Notably, quitting was not judged as a switch, and this approach was adopted for all safety outcomes and the continuous outcome of effectiveness.

In order to investigate the potential independent predictors of continuous and categorical outcomes, we used, respectively, multivariate random-effect linear and logistic regressions[43,44], with geographical region as the cluster unit. We set a multivariate model for each of the above three analytical approaches. The following baseline characteristics were included *a priori* into the

models predicting effectiveness outcomes: 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. The models predicting safety (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) to reduce overfitting. No missing data imputation technique was adopted, because missing data were <1% for all variables. Significance was set at 0.05 (two-tailed) for all analyses, which were carried out using Stata 13.1 (Stata Corp., College Station, TX, USA, 2014).

Results

Of the 1355 enrolled subjects, 959 provided data at least once (70.8%) and were included in the analytical approach A1 (Figure 1). After six years of follow-up, data were available for a total of 912 subjects (50.4 years on average, 56.3% males). According to baseline status, 228 were e-cig users, 469 tobacco smokers, and 215 dual users. These subjects were included in the analytical approach A2.

Health Outcomes

A PSRD was recorded in 90 subjects (9.9%), with no significant differences by baseline group: 11.4%, 8.1% and 12.1% PSRD were observed among baseline e-cig users, tobacco smokers, and dual users, respectively (Table I, analytical approach A2). Similar results were observed when the analyses were restricted to non-switchers (Table I, A3). Also, no significant differences were found when only cancers (n=40 overall), or mouth irritation (n=43) were considered, both in the complete and restricted sample. Moreover, self-reported health showed a very small change over time in all groups (Table I).

The results did not differ substantially when the sample was restricted to the 285 participants who did not switch smoking/vaping group, and were visited or had their outcomes confirmed through a linkage with hospital discharge abstracts: as compared with tobacco smokers, PSRD or cancer rates were lower among e-cig or dual users, but the differences were still not significant (Table I).

Multivariate analyses entirely confirmed univariate results (Table II). Overall, 11 deaths were registered during the six years of follow-up: 3 among tobacco smokers, 5 among e-cig users, and 3 among dual users (p>0.2).

Outcomes of Effectiveness

A total of 64.0% of the baseline e-cig users remained abstinent from tobacco smoking during the six years of follow-up. Among baseline tobacco smokers and dual users, 33.9% and 38.6% achieved tobacco abstinence, respectively (p<0.05 only for the difference between e-cig users and the other groups; Table III, analytical approach A2). No differences across baseline groups were found in the proportion of subjects who quit either tobacco and/or e-cigarettes: 26.3%, 26.4% and 23.7% achieved complete abstinence among e-cig users, tobacco smokers and dual users, respectively (all p>0.05; Table III, A2). Both outcomes showed similar results when the larger, 12-month sample was used (Table III, A1).

A significant decrease in the mean number of tobacco cigarettes smoked daily was observed among both dual users and tobacco smokers, but the reduction was only slightly higher among dual users (-6.0 *vs.* -5.2, respectively; Table III, A2). When the analyses were repeated, including only the subjects who did not switch (Table III, A3), the dual users showed a significantly larger reduction, as compared to tobacco smokers, of the daily number of tobacco cigarettes (-11.5 *vs.* -4.2, p<0.001). Again, the multivariate analyses substantially confirmed the univariate results (Table IV).

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

The participants that changed their exposure status (e.g., from e-cig only to dual use) at least once during the follow-up were defined as "switchers". Quitting all products was not defined as "switching", because this is an outcome of effectiveness. The smoking/vaping pathway of all participants during the follow-up, including switching category (yes or no), have been reported in the **Supplementary Figure 1**: 39.5% of the participants switched product during the six years of follow-up, with wide differences across groups: 15.1% of tobacco smokers; 48.2% of e-cig users; and 83.3% of dual users. As a consequence, the analyses restricted to those who never switched were based on a scarce number of e-cig users (n=118) and dual users (n=36), and the results should be interpreted with caution (Tables III and IV, analytical approach A3).

