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DETERMINANTS OF SMOKING CESSATION AND INITIATION IN ITALY, WITH FOCUS ON RESPIRATORY SYMPTOMS AND USE OF ELECTRONIC CIGARETTE

S.S.D. MED01/Statistica Medica

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To Vincenzo,

who has allowed me to study when necessary and taught me

to overcome obstacles with optimism.

To Benedetta and Barbara,

to remind you that it is never too late to reach your goals,

revive your dreams and reinvent yourself.

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Introduction

Tobacco smoking is the principal risk factor for premature mortality all over the world, causing more than 6.4 million deaths yearly (Global Burden of Disease, 2015). It represents the main risk factor for respiratory diseases (Shinohara et al., 2012), being responsible for up to 80-90% of COPD cases (Liu et al., 2015). Moreover, second hand tobacco smoke exposure is an alarming and important environmental factor for allergic diseases; even its prenatal exposure has been detected as risk factor for asthma, respiratory infection and eczema in offspring (Accordini et al., 2018, Thacher et al., 2014, Shinohara et al., 2012).

The tobacco smoking prevalence has been decreasing in almost all over the world for the last decade, except for the WHO African and East Mediterranean regions, where the trends do not change (Fig. 1, taken by WHO report, 2018). Average rate of current smoking among adults have declined globally from 26.9% in 2000 to 20.2% in 2015. In European countries smoking prevalence ranged from 37.3% in 2000 to 29.9% in 2015 among people aged more ≥ 15 years; WHO report (2018) foresees that in Europe the prevalence will decrease to 26.3% in 2025, even though the target is 22.4% (WHO report 2018 and 2017).

The implementation of tobacco control policies in many countries, ranging from graphic pack warnings and advertising bans to no smoking areas represented the most relevant reason for decreasing smoking prevalence. The 63% of the world's population was estimated to have taken advantages of at least one comprehensive tobacco control measure (Who report 2017).

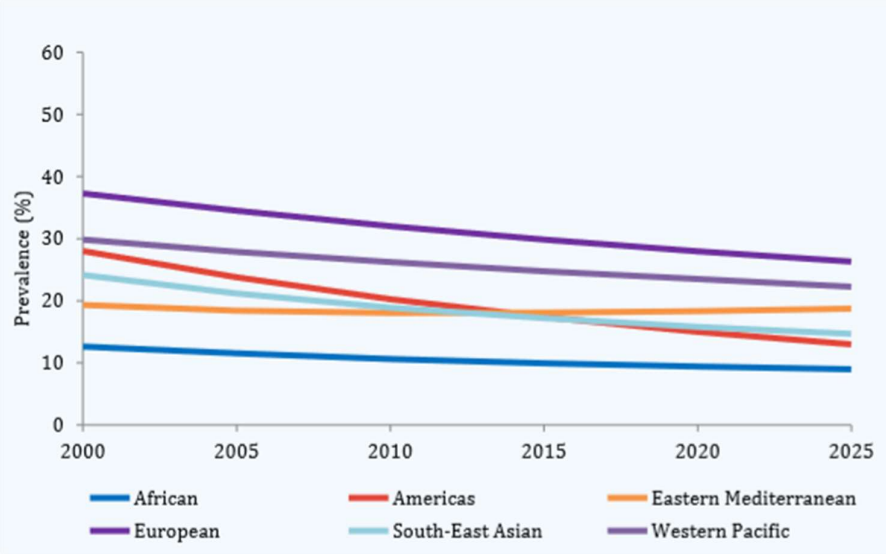


Figure 1. Age-standardized fitted and projected rates of prevalence of tobacco smoking among people aged ≥ 15 years, both sexes, by WHO region, 2000–2025 (taken by WHO report, 2018).

Unfortunately, the global decreasing of smoking rate does not correspond to a smaller number of smoking people and the reason is the population growth [Who report 2017]. In 2007, there were 1.1 billion smokers in the world and this number did not change by 2015. Furthermore, the prevalence of smoking depends not only on the rates of smoking cessation but also on the rates of smoking initiation. In order to implement effective public health policies reducing smoking prevalence, it is necessary to understand trends and to analyze thoroughly the determinants of smoking cessation and initiation in the population.

Smoking cessation has been extensively studied and described as a complex phenomenon involving several psychological (Castro 2014), social (Kong 2012; Jackson 2015) and health care factors (Filippidis 2014). Literature data agreed that number of cigarettes smoked daily, age at smoking initiation [Masaoka 2017] and smoking duration [Yang 2015; Masaoka 2017] were inversely related to smoking cessation (Bush 2012);

whereas, health status is still debated. Health concerns were the main motivation to stop smoking (Gallus 2013), including worries for fetal health in pregnant women (Smedberg 2014); furthermore, subjects with COPD were more willing to receive aids to stop smoking than controls (Melzer 2016; Hilberink 2006), even if they would not reach their purpose. On the contrary, an American survey on quitline users found that healthy smokers were more likely to stop than smokers with chronic diseases, including asthma and COPD (Bush 2012).

As for smoking cessation, psychological and social factors (friends, parents, siblings, movies) had been amply described as determinants of smoking initiation [Lee et al., 2018, Muttarak et al., 2013]. A European study conducted in 2010 showed that friends were the principal factor influencing smoking initiation, especially among younger women, and that most of participants began smoking in adolescence [Oh et al., 2010]. The influence of peers was also reported in Italy [Muttarak et al., 2013] and in a larger European study (Filippidis et al., 2015). An alarming rate of smoking initiation had been found in early adolescence in three European studies (Marcon et al., 2018; Nuyts et al., 2018; Filippidis et al., 2015).

While factors affecting smoking initiation among adolescents had been extensively studied [Muttarak 2013; Filippidis 2015; Nuyts 2018], data on smoking re-initiation among adults trying to stop smoking were sparse [Samin 2018, Wetter et al., 2004].

Smoke-free policies must pay attention to the devices marketed by the manufacturing companies to help people quit smoking, as Electronic Nicotine Delivery Systems (ENDS) and Electronic Non-Nicotine Delivery Systems (ENNDS), which

include electronic cigarettes (e-cigarettes) [ENDS/ ENNDS. Geneva: Conference of the Parties to the WHO Framework Convention on Tobacco Control; 2016].

Electronic cigarettes (e-cigarettes) use has been spreading around the world rapidly [Ayers et al. 2011; Siegel et al. 2011; Pippard et al., 2017]. Indeed, the idea that e-cigarette was safer than tobacco smoking was very common in the population, conditioned by manufacturers' advertisements.

