

Online only supplementary material

Outcome variables and analysis

All variables were self-reported, with the exception of tobacco smoking cessation, that was tested using portable CO analyzers in a sub-sample of quitters and non-relapsing e-cigarette users, and adverse events, that were checked in the subjects from the Abruzzo Region through data linkage with hospital discharge abstracts (Italian SDO) [1]. The following diseases occurred during the 24-month follow-up were considered as "possibly related adverse events": Chronic obstructive pulmonary disease (COPD - ICD-9-CM codes in any diagnosis field 490, 490.0, 491.1, 491.2, 491.21, 491.8, 491.9, 492.0, 492.8, 494, 494.0, 494.1, 496, 493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92), Myocardial infarction and/or angina (410.0-410.9), Congestive heart failure (428.0-428.9), Transitory cerebrovascular ischemia or stroke (435.0-435.9 or 433.0-434.9), any cancer (140-208.9). Additional possibly related serious adverse events were directly requested to the participants, with a special attention on mouth irritation.

The self-rated health status was measured through a specific item of the Italian version of the validated EuroQol EQ-D5L questionnaire [2] "How would you rate your current overall health status on a scale from 1 (worst imaginable) to 10 (best imaginable)?"

The outcomes that might have been influenced by a switch in product use during the follow-up (i.e. a smoker of tobacco cigarettes only switching to e-cigarettes only) were reported twice: by product use at baseline and by both product use at baseline and at 24 months, thus creating nine or twelve categories (according to whether the quitters of all products - tobacco and e-cigarettes - were to be included or not):

1. Baseline users of e-cigarettes only who quit e-cigarettes and did not re-start tobacco smoking (at 24 months);
2. Baseline users of e-cigarettes only who continued to use e-cigarettes only;
3. Baseline users of e-cigarettes only who continued to use e-cigarettes and also relapsed to tobacco smoking;
4. Baseline users of e-cigarettes only who ceased e-cigarette use and relapsed to tobacco smoking;
5. Baseline smokers of tobacco cigarettes only who quit tobacco smoking and did not start e-cigarette use;
6. Baseline smokers of tobacco cigarettes only who quit tobacco smoking and started e-cigarette use;
7. Baseline smokers of tobacco cigarettes only who continued to smoke tobacco cigarettes only;
8. Baseline smokers of tobacco cigarettes only who continued to smoke tobacco cigarettes and also started e-cigarette use;
9. Baseline smokers of tobacco and also users of e-cigarettes (dual users) who quit both tobacco smoking and e-cigarette use;
10. Baseline dual users who quit tobacco smoking and continued to use e-cigarettes only;
11. Baseline dual users who quit e-cigarette use and continued to smoke tobacco cigarettes only;
12. Baseline dual users who continued to smoke tobacco and also use e-cigarettes.

Secondary findings

Co levels to check tobacco cigarette abstinence

Of the 58 subjects who declared tobacco smoking cessation from 12 to 24 months, 29 underwent a test to detect exhaled CO levels, with CO levels suggestive of tobacco smoking (>10 ppm) [3] only for one subject, who was accordingly re-classified.

Multivariate analyses - other predictors

At multivariate analyses, the only other significant predictors of tobacco smoking abstinence or either product (both tobacco and electronic cigarettes) abstinence were years of previous tobacco smoking (ORs 0.98 and 0.96, respectively, with both $p < 0.01$), BMI (for tobacco cessation only; OR 1.07 and $p = 0.002$ for each BMI unit increase), educational level (for either product abstinence only; OR 1.30 and $p = 0.047$ for one

category increase), and the amount of tobacco cigarettes smoked per day (for either product abstinence only; OR 0.46 and $p=0.002$ for the highest tertile vs the lowest tertile). An older age (ORs 1.51; $p<0.001$) and either product abstinence during follow-up (OR 2.48; $p=0.023$) were significantly associated with a higher likelihood of reporting a potentially-related serious adverse event. Only the daily number of tobacco cigarettes at baseline was significantly, inversely associated with their reduction during follow-up (regression coefficient -0.59; $p<0.001$). Finally, older age (regression coefficient -0.07 for 1-year increase; $p=0.035$), diabetes (-0.57; $p=0.020$) and a lower EuroQol score at baseline (-0.64; $p<0.001$) were significantly associated with a decrease in EuroQol score during the 24 months of follow-up.

References

- [1] Manzoli L, La Vecchia C, Flacco ME, *et al.* Multicentric cohort study on the long-term efficacy and safety of electronic cigarettes: study design and methodology. *BMC Public Health* 2013;**13**:883.
- [2] EuroQol Group. European Quality of Life Questionnaire. 2013.
- [3] Vansickel AR, Cobb CO, Weaver MF, *et al.* A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010;**19**(8):1945-1953.