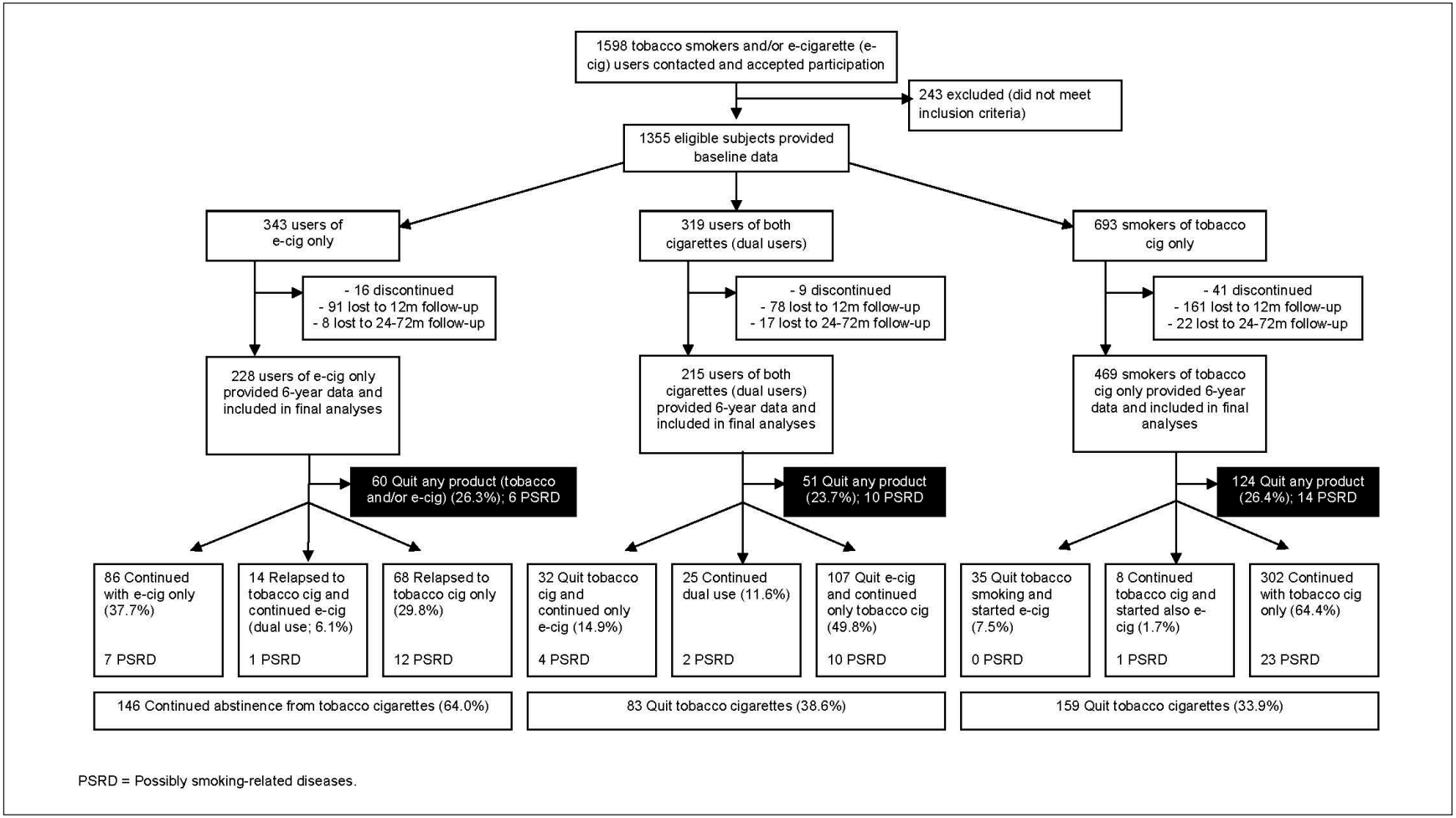

Figure 1. Flow of the participants and numbers of quitters and possibly-related serious adverse events.