The scientific community debated about e-cigarette use. The Royal College of Physicians stated that e-cigarette represents a "viable harm-reduction option" with respect to tobacco smoking and that "the hazard to health arising from long-term vapour inhalation from the e-cigarettes available today is unlikely to exceed 5% of the harm from smoking tobacco" [Royal College of Physicians, 2016]. Accordingly, a simulation study predicted that, if common cigarettes were replaced by e-cigarettes over the next ten years, between 1.6 and 6.6 million premature deaths would be avoided in the United States in the current century [Levy 2018].

On the contrary, although it was acknowledged that potentially toxic chemicals were fewer and less concentrated in e-cigarette aerosol as compared to conventional cigarettes, the European Respiratory Society (ERS) stated that "there is no evidence that e-cigarettes are safer than tobacco in the long-term" [Bals et al., 2018]. Moreover, according to the same ERS report "there is not enough evidence to support that e-cigarettes are an aid to smoking cessation" and "there is conflicting data that use of e-cigarettes results in a renormalisation of smoking behaviour or for the gateway hypothesis" [Bals R. et al., 2018]. Other studies supported the notion that e-cigarettes could not be considered harmless, despite being less noxious than conventional tobacco

cigarettes, [Pisinger et Dossing, 2014], because they also contained several unstudied and unregulated compounds [Vardavas et al., 2017].

Moreover, while trends in tobacco smoking have been extensively studied, literature data on use of e-cigarettes are sparse. In the Eurobarometer survey, performed on the European Union population in 2012, only 7.2% of people aged 15 years or older reported to have ever used e-cigarette; however, ever use was higher among students and people younger than 35 years [Ooms 2016]. Accordingly, a cross-sectional study on the Italian general population [Gallus et al., 2014] reported that the use of the electronic cigarette decreased with advancing age, being the highest among people aged 15-24 years: 94.8% of interviewed in this age range had heard about e-cigarette, 9.2% of them had tried it and 2.4% were regular users. During the 2015, e-cigarettes were the most commonly used tobacco product among middle (5.3%) and high (16.0%) school students in the United States [Singh 2016].

From a public health perspective, the major question dealing with e-cigarette is its relation with tobacco smoking: does e-cig decrease smoking consumption and promote smoking cessation, or does it represent a gateway to nicotine addiction and consequently to tobacco smoking initiation? Early studies among tobacco smokers suggested that e-cigarettes could be a useful tool both to decrease smoking consumption [Polosa 2011] and to increase smoking cessation [Bullen 2013; Biener 2015], while later studies questioned the role in promoting sustained smoking abstinence [Manzoli 2017; Pasquereau 2017]. A Cochrane Review, updated in 2016, concluded that nicotine e-cigarettes helped smokers stop smoking in the long term compared with placebo e-cigarettes, but the evidence was rated low under the GRADE system [Hartmann-Boyce 2016]. An opposite conclusion was achieved by a meta-analysis of 38 studies focused on e-cigarettes and smoking cessation in real-world and clinical settings: the odds of quitting

traditional cigarettes were 28% lower in those who used e-cigarette compared with those who did not [Kalkhoran et al., 2016].

On the other hand, it is widely accepted that e-cigarettes could be useful in decreasing smoking consumption. In a French longitudinal study dual users, i.e. tobacco plus e-cigarette users, were more likely to have halved cigarette consumption after a 6-month follow-up than exclusive tobacco smokers (25.9% vs 11.2%), but not to have stopped smoking (12.5% vs 9.5%) [Pasquereau 2017]. Similar results were obtained in an Italian study, where the mean daily number of tobacco cigarettes decreased by 1.6 among subjects remaining tobacco smokers and by 6.5 among subjects remaining dual users, while 24-months abstinence was 23.1% in people consuming only tobacco cigarettes vs 26.0% in dual users [Manzoli 2017].

Among adolescents e-cigarettes seem to be a gateway to tobacco smoking. A recent meta-analysis on people aged 14-30 years found that the risk of tobacco smoking was 3-4 times higher in e-cigarettes ever users than in never users [Soneji et al 2017]. In an American cohort study on non-daily cigarette smokers aged 18—24 years, e-cigarette use was associated with an increase in cigarette quantity after 12 months [Doran et al 2017]. E-cigarettes seem to play a similar role in tobacco smoking initiation also in adults. Indeed, in an Italian longitudinal study on people aged 30-75 years, the risk to have switched to tobacco smoking after 2 years was twofold higher than the probability to have quitted whatever type of smoking (38.9% vs 18.8%) among exclusive e-cigarette users [Manzoli 2017]. Conversely, only 26% of dual users quitted tobacco smoking while 57.4% started smoking only tobacco.

The increase in e-cigarette use, particularly among teenagers and young adults [Ooms 2016; Gallus 2014; Singh 2016], as well as the limited evidences regarding their

safety profile [Pisinger 2014], highlights the urgent need of reinforcing education and awareness on e-cigarettes use, starting from school and university educational programs. In this respect, the smoking attitudes and behaviours of nursing students are particularly important, as nurses can play a central role in promoting healthy habits and counselling their patients about smoking cessation [Rice et al., 2017]. However, little is known on e-cigarette use among nursing students in Europe. In 2013 among French military nursing students, the prevalence of e-cigarette regular use was 25%, while up to 36% of students had tried e-cigarette at least once [Guillet et al., 2015]. Moreover, studies on medical/health professional students found a large variability in e-cigarette current use, the proportion of current vapers ranging from 1.6% [Zhou et al., 2015] to 20.6% [Franks et al., 2017]. Up to now, there are no data on e-cigarettes use among Italian nursing students.

My PhD research focused on the determinants of smoking cessation and initiation in Italy. Firstly, I estimated the cumulative incidence of smoking cessation and re-initiation in Italian population-based cohorts and evaluated the determinants of smoking cessation and re-initiation, focusing on respiratory disorders and smoking characteristics at baseline. Finally, I investigated the diffusion of e-cigarette among nursing students in North-Eastern Italy and explored its use as determinant of smoking cessation and initiation.

First topic

"Cumulative incidence and determinants of smoking cessation and re-initiation in Italy"

Methods

Study design

Smoking cessation and re-initiation were investigated in three population-based cohorts, recruited in Italy between 1998 - 2000. The enrollment and follow-up of the three cohorts have been previously described [Verlato et al., 2016]. Briefly, two cohorts had been enrolled in the frame of the Italian Study on Asthma in Young Adults (ISAYA) in Verona (Northern Italy) and Sassari (Mediterranean island of Sardinia) [Verlato et al., 2006], while the third cohort had been recruited in Verona in the frame of the Italian Study on the Incidence of Asthma (ISIA) [Verlato et al., 2003].