Table S1. Baseline characteristics of the subjects completing the 24-month follow-up.

Variables	<i>Cigarette use at baseline</i>				p^A	p^B	p^C
	E-cigarettes only (<i>n</i> =229)	Tobacco cigarettes only (<i>n</i> =480)	Dual use (<i>n</i> =223)	Overall (<i>N</i> =932)			
Mean age in years (SD)	45.3 (10.7)	44.0 (11.8)	44.3 (12.0)	44.4 (11.6)	0.3	0.9	0.4
Male gender, %	62.9	48.8	65.5	56.2	<0.001	<0.001	0.7
Mean BMI (SD)	24.8 (3.9)	24.3 (4.0)	24.9 (4.0)	24.6 (3.9)	0.3	0.15	0.8
Married, %	61.1	54.0	56.1	56.2	0.14	0.8	0.3
Employed, %	80.4	79.8	74.4	78.7	0.9	0.16	0.2
<i>Educational level, %</i>							
- Elementary / Middle	21.0	21.7	22.0	21.6	0.8	0.8	0.8
- High school	55.0	42.3	47.1	46.6	0.002	0.2	0.09
- Bachelor or higher	24.0	36.0	30.9	31.9	0.001	0.19	0.10
<i>Physical activity</i>							
- At work, %	19.2	19.6	16.1	18.7	0.9	0.2	0.3
- Weekly hours at work, mean (SD)	23.8 (18.4)	26.7 (16.6)	22.9 (19.0)	25.3 (17.5)	0.4	0.3	0.9
- At home, %	47.6	48.3	51.6	48.9	0.8	0.4	0.4
- Weekly hours at home, mean (SD)	5.3 (4.7)	5.2 (5.6)	5.3 (4.6)	5.3 (5.1)	0.9	0.9	0.9
<i>Alcohol use</i>							
Regular alcohol intake, %	20.1	29.0	27.4	26.4	0.007	0.5	0.06
Mean alcohol units daily (SD)	2.2 (1.2)	2.1 (1.6)	2.1 (1.0)	2.1 (1.4)	0.8	0.9	0.8
<i>Cardiovascular risk and health</i>							
- Hypertension, %	13.5	11.5	10.3	11.7	0.5	0.5	0.2
- Diabetes, %	4.4	3.1	4.0	3.7	0.5	0.5	0.9
- Hypercholesterolemia, %	8.3	8.8	10.3	9.0	0.7	0.5	0.4
- Self-reported health, mean (SD) [€]	8.0 (1.3)	7.8 (1.3)	7.7 (1.2)	7.8 (1.3)	0.06	0.6	0.032
- Low (<6) self-reported health [€] , %	4.8	5.4	3.1	4.7	0.7	0.17	0.4
<i>All products use pattern, mean (SD)</i>							
- Years of tobacco smoking	21.4 (10.3) [‡]	22.2 (12.2)	25.2 (12.9)	22.7 (12.1)	0.29	0.004	<0.001
- N. tobacco cigarettes daily	--	14.1 (8.1)	15.1 (9.9)	14.4 (8.7)	--	0.2	--
- Months of e-cigarettes use	8.8 (5.2)	--	8.3 (4.4)	8.6 (4.7)	--	--	0.5
- N. e-cigarette daily puffs	162 (280)	--	96 (148)	130 (227)	--	--	0.004
- EC nicotine dose in mg	8.8 (5.2)	--	11.0 (5.6)	9.9 (5.5)	--	--	<0.001
<i>E-cigarettes by nicotine dose, %</i>							
- No nicotine	12.8	--	5.8	9.4	--	--	0.012
- 3 to 8 mg	23.3	--	18.0	20.7	--	--	0.17
- 9 mg	40.2	--	34.5	37.4	--	--	0.22
- 10 to 24 mg	23.7	--	42.2	32.5	--	--	<0.001
- Former tobacco smoking, %	100.0	100.0	100.0	100.0	--	--	--
- Use of other tobacco products ^ψ , %	0.8	0.4	0.9	0.6	0.16	0.6	0.7
- Use of other nicotine products ^Ω , %	0.4	0.0	0.0	0.1	0.15	--	0.3
<i>Reasons of e-cigarette use ^φ</i>							
- Stop tobacco smoking, %	74.2	--	45.7	60.0	--	--	<0.001
- Reduce tobacco smoking, %	17.0	--	56.5	36.5	--	--	<0.001
- Indoor smoking, %	16.2	--	11.7	13.9	--	--	0.2

[€] EuroQol final question, ranging from 1 (feel very bad) to 10 (perfectly healthy). This item had 30 missing values.