Table I. Rates of possibly smoking-related diseases ψ 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 6-year follow-up data	11.4 (26/228)	8.1 (38/469)	12.1 (26/215)
A3. Analyses restricted to non switchers only, with all data at 72 months	10.2 (12/118)	8.5 (34/398)	11.1 (4/36)
Analyses further restricted to the participants with a visit or hospital discharge data available			
A2.	12.0 (25/208)	13.1 (26/198)	14.6 (24/164)
A3.	10.0 (11/110)	15.4 (23/149)	15.4 (4/26)
Cancer			
A2.	6.6 (15/228)	3.6 (17/469)	3.7 (8/215)
A3.	5.1 (6/118)	3.8 (15/398)	5.6 (2/36)
Analyses further restricted to the participants with a visit or hospital discharge data available			
A2.	6.7 (14/208)	6.6 (13/198)	4.3 (7/164)
A3.	4.6 (5/110)	8.0 (12/149)	7.7 (2/26)
Mouth irritation			
A2.	6.6 (15/228)	4.5 (21/469)	3.3 (7/215)
A3.	6.8 (8/118)	3.5 (14/398)	0.0 (0/36)
Self-rated health – Mean difference baseline-6 years	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
A2.	-0.1 (1.9)	-0.1 (1.5)	0.0 (1.8)
A3.	-0.2 (1.8)	-0.1 (1.4)	+0.2 (2.1)

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.

Concerning smoking/vaping pathways, of the 343 subjects who switched smoking/vaping group at the 12-, 24- or 48-month assessments, 32.9% (n=113) switched group again during the follow-up. Among the 62 baseline tobacco smokers who changed status, 45 initially switched to e-cig use only. Of them, 26 remained abstinent from tobacco, whereas 19 switched back to tobacco (only, or dual use). Among the 105 baseline e-cig users that changed status, 72 made the first switch to tobacco smoking only. After this switch, only 15 subjects made an additional attempt to quit tobacco. Among the 176 baseline dual users that changed status, 141 made the first switch to tobacco smoking only (114 of them switched after 12 months of follow-up). After this switch, only 30 participants made another attempt to cease smoking.

With regard to the rate of quitting (of all products) failures, more than half of the participants of all groups were able to maintain abstinence after the first quit attempt: 64.8% (94/145) among those who quit from tobacco (only) smoking; 78.1% (50/64) among e-cig users; 61.1% (22/36) among dual users.

A total of 514 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, 505 tried e-cig during 12-, 24-, or 48-month follow-up assessments, and 121 (24.0%) were able to quit the use of all products. A slightly higher cessation rate (28.0%) was observed among the 407 participants who never used e-cig during previous follow-up evaluations.

Discussion

This report summarizes the longest available evidence on e-cig safety and effectiveness *vs.* tobacco smoking, adding important confirmation to previous results[36-38], and describing "real-world" vaping and smoking pathways for more than a quinquennium.

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 6-year follow-up data		
– Tobacco smokers (ref. cat.)	1 (–)	–
– E-cig. users	1.17 (0.64-2.13)	0.6
– Dual users	1.48 (0.81-2.70)	0.2
A3. Analyses restricted to non switchers only, with all data at 72 months		
– Tobacco smokers (ref. cat.)	1 (–)	–
– E-cig. users	0.88 (0.40-1.93)	0.7
– Dual users	1.28 (0.38-4.31)	0.7
Self-rated health score Difference baseline-6 years	**Adj. coefficient (95% CI)**	**p^B**
A2. Analyses by baseline status, including only the participants with 6-year follow-up data		
– Tobacco smokers (ref. cat.)	0 (–)	–
– E-cig. users	-0.19 (-0.42; 0.05)	0.12
– Dual users	0.16 (-0.08; 0.39)	0.19
A3. Analyses restricted to non switchers only, with all data at 72 months		
– Tobacco smokers (ref. cat.)	0 (–)	–
– E-cig. users	-0.24 (-0.62; 0.14)	0.2
– Dual users	0.43 (-0.33; 1.19)	0.3

[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 six 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	26.7 (63/236)	25.9 (127/491)	22.4 (52/232)	
A2. Analyses by baseline status, including only the participants with 6-year follow-up data	26.3 (60/228)	26.4 (124/469)	23.7 (51/215)	
Continuous tobacco abstinence from baseline or cessation from tobacco during follow-up				
A1. Analyses by baseline status, including the larger 12-month sample	64.4 (152/236)	33.0 (162/491)	36.6 (85/232)	<0.001[A]; <0.001[B]
A2. Analyses by baseline status, including only the participants with 6-year follow-up data	64.0 (146/228)	33.9 (159/469)	38.6 (83/215)	<0.001[A]; <0.001[B]
Number of tobacco cigarettes per day - Mean difference 4y-baseline	**E-cig. % (n/N)**	**Tobacco cig. % (n/N)**	**Dual use % (n/N)**	**p^***
A2. Analyses by baseline status, including only the participants with 6-year follow-up data	–	-5.2 (9.5)	-6.0 (11.7)	
A3.Analyses restricted to non switchers only, with all data at 72 months	–	-4.2 (9.2)	-11.5 (10.8)	<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.