By the end of baseline period, the three cohorts comprised 5933 subjects overall, who had answered a screening questionnaire on socio-demographic characteristics, respiratory disorders, smoking habits and socio-economic burden [de Marco 1999]. The Verona and Sassari-ISAYA cohorts comprised respectively 2166 and 2055 subjects aged 20-46 years, while the Verona-ISIA cohort was slightly older, comprising 1712 subjects aged 28-54 years.

The three cohorts were recontacted in 2007-2009 after a follow-up of 9.1 ± 0.8 years (mean ± SD) in the frame of the Gene-Environment Interactions in Respiratory Diseases (GEIRD) [GEIRD 2010], whose protocol is available at www.geird.org. Subjects were administered by mail the GEIRD screening questionnaire [GEIRD 2010],

containing the same questions on respiratory disorders and smoking habits used at baseline. Non-responders were contacted again, first by mail then by phone.

Assessment of smoking habits

Subjects were classified as:

1) current smokers, if they reported to have smoked at least one cigarette per day or one cigar a week for as long as one year, and also in the last month;

2) ex-smokers if they had smoked the same minimum amount previously reported, but had stopped smoking for at least one month before the interview;

3) never smokers otherwise.

To investigate smoking cessation and its determinants, the study focused on current smokers at baseline, who were re-evaluated at follow-up to determine whether they were persistent smokers or had quit smoking for at least one month before the interview. Instead, to investigate smoking re-initiation and its determinants, the study focused on ex-smokers at baseline, who were re-evaluated at follow-up to determine whether they were persistently abstinent from smoke or had relapse smoking.

Baseline smoking intensity was assessed as the number of cigarettes smoked daily. Cumulative smoke exposure in pack-years was computed as years of smoking (difference between age at interview and age at start smoking) multiplied by the average daily consumption of 20-cigarette packs. Furthermore, two more variables, age at smoking initiation and years of smoking abstinence until baseline, were analyzed as determinants of smoking cessation and re-initiation respectively.

Self-reported smoking status had been validated in the ECRHS survey performed in Verona in 1991–93, where a good agreement (Cohen's $\kappa = 0.93$) had been found between self-reported smoking and serum cotinine levels [Olivieri 2002].

Assessment of respiratory disorders

Current asthma was assumed when a subject affirmatively answered to the question "Have you had one asthma attack in the last 12 months" or/and "Are you currently taking any medicine for asthma?" Allergic rhinitis was defined by a positive answer to the question 'Do you have any nasal allergies including hay fever?' and chronic bronchitis by a positive answer to the question "Have you had cough and phlegm on most days for a minimum of three months a year and for at least two successive years?'.

Statistical analyses

Significances of differences in response to follow-up questionnaire or in status of smoking habits were evaluated by Fisher's exact test or chi-squared test for nominal variables, chi-square for trend for ordinal variables, and Wilcoxon-Mann-Whitney test for skewed distributed continuous variables.

The 95% confidence interval of cumulative incidence was computed by the binomial exact method.

Potential determinants of smoking cessation and re-initiation were further evaluated in multivariable analysis, accomplished by logistic regression models, where smoking cessation or re-initiation were the response variables. If smoking cessation was the response variable, centre, gender, age class (20–31.3, 31.3-42.6, 40-53.9 years old), asthma (or allergic rhinitis or chronic bronchitis), cigarettes smoked daily (1-5, 6-10, 11-

15, 16-40) and age of smoking initiation (8-15, 16-17, 18-19, >=20 years) were the explanatory variables. If smoking re-initiation was the response variable, centre, gender, age class (20–31.3, 31.3-42.6, 40-53.9 years old), asthma (or allergic rhinitis or chronic bronchitis), cigarettes smoked daily (1-5, 6-10, 11-15, 16-40) and years of smoking abstinence until baseline (<3, 3-7.4, 7.5-13.4, >13.5 years) were the explanatory variables. Respiratory disorders were separately introduced into different models, since they were strongly collinear [Compalati 2010], as well as the number of smoked pack-years, since it was collinear with age of smoking initiation. Standard errors were adjusted for intra-cohort correlation. Goodness of fit of logistic models was tested by the Hosmer-Lemeshow test [Hosmer 2013]. The analyses were performed in Stata 14 (Statacorp, Texas) and statistical significance was set at $p<0.05$.

Results

Response to follow-up

Of the initial cohort of 5933 subjects, 3597 (60.6%) answered the follow-up questionnaire in 2007-2009 after an average follow-up of 9.1 ± 0.8 years (mean ± SD). Response was significantly affected by type of cohort and smoking habits. A different mix of responses was observed among the three cohorts: Verona cohorts achieved a higher response percentage (1325/1712 = 77.4% and 1459/2166=67.4% respectively for Verona-ISIA and Verona-ISAYA) than the Sassari cohort (813/2055 = 39.6%). Moreover, response percentage was the highest among ex-smokers (761/1166 = 65.3%), intermediate among never smokers (1808/2877 = 62.8%) and the lowest among current smokers (1027/1874 = 54.8%).

Changes in smoking habits

Smoking habits at follow-up were not reported by 114 subjects, in detail by 26 never smokers, 26 ex-smokers and 62 current smokers. The analysis on determinants of smoking cessation and re-initiation focused on responders to smoking habit's follow up item, respectively on 965 and 735 subjects that were current smokers and ex-smokers at baseline (Fig. 2).

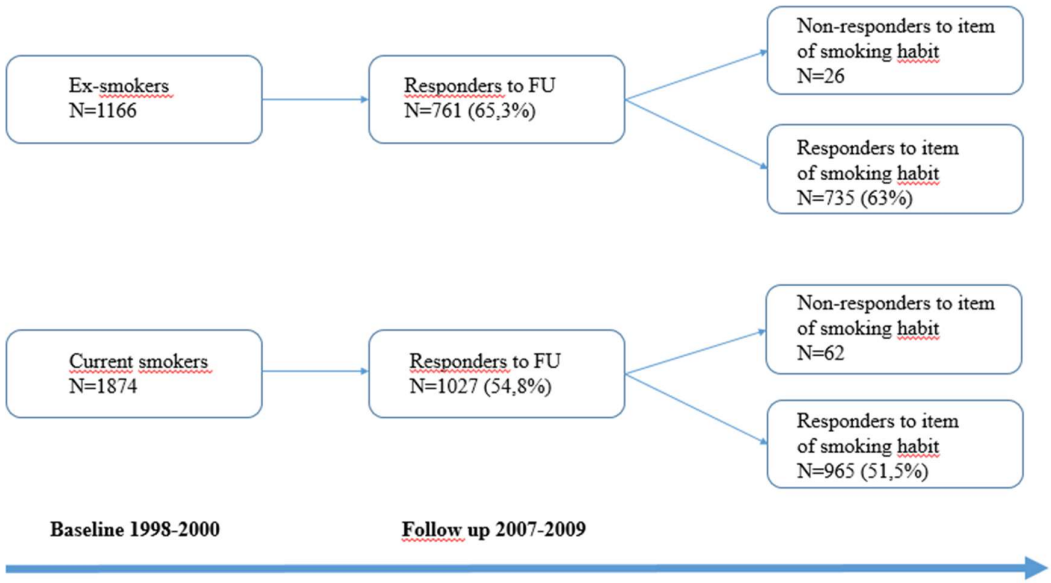


Fig.2. Number of subjects responding to FU. Non-responders to item of smoking habits were excluded from the analysis.