^ψ Cigars or tobacco chewing. ^Ω Nicotine patch or gums. ^φ More than one answer allowed. [‡] Years of former tobacco smoking for e-cigarette only users.

P for the comparison: ^A Tobacco only vs electronic cigarettes only; ^B Tobacco only vs dual use; ^C E-cigarettes only vs dual use.

Table S2. Characteristics of the 38 subjects experiencing a possibly-related serious adverse event during the 24-month follow-up.

Age ^A	Sex ^A	BMI ^A	EuroQoL ^A	Baseline - 24 months cigarette use ^B	Baseline number of tobacco cigarettes	Quit all cigarettes ^C	PR-sAE
74	M	23.2	6	E-cig-E-cig	0	No	Cancer, others ^D
56	M	22.2	10	E-cig-E-cig	0	No	Cancer, others
43	F	22.1	7	E-cig-Tobacco	0	No	Cancer, others
72	F	19.5	8	E-cig-Tobacco	0	No	Cancer, others
36	M	21.9	9	E-cig-Tobacco	0	No	Cancer, others
68	F	27.3	6	E-cig-Quit	0	Yes	Cancer, others
75	M	24.6	8	Dual-Tobacco	20	No	Cancer, others
47	F	24.8	8	Dual-Tobacco	5	No	Cancer, others
62	F	28.7	9	Dual-Tobacco	20	No	Cancer, others
43	F	22.1	8	Tobacco-E-cig	15	No	Cancer, others
45	F	23.9	5	Tobacco-Tobacco	15	No	Cancer, others
60	F	22.0	7	Tobacco-Tobacco	10	No	Cancer, others
56	F	25.0	10	Tobacco-Tobacco	12	No	Lung cancer
62	M	27.7	7	Tobacco-Quit	5	Yes	Blood cancer
35	F	22.3	8	E-cig-Tobacco	0	No	COPD
61	M	21.7	5	Dual-Tobacco	20	No	COPD
43	F	23.9	8	Dual-Tobacco	20	No	COPD
62	F	23.5	6.5	Dual-Quit	15	Yes	COPD
54	F	26.6	7	Tobacco-Tobacco	20	No	COPD
42	F	20.2	8	Tobacco-Quit	15	Yes	COPD
37	F	18.3	8	Tobacco-Quit	20	Yes	COPD
53	M	22.9	7	E-cig-Quit	0	Yes	Myocardial infarction
39	M	31.1	7	Dual-E-cig	10	No	Myocardial infarction
63	M	29.0	6	Dual-Quit	50	Yes	Myocardial infarction
69	M	24.2	8	Tobacco-Tobacco	8	No	Myocardial infarction
59	M	26.9	7	Tobacco-Tobacco	15	No	Myocardial infarction
47	F	40.9	5	Dual-E-cig	10	No	Pneumonia
74	F	29.1	8	Dual-Tobacco	20	No	Pneumonia
32	M	24.6	8	Dual-Tobacco	25	No	Pneumonia
57	M	25.3	9	Tobacco-Quit	15	Yes	Pneumonia
52	M	27.2	9	E-cig-Tobacco	0	No	Heart failure
67	F	26.2	7	Dual-E-cig	15	No	Heart failure
71	M	23.9	7	Dual-Tobacco	30	No	Heart failure
53	M	22.5	7	E-cig-Dual	0	No	Stroke
53	M	24.9	8	Tobacco-Tobacco	25	No	Stroke
60	M	27.4	8	Tobacco-Quit	15	Yes	Stroke
58	M	23.7	9	Dual-Quit	10	Yes	Angina
56	F	25.8	8	Tobacco-Tobacco	15	No	Angina

^A At baseline. ^B Product use at baseline and at 24-month follow-up (e.g. Ecig-Dual = use of e-cigarettes only at baseline, use of both electronic and tobacco cigarettes at 24 months). ^C Abstinence/cessation of all products (both tobacco and electronic cigarettes) at 24-month follow-up. ^D All other cancers excluding cancer of the larynx, lung, esophagus, pancreas, cervix, kidney, bladder, and hematological. PR-sAE = Possibly-related serious adverse event. EuroQoL = EuroQoL final question, ranging from 1 (feel very bad) to 10 (perfectly healthy). COPD = Chronic obstructive pulmonary disease.

Figure S1. Tobacco and/or e-cigarette use throughout the follow-up of the 38 subjects experiencing a possibly-related serious adverse event (sAE) at 24 months. E = E-cigarette use only; T = Tobacco cigarette smoking only; D = Dual use. Each box represents a participant. The boxes of those who quit either product (tobacco and/or electronic cigarettes) have been left empty; the boxes of the subjects experiencing a sAE have been marked in black.