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 6 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	0.99 (0.69-1.43)	0.9
– Dual users	0.88 (0.60-1.29)	0.5
A2. Analyses by baseline status, including only the participants with 6-year follow-up data		
– Tobacco only smokers (ref. cat.)	1 (–)	–
– E-cig. only users	0.95 (0.65-1.38)	0.8
– Dual users	0.91 (0.62-1.35)	0.6
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	3.53 (2.92-4.95)	<0.001
– Dual users	1.18 (0.84-1.65)	0.4
A2. Analyses by baseline status, including only the participants with 6-year follow-up data		
– Tobacco only smokers (ref. cat.)	1 (–)	–
– E-cig. only users	3.34 (2.37-4.70)	<0.001
– Dual users	1.22 (0.86-1.73)	0.3
Number of tobacco cig. per day - Difference 6y-baseline	**Adj. coefficient (95% CI)**	p^B
A2. Analyses by baseline status, including only participants with 6-year follow-up data		
– Tobacco only smokers (ref. cat.)	0 (–)	–
– Dual users	0.43 (-0.98; 1.83)	0.6
A3. Analyses restricted to non switchers only, with all data at 72 months		
– Tobacco only smokers (ref. cat.)	0 (–)	–
– Dual users	6.51 (3.77; 9.26)	<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.

First, after six years of follow-up, no evidence of harm reduction emerged among e-cig users, as compared to tobacco smokers. This finding was consistent for all health outcomes (including cancer), and across all analytical approaches. Additionally, e-cig use did not substantially improve self-reported health. Our results are in line with those of several prior studies, all suggesting the absence of a net health benefit among e-cig users when compared to traditional tobacco smokers [19-21,24-26,45-49], while other studies outlined potential positive effects of e-cig in the regulation of cardiovascular[18,50], or laboratory[32,51-53] parameters. However, the interpretation of these studies must take into account the short duration of their follow-up, never exceeding 3.5 years[20], while any decrease in the excess risk of tobacco smoking may take a minimum of five years to emerge[54]. Thus, the strength of the evidence either in favor or against any harm reduction resulting from the exclusive use of e-cig was severely limited, and additional long-term data were strongly awaited. In this scenario, although the present findings add further evidence, additional studies with even longer follow-ups are required: in a sample composed by former smokers, a decade would be more appropriate to detect significant risk reductions for cancers or cardiovascular diseases[54].

Second, although the complete switch to e-cig confirmed to help tobacco quitters to remain abstinent from smoking, with six-year relapse rates lower than 40%, the use of e-cig in addition to tobacco smoking (dual use) proved to be only marginally useful to promote smoking cessation:

the quitting rates (of both tobacco and/or e-cig) among baseline dual users were comparable to those of baseline tobacco smokers (with about 80% of dual users relapsing to tobacco smoking at some time during follow-up), and, in line with the 4-year assessment[38], the reduction of tobacco cigarettes smoked per day was non significantly different between dual users and tobacco only smokers. In the heterogeneous scenario currently available, with differences in study design, analytical approaches, comparator groups and selected populations, and relatively short follow-up[20], our results support, on one side, the encouraging role of e-cig alone, also in the long term, in helping tobacco smokers remaining abstinent, consistent with previous studies showing higher tobacco abstinence rates among e-cig users[27,33] (who were also more likely to attempt and successfully quit[23,55]). On the other side, the present findings indicate what has been previously shown on the absence of any benefit when e-cig are used in combination with tobacco cigarettes[47,56-61]. In contrast to these findings, however, some analyses showed lower tobacco abstinence rates among e-cig users[21,24,25,28,48,62,63], or even encouraging results for dual use (higher quitting rates and lower relapsing rates as compared to traditional smoking)[23,64]. Some of these studies, however, enrolled subjects less motivated to quit[25,28,48,63]; in addition, bans against e-cigarette sales[62] may have contributed, at least in part, to the low quitting rates among e-cig users reported in some previous analyses[65,66]. Moreover, another element may have contributed to explain the favourable results achieved among dual users in some recent surveys: second- or third-generation e-cig are more effective than older versions in nicotine delivery, thus reducing nicotine withdrawal symptoms and improving sustained nicotine abstinence[38].