During the follow-up, smoking cessation largely exceeded smoking initiation. Indeed 312 subjects out of 965 current smokers at baseline (32.3%, 95% CI 29.4-35.4%) had stopped smoking at follow-up examination, while 18 subjects out of 1782 never smokers (1.0%) had started smoking, and 86 out of 735 ex-smokers (11.7%) had resumed smoking. In addition, 2 subjects had started and stopped smoking during follow-up.

Possible selection bias in participation to the follow-up

Selection bias, possibly arising from low response rate, was evaluated by comparing baseline characteristics of subjects participating and not participating in the follow-up. As shown in Table 1, response to follow-up was higher in the Verona cohorts and in women, and increased with increasing age both in baseline current smokers and ex-smokers. As regards occupation, participation was the highest among clerks, workmen and housewives, and the lowest among unemployed. Smokers with chronic bronchitis were less likely to participate in the follow-up, while nasal allergies and asthma did not influence participation. Compared to responders to follow-up, non-responders smoked more cigarette per day at baseline among current smokers, and had been abstaining from smoking for a lower period among ex-smokers.

Table 1. Characteristics of responders and non-responders to the follow-up, among current smokers and ex-smokers at baseline. Non-responders comprised people who either did not return the whole questionnaire or did not answer the question on smoking habits (item non-responders). Categorical variables are presented as absolute values with percent values in parentheses, while continuous variables are presented as median (25^{th} percentile – 75^{th} percentile) (see next page).

	Baseline smokers			Baseline ex-smokers		
	Responders 965 (51.5%)	**Non responders 909 (48.5%)**	**p-value**	**Responders 735 (63%)**	**Non responders 431 (37%)**	**p-value**
Centre			**<0.001**			**<0.001**
Verona ISIA	305 (66.3)	155 (33.7)		323 (77.8)	92 (22.2)	
Verona ISAYA	412 (59.2)	284 (40.8)		276 (64.6)	151 (35.4)	
Sassari ISAYA	248 (34.5)	470 (65.5)		136 (42.0)	188 (58.0)	
Sex			**<0.001**			0.058
Men	519 (48.1)	561 (51.9)		379 (60.5)	247 (39.5)	
Women	446 (56.2)	348 (43.8)		356 (65.9)	184 (34.1)	
Age class (years)			**<0.001**			**<0.001**
[20 – 31.3]	313 (47.9)	340 (52.1)		122 (49.4)	125 (50.6)	
[31.3 – 42.6]	374 (50.1)	373 (49.9)		390 (63.6)	223 (36.4)	
[42.6 – 53.9]	278 (58.6)	196 (41.4)		222 (72.8)	83 (27.2)	
Occupation			**<0.001**			**<0.001**
Businessman	142 (50.5)	139 (49.5)		116 (60.4)	76 (39.6)	
Clerk	324 (56.2)	253 (43.8)		255 (65.1)	137 (34.9)	
Workman	187 (52.4)	170 (47.6)		141 (71.6)	56 (28.4)	
Unemployed	48 (33.6)	95 (66.4)		17 (34)	33 (66)	
Housewife	88 (55.3)	71 (44.7)		90 (67.7)	43 (32.3)	
Student	82 (48.0)	89 (52.0)		21 (42.9)	28 (57.1)	
Others	89 (50.3)	88 (49.7)		93 (62.4)	56 (37.6)	
Nasal allergies			0.625			0.884
No	790 (51.8)	734 (48.2)		563 (62.7)	335 (37.3)	
Yes	163 (50.3)	161 (49.7)		162 (63.3)	94 (36.7)	
Asthma			0.092			0.236
No	923 (51.8)	858 (48.2)		668 (62.3)	405 (37.7)	
Yes	35 (42.2)	48 (57.8)		57 (69.5)	25 (30.5)	
Chronic bronchitis			**0.033**			0.182
No	772 (52.8)	690 (47.2)		634 (63.5)	364 (36.5)	
Yes	178 (46.6)	204 (53.4)		82 (57.7)	60 (42.3)	
Cigarette smoked daily	10 (7-20)	15 (10-20)	**<0.001**	10 (6-20)	10 (6-20)	0.557
Age at smoking initiation	17 (15-19)	17 (15-18)	0.380	----	----	----
Pack-years	9.0 (4.1-18.1)	9.4 (4.5-17.0)	0.737	12.6 (6.3-21)	15.1 (5.1-27.7)	0.872
Abstinence years	-----	-----	-----	8.4 (3.1-13.9)	6.5 (2.3-11.3)	**0.002**

p-value were computed by Fisher's exact test or chi-squared test for nominal variables, chi-square for trend for age, and Wilcoxon-Mann-Whitney for continuous variables.

Determinants of smoking cessation

Cumulative incidence of smoking cessation decreased with advancing age (Table 2). Accordingly, quitting smoking more frequently occurred in the younger ISAYA cohorts than in the older ISIA cohort. Smokers' occupation markedly influenced smoking cessation, whose cumulative incidence ranged from 20-25% among housewives and others to nearly 50% among students. People suffering from asthma were more likely to stop smoking, while allergic rhinitis and chronic cough/phlegm did not significantly affect smoking cessation. As regards baseline smoking habits, cumulative incidence of smoking cessation significantly increased as the number of cigarettes smoked daily and pack-years decreased.

Table 2. Cumulative incidence of smoking cessation as a function of socio-demographic characteristics, respiratory symptoms and baseline smoking habits, in a sample of 965 baseline current-smokers.

	Current smokers at baseline	Absolute (per cent) frequency	*p*-value
Centre			**0.008**
Verona-ISIA	305	78 (25.6)	
Verona-ISAYA	412	**149 (36.2)**	
Sassari-ISAYA	248	**85 (34.3)**	
Sex			0.129
Male	519	179 (34.5)	
Female	446	133 (29.8)	
Age class (years)			**<0.001**
[20 – 31.3]	361	**144 (39.9)**	
[31.3 – 42.6]	412	118 (28.6)	
[42.6 – 53.9]	192	50 (26.0)	
Occupation			**0.009**
Businessman	142	46 (32.4)	
Clerk	324	107 (33.0)	
Workman	187	64 (34.2)	
Unemployed	48	15 (31.2)	
Housewife	88	22 (25)	
Student	82	**39 (47.6)**	
Retired and others	89	18 (20.2)	
Allergic rhinitis			0.097
No	790	245 (31.0)	
Yes	163	62 (38.0)	
Asthma			**0.043**
No	923	293 (31.7)	
Yes	**35**	**17 (48.6)**	
Chronic bronchitis			0.510
No	772	254 (32.9)	
Yes	178	54 (30.3)	
Cigarettes smoked daily			**<0.001**
1-5	**195**	**71 (36.4)**	
6-10	**295**	**114 (38.6)**	
11-15	182	48 (26.4)	
16-40	263	56 (21.3)	
Age of smoking initiation			0.860
8-15	252	73 (29.0)	
16-17	262	73 (27.9)	
18-19	207	58 (28.0)	
>20	185	58 (31.4)	
Pack-years			**<0.001**
<5	**272**	**99 (36.4)**	
[5-10)	**211**	**69 (32.7)**	
[10-15)	141	42 (29.8)	
[15-80)	274	50 (18.2)	

p-value were computed by Fisher's exact test or chi-squared test for categorical variables, and by chi-square for trend for continuous categorized variables (age, cigarettes smoked daily, age at smoking initiation, pack-years)

Results of univariable analysis were confirmed by multivariable analysis. The odds of smoking cessation significantly decreased with increasing smoking intensity (Table 3). When considering cumulative smoking exposure, the effect became even stronger: with respect to a cumulative smoking exposure <5 pack-years, the OR of smoking cessation significantly decreased to 0.73 (0.55-0.97) and 0.42 (0.22-0.79) respectively in people who had smoked 10-14 and >=15 pack-years. Smoking cessation was not significantly affected by age at smoking initiation.

As regards respiratory disorders, asthma was associated with a two-fold increase in the probability of smoking cessation (Table 3), while allergic rhinitis and chronic bronchitis had no effect, the OR being respectively 1.11 (0.97-1.26; p=0.130) and 1.07 (0.60-1.90; p=0.822). In addition, smoking cessation was significantly higher in the ISAYA-cohorts and lower in women and in people aged 31.3 - 42.6 years.

Table 3. Influence of socio-demographic characteristics, respiratory disorders, baseline smoking intensity and duration on smoking cessation, evaluated by a multivariable logistic model.

	OR (95% CI)	*p*-value
Centre		
Verona-ISIA	1	
Verona-ISAYA	**1.56 (1.42-1.72)**	**<0.001**
Sassari-ISAYA	**1.24 (1.13-1.36)**	**<0.001**
Sex (women vs men)	**0.70 (0.54-0.91)**	**0.009**
Age class (years)		
[20 – 31.3]	1	
[31.3 – 42.6]	**0.83 (0.72-0.95)**	**0.006**
[42.6 – 53.9]	0.89 (0.65-1.21)	0.444
Asthma (Yes vs No)	**2.10 (1.03-4.31)**	**0.042**
Cigarettes smoked daily		
1-5	1	
6-10	1.24 (0.78-1.98)	0.352
11-15	0.70 (0.44-1.11)	0.130
16-40	**0.55 (0.33-0.92)**	**0.022**
Age of smoking initiation		
8-15	1	
16-17	0.87 (0.70-1.07)	0.176
18-19	0.83 (0.53-1.30)	0.408
>20	1.05 (0.88-1.25)	0.578

p values were computed by the Wald test

Determinants of smoking re-initiation

Cumulative incidence of smoking re-initiation decreased with advancing age, as for smoking cessation: the higher probability of relapsing smoke was observed in the age class of 20-31.3 years (Table 4). People suffering from allergic rhinitis and chronic bronchitis were more likely to relapse smoking, while asthma did not significantly affect smoking re-initiation. As regards baseline smoking habits, cumulative incidence of re-initiation exponentially increased with shortening smoking abstinence, while number of daily cigarettes and pack-years smoked before abstinence did not affect smoking re-initiation.

Results of univariable analysis were confirmed by multivariable analysis. The odds was significantly lower in the Verona-ISAYA cohort and not significantly influenced by sex (Table 5). The adult age (42.6 - 53.9 years) seemed to reduce the likelihood of relapsing smoke. The odds was significantly higher among subjects smoking more than six cigarettes per day; in particular, this probability was significantly higher for 6-10 and 16-40 cigarettes smoked per day. The odds decreased with the increase of abstinence duration. The probability of re-initiation decreased with the enhancement of smoking abstinence before baseline.

As regards respiratory disorders, allergic rhinitis and chronic bronchitis significantly increased the likelihood of smoking re-initiation, the OR being respectively 1.79 (1.29-2.48; $p<0.001$) and 1.85 1.74-1.97; $p<0.001$), whereas asthma had no effect (OR=1.22 (0.63-2.37; $p=0.593$).

Table 4. Cumulative incidence of smoking re-initiation, as a function of socio-demographic characteristics, respiratory symptoms and previous baseline smoking habits in a sample of 735 baseline ex-smokers (see next page)

	Ex-smokers at baseline	Absolute (per cent) frequency	*p*-value
Centre			0.087
Verona-ISIA	323	31 (9.6)	
Verona-ISAYA	276	32 (11.6)	
Sassari-ISAYA	136	23 (16.9)	
Sex			0.819
Male	379	43 (11.3)	
Female	356	43 (12.1)	
Age class (years)			**<0.001**
[20 – 31.3]	122	**22 (18)**	
[31.3 – 42.6**]**	390	52 (13.3)	
[42.6 – 53.9**]**	222	12 (5.4)	
Occupation			0.222
Businessman	116	17 (14.7)	
Clerk	255	28 (11)	
Workman	141	17 (12.1)	
Unemployed	17	5 (29.4)	
Housewife	90	9 (10)	
Student	21	3 (14.3)	
Retired and others	93	7 (7.53)	
Allergic rhinitis			**0.038**
No	563	59 (10.5)	
Yes	162	**27 (16.7)**	
Asthma			0.528
No	688	78 (11.7)	
Yes	57	8 (14)	
Chronic bronchitis			**0.006**
No	634	66 (10.4)	
Yes	82	**17 (20.7)**	
Cigarettes smoked daily			0.902
1-5	148	11 (7.43)	
6-10	216	39 (18.1)	
11-15	117	10 (8.5)	
16-40	187	23 (12.3)	
Pack-years			0.087
<5	170	27 (15.9)	
[5-10)	87	25 (28.7)	
[10-15)	58	15 (25.9)	
[15-80)	56	12 (21.4)	
Abstinence duration (years)			**<0.001**
<3 years	153	**42 (27.5)**	
3-7.4 years	140	20 (14.3)	
7.5-13.4 years	167	13 (7.8)	
>13.5 years	169	6 (3.6)	

p-value were computed by Fisher's exact test or chi-squared test for categorical variables, and by chi-square for trend for continuous categorized variables (age, cigarettes smoked daily, age at smoking initiation, pack-years).