A growing body of evidence[33,58,59,67], although still limited, has focused on the pathways of use of e-cig or dual users, followed for a maximum of 3 years. In contrast with previous findings that most e-cig users are able to remain so[58,59,67], and about two thirds of dual users shift to e-cig alone during follow-up[33], we found patterns of use largely varying throughout the six years of follow-up. Less than one fifth of baseline tobacco smokers made an attempt to use e-cig (alone or in combination), while half of e-cig users, and more than 80% of dual users switched group at least once during follow-up, mostly to restart with tobacco smoking (alone or combined). Additionally, once a relapse to tobacco was made, only a minority of baseline e-cig and dual users performed a further attempt to quit. However, more than 60% of quitting attempts proved successful irrespective of baseline group, notably with no significant differences between ever and never e-cig users. Taken together, these findings add to the existing evidence[6,68,69] on the dramatic reluctance of tobacco smokers to change their habit over and beyond quitting, and suggest that, 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. The higher switching rates from e-cig or dual use that we found in our sample may be explained, at least in part, by the presence in our study of multiple assessment performed throughout a long period of time, as compared to prior studies with shorter follow-up and only baseline-endline assessments[33,58,59,67]. This approach allowed us to literally monitor, for each patient, all changes occurred throughout six years, thus providing a multifaceted pattern, more complex to interpret but also more adherent to the high variability of a "real life" scenario. Additionally, increasing evidence suggests that, among former tobacco smokers, the use of first-generation devices (with low nicotine concentration) is a strong predictor of stopping e-cig use to switch back to tobacco[67,70,71]. It is possible that a large proportion of baseline e-cig and dual users enrolled in our sample used older devices. Unfortunately, however, we were not able to verify such hypothesis because we did not collect data on the type of e-cig used.

Some limitations of the study must be considered. First, although false assertions were rare (<10 overall, during all evaluations), part of the data were self-reported: we were able to confirm the cessation of tobacco smoking - through a test of carbon monoxide levels - in only 50% of the quitters, and only 62.8% of the participants had their health data checked through direct visits or hospital discharge abstracts. Second, 29.2% of the participants were lost at the first follow-up. However, responders and non-responders were comparable for most variables[36], and the rate of subsequent losses was very low. Third, similar to several observational studies in the field, 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[58]. However, the rates of tobacco abstinence and all-smoking cessation did not differ by nicotine concentration ([36], 6-year data not shown), and ob-

servational studies, which imply a free choice of product, may represent a better picture of the real world experiences[72].

Conclusions

After six 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. Although the follow-up is the longest to date, and the findings add to the growing evidence on the concerns on the health benefit of e-cig, further studies with follow-ups approaching a decade are required to elucidate the long-term impact on cancer or cardiovascular risk. Regarding the potential effectiveness of vaping for smoking cessation, the complete switch to e-cig, when persistent, did help tobacco quitters to remain abstinent from smoking, but the combined e-cig use 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, rising important issues for the classification of these subjects, and suggesting that more 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.

Author Contributions

Conceptualization, M.E.F. and L.M.; methodology, M.E.F., M.Fi., C.A.M., M.Fe., M.R.G., G.L., F.B., and L.M.; software, C.A.M., F.B., and L.M.; validation, C.M., M.Fe., and G.L.; formal analysis, M.E.F., C.A.M., and L.M.; investigation, M.Fi., F.B., C.M., and M.R.G.; resources, M.E.F., M.Fi., M.Fe., C.M., G.M.P., and L.M.; data curation, L.M.; writing-original draft preparation, M.E.F. and L.M.; visualization, G.M.P.; writing-review and editing, M.Fi., M.Fe., G.L.; supervision, M.Fe., and G.L.; project administration, L.M., and M.R.G.; funding acquisition, L.M. and G.M.P.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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