Table 5. Influence of socio-demographic characteristics, respiratory disorders, baseline smoking intensity and years of abstinence duration up to baseline on smoking re-initiation at follow up, among baseline ex-smokers, evaluated by a multivariable logistic model.

	OR (95% CI)	*p*-value
Centre		
Verona-ISIA	1	
Verona-ISAYA	**0.86 (0.80-0.91)**	**<0.001**
Sassari-ISAYA	1.08 (0.97-1.20)	0.170
Sex (women vs men)	1.18 (0.77-1.79)	0.448
Age class (years)		
[20 – 31.3]	1	
[31.3 – 42.6]	0.99 (0.57-1.71)	0.961
[42.6 – 53.9]	**0.34 (0.22-0.54)**	**<0.001**
Asthma (Yes vs No)	1.22 (0.63-2.37)	0.559
Cigarettes smoked daily		
1-5	1	
6-10	**3.19 (2.01-5.07)**	**<0.001**
11-15	1.26 (0.58-2.73)	0.550
16-40	**2.41 (1.41-4.14)**	**<0.001**
Abstinence duration (years)		
<3 years	1	
3-7.4 years	**0.46 (0.34-0.63)**	**<0.001**
7.5-13.4 years	**0.23 (0.18-0.29)**	**<0.001**
>13.5 years	**0.15 (0.06-0.36)**	**<0.001**

p values were computed by the Wald test

Discussion

The main results of the present longitudinal study are:

1. About one third of current smokers stopped smoking after a 9-year follow-up and they largely exceeded the numbers of ex-smokers that relapsed smoking.

2. As regards respiratory disorders, the probability of quitting smoking was affected neither by allergic rhinitis nor chronic cough/phlegm, while being doubled by current asthma; on the opposite, the probability of re-start smoking increased by almost two times for allergic rhinitis and chronic cough/phlegm.

3. Smoking intensity and cumulative smoke exposure in pack-years were inversely related with smoking cessation and were the most important predictors, in agreement with the current literature [Bush 2012; Yang 2015; Masaoka 2017].

4. Smoking abstinence duration before baseline was inversely related with smoking re-initiation and was the most important predictor.

Cumulative incidence

In the present study cumulative incidence of smoking cessation (32.3%) was almost three time the cumulative incidence of smoking re-initiation (11.7%) after a 9-year follow-up, similar to values of 22.2% for quitting and 10.9% for relapsing found by a Swiss study after a 5-year follow-up [Samim 2018].

Determinants of smoking cessation

Concern for own health status was the most important reason to stop smoking: in an Italian national survey, 43.2% of ex-smokers had stopped smoking for a current health

condition and an additional 31.9% to avoid future health problems [Gallus 2013]. At variance the PASSI study reported that the presence of at least one chronic disease or a bad health status did increase quit attempts, but not successful ones [Coppo 2017] in agreement with American surveys [Bush 2012; Melzer 2016; Hilberink 2006].

The present study supports the role of health status in promoting smoking cessation. However, only a severe disease as asthma increased quitting smoking, while milder diseases as rhinitis or chronic cough/phlegm had no effect. Accordingly, the smoking prevalence in patients with asthma was observed as almost halved during a 7-years period in an observational Sweden study (Stegberg, 2018). At variance, an American survey on quitline users found that neither asthma nor COPD increased smoking cessation, but rather decreased it [Bush 2012].

Men were slightly more likely to stop smoking than women. According to previous cross-sectional studies finding youger age as affecting significantly smoking cessation [Coppo 2017; Samim 2018], the present longitudinal study confirmed that older adults had lower probability to stop smoking compared to youngest; in particular among the 31.3-42.6 age class.

Determinants of smoking re-initiation

Early age was found as a strong determinant of smoking initiation into three European studies. Among 119,104 subjects from 17 countries involved in the Ageing Lungs in European Cohorts consortium, the rates of smoking initiation showed a marked increase after 1990 in all regions during early adolescence (11–15 years) (Marcon et al., 2018). Moreover, in the Eurobarometer 77.1 survey (2012) including data of 4442 ever smokers from 27 European countries, 68.1% started smoking regularly when they were <18 years old and the mean age of onset of regular smoking was 16.6 years (Filippidis et

al., 2015). In the Netherlands, among the 13163 respondents born between 1980 and 1995, the 67.2% initiated smoking between 12 and 16 years of age and the peak age of initiation was 16 years (Nuyts et al.2018).

Even though our data referring to subjects aged 20-54 years, we confirmed age as having an important influence on smoking relapse since the higher percentage of relapsing smoke was observed in the youngest age class (20-31.3 years) and ex-smokers aged more than 42.6 years at baseline had the higher probability to remain abstinent from nicotine than the youngest subjects.

The present study points out principally the effect of health status in furthering smoking initiation: subjects with milder respiratory conditions, as rhinitis or chronic cough/phlegm, had less concerns about their health and had an increased likelihood of start smoking, while asthma had no effect.

Strengths and limitations

The present study has several strengths. First, most studies on smoking cessation were carried on adolescents or young adults [Samim 2018], while studies on middle aged people were sparse. Moreover, most studies performed in Italy were either cross-sectional [Coppo 2017] or retrospective [Gallus 2013], while the present study was a prospective cohort study. Furthermore, all studies on determinants of smoking initiation considered only psychological and social factors, beside age; this is the first study investigating respiratory diseases as potential determinants of re-starting smoking.

The main limitation was the low response to follow-up for smoking cessation. Although non-responders were re-contacted twice by mail and by phone, only 54.8% of current smokers answered the follow-up questionnaire, and only 51.5% filled in questions

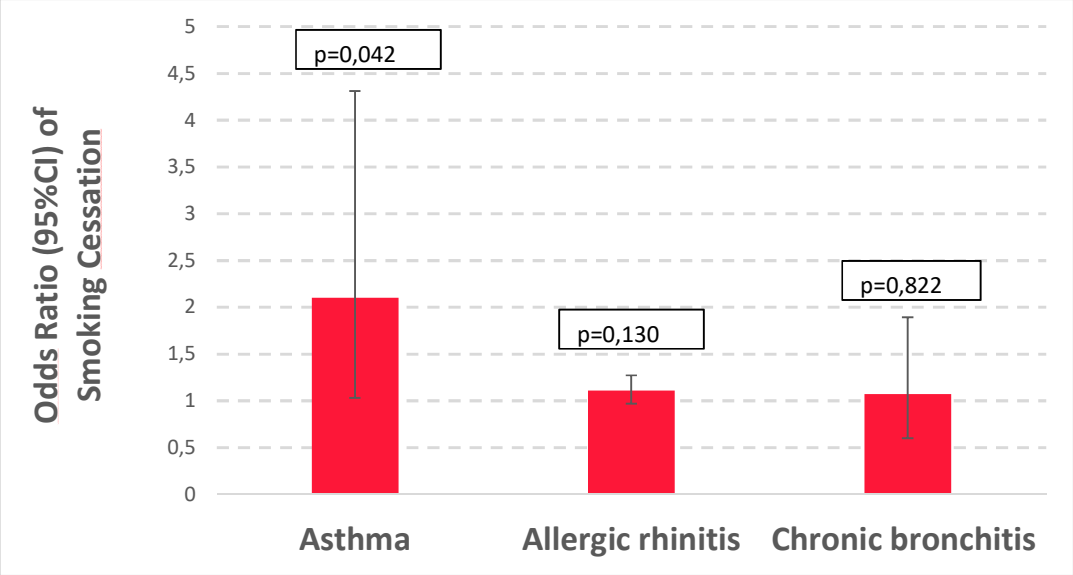
on smoking habits. These percentages were higher for ex-smokers: 65.3% of them answered the follow-up questionnaire, and 63% filled in questions on smoking habits. Although it largely affected prevalence estimates [Verlato 2010], non-response should not affect associations between determinants and outcome [Johannessen 2014]. So that the estimate of cumulative incidence should be interpreted with caution, while the measures of association can be taken more confidently. As the response percentage was rather low, a sensitivity analysis was applied.

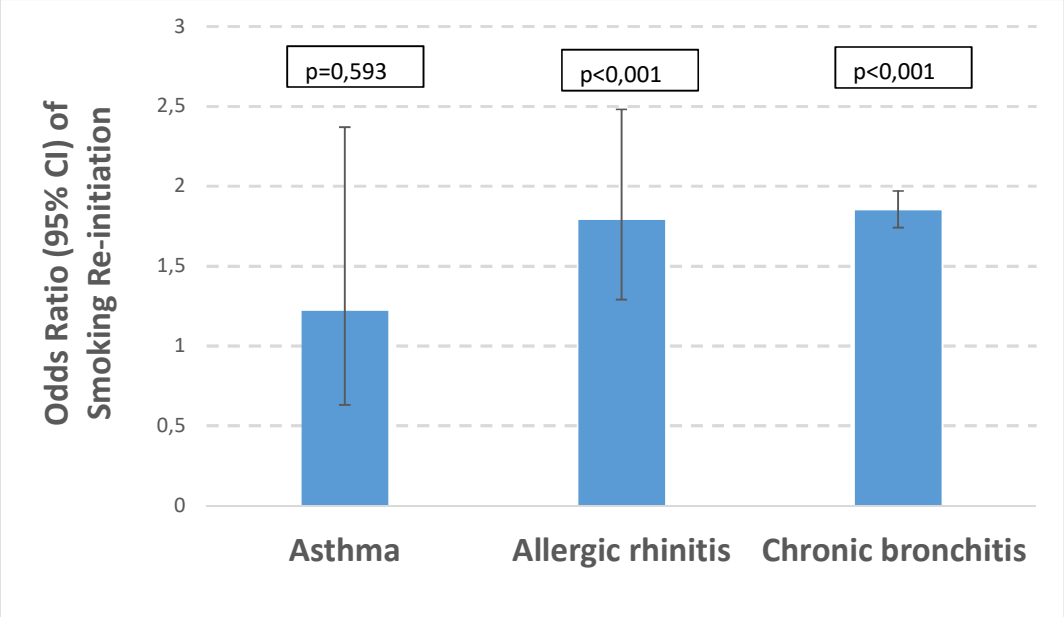
Conclusions

In the third millennium about one third of current smokers stopped smoking after a 9-year follow-up and they widely exceeded the number of ex-smokers relapsing in the same period. Smoking cessation was enhanced in people with asthma, but not in people with allergic rhinitis or chronic cough/phlegm and the effect of these respiratory determinants was the opposite for smoking initiation. Quitting smoking was more common among light smokers; while relapsing among youngest and being few years abstinent ex-smokers.

Effective public health policies reducing smoking prevalence should focused on promoting smoking cessation, working more on women and heavy smokers and sensitizing mostly subjects affected by milder respiratory diseases regard to the health complications from exposure to nicotine.

Figure 3. Odds Ratio of smoking cessation (panel above) and re-initiation (panel below) as a function of respiratory disorders. The risk of smoking cessation was investigated among 893 current smokers while the risk of smoking initiation among 603 ex-smokers at baseline. OR and p values were obtained by a logistic model, controlling for centre, sex, age, number of cigarettes smoked and age of smoking initiation for smoking cessation, and controlling for centre, sex, age, number of cigarettes smoked and years of abstinence duration until the baseline for smoking re-initiation.





SECOND TOPIC

"Knowledge and use of e-cigarette among nursing students: results from a cross-sectional survey in North-Eastern Italy"

Second topic of my research was conducted in the frame of the study "Knowledge and use of e-cigarette among nursing students: results from a cross-sectional survey in North-Eastern Italy" (Federica Canzan, Eliana Finocchio, Francesca Moretti, Silvia Vincenzi, Alex Tchepnou Kouaya, Oliva Marognolli, Albino Poli, Giuseppe Verlato), submitted but not yet published.

Methods

This cross-sectional survey was performed on September 2015 among all undergraduate nursing students enrolled in the Verona University. School of nursing is composed by 5 centers in the North-Eastern Italy, three located in the plane (Verona, Vicenza, Legnago) and two located in a valley inside the Alps (Trento, Bolzano).

Students were administered an Italian version of the French questionnaire ETINCEL-OFDT ("Enquête téléphonique pour l'information sur la cigarette électronique» of the "Observatoire français des drogues et des toxicomanies») [Lermenier et al., 2017] focused on e-cigarette use and tobacco smoking habits. The original version of the questionnaire was translated into Italian by a native Italian speaker and back-translated by a native French speaker. An expert panel, which was composed by two nursing teachers and one sociologist, identified and resolved the inadequate expressions/concepts of the translation. The result of this process produced a complete translated version of the questionnaire. Students were fully informed about the purpose of the research and asked to participate. All participants anonymously answered the

questionnaire in about 15 minutes before the laboratory's session scheduled to complete the nursing course.

Smoking status was defined by asking participants if they currently smoked and how frequently. Smokers were classified as "regular smokers" if they reported to smoke either daily or several times a week, and "occasional smokers" if they smoked less frequently, i.e. "once a week", "two-three times a month" or "once a month". "Past smokers" were subjects who had smoked during lifetime but did not smoke at the time of the survey. Subjects who had never smoked or had just tried smoking were considered "never smokers".

Participants were also asked about awareness on e-cigarettes, past and present use, or intention to try it in the future. Participants currently using both electronic and conventional cigarettes were classified as "dual users". They were asked about the main reasons for using e-cigarettes checking among a list of several options (including ''to quit smoking'', "to reduce cigarette consumption", "to reduce harmful health effects"). Finally, former smokers were asked if e-cigarettes consumption had helped them quit smoking.

Statistical analyses

The relation between tobacco smoking and e-cigarette use was evaluated by Fisher's exact test or chi-square for trend. The influence of tobacco smoking on e-cigarette ever use was further investigated by a multivariable logistic model, controlling for centre, sex, university class, family history of smoking habits, and smoking habits among current housemates.

The effects of e-cigarette ever use on smoking initiation and smoking cessation were investigated by applying two separate logistic regression models which estimated respectively, 1) the Odds Ratios (ORs) of being an ever smoker in the whole sample, 2) the ORs of being an ex-smoker among ever smokers. Centre, sex, university class, family history of smoking habits, and smoking habits among current housemates were also introduced in the logistic models as potential confounders. Standard errors were adjusted for intra-centre correlation. Statistical significance was set at $p < 0.05$ and significance of the ORs was computed by the Wald test. Stata(R) software (Texas, USA, version 14.0) was used for statistical analysis.

Results

Among the 2020 students attending the courses, 1463 (72.4%) answered and returned the questionnaire. Most responders were female (1108/1438=77.1%) and mean (SD) age was 23.2 (4.2) years.

Nearly all students (1379/1456=94.7%) had awareness about e-cigarettes. About one third (442/1460=30.3%, 95% CI 27.9-32.7%) had ever used e-cigarettes, but only 2.1% (31/1452, 95% CI 1.5-3.0%) declared to be "current e-cigarette users", i.e. to have been using e-cigarette for the last month. Very few (21/1015=2.1%) among those who had never tried e-cigarettes were willing to try them.

Both ever and current users of e-cigarettes were more prevalent among men. Ever or current use was not significantly affected by either class or centre (Table 6). Of note, ever use tended to be more common in centres located in the plane than in centres in Alpine valleys (p=0.065). Age was similar in people who had tried or never tried e-cigarettes

(23.2±4.4 vs 23.1±3.8 years; p=0.125) as well as among current users and other people (23.2±4.2 vs 24.1±5.1 years; p=0.384). Ever use of e-cigarettes was more frequently reported by students whose relatives/housemates smoked either e-cigarettes or tobacco.

Table 6. Main characteristics of Verona nursing students, as a function of e-cigarette use.

	E-cigarette ever users (n=442)	*P* value	E-cigarette current users (n=31)	*P* value
Sex*		**<0.001**		**0.048**
Men	**144/329 (43.8)**		**12/324 (3.7)**	
Women	**291/1107 (26.3)**		**19/1104 (1.7)**	
Class*		0.738		0.398
1st	140/451 (31.0)		10/447 (2.2)	
2nd	141/474 (29.7)		13/471 (2.8)	
3rd	160/533 (30.0)		8/532 (1.5)	
Centre		0.065		0.782
Verona	191/579 (33.0)		10/574 (1.7)	
Vicenza	77/238 (32.4)		7/238(2.9)	
Legnago	63/199 (31.7)		4/198 (2.02)	
Trento	42/177 (23.7)		3/176 (1.7)	
Bolzano	69/267 (25.8)		7/266 (2.6)	

Numbers of ever or current users of e-cigarette were reported with percent frequencies between parentheses. *P* values were computed by the Fisher's exact test for sex and centre, and by chi-squared test for trend for class. Significant results were highlighted in bold.
*Information on sex and university class was not reported by 25 and 2 students, respectively.

Prevalence values were much higher for tobacco smoking: 591 out of 1444 responders (40.9%, 95% CI 38.4-43.5%) reported to smoke currently. In particular, 407 responders (28.2%) were classified as regular smokers, as they declared that they had been smoking daily or several times per week for the previous month, while 169 (11.7%) were classified as occasional smokers, as they reported that they had been smoking once a week or less frequently. Never smokers were nearly half of the studied population (683/1444=47.3%), while past smokers were only 10.1% (146/1444). Fifteen smokers, who had given no information about their smoking frequency, and 24 non-smokers, who had not answered about their past smoking history, were excluded from multivariable analyses. As for the e-cigarette use, tobacco smoking habits were more prevalent among males than females and among students whose relatives/housemates smoked either tobacco or e-cigarettes. Tobacco smoking habits were not significantly affected either by class or by centre (Table 7).

Table7. Main characteristics of Verona nursing students, as a function of tobacco smoking.

	n	Past smokers (n=146)	Occasional smokers (n=169)	Regular smokers (n=407)	*P* value
Sex*					**0.002**
Men	312	**39 (12.5)**	**37 (11.9)**	**111 (35.6)**	
Women	1070	**105 (9.8)**	**130 (12.1)**	**283 (26.4)**	
Class*					0.137
1st	430	30 (7.0)	60 (14.0)	122 (28.4)	
2nd	461	62 (13.4)	50 (10.8)	118 (25.6)	
3rd	512	54 (10.5)	58 (11.3)	166 (32.4)	
Centre					0.430
Verona	549	48 (8.7)	65 (11.8)	168 (30.6)	
Vicenza	236	21 (8.9)	30 (12.7)	69 (29.2)	
Legnago	197	24 (12.2)	21 (10.7)	59 (29.9)	
Trento	172	21 (12.2)	25 (14.5)	35 (20.3)	
Bolzano	251	32 (12.7)	28 (11.2)	76 (30.3)	

Numbers of past, occasional and current smokers were reported with percent frequencies between parentheses. *P* values were computed by the Fisher's exact test for sex, chi-squared test for trend for class and by chi-squared test for centre. Significant results were highlighted in bold.
*Information on sex and university class was not reported by 25 and 2 students, respectively.

A strong association was observed between tobacco smoking and e-cigarette use. In particular, ever use of e-cigarettes was reported by 57.2% (338/591) of current tobacco smokers and 12.0% (102/852) of the other students ($p<0.001$). In detail, the proportion of "e-cigarettes ever use" was as low as 7.3% (50/682) among never smokers, increased to 32.2% (47/146) among ex-smokers and 39.0% (66/169) among occasional smokers, and peaked to 66.3% (270/407) among regular smokers (chi-square for trend: $p<0.001$) (Figure 4).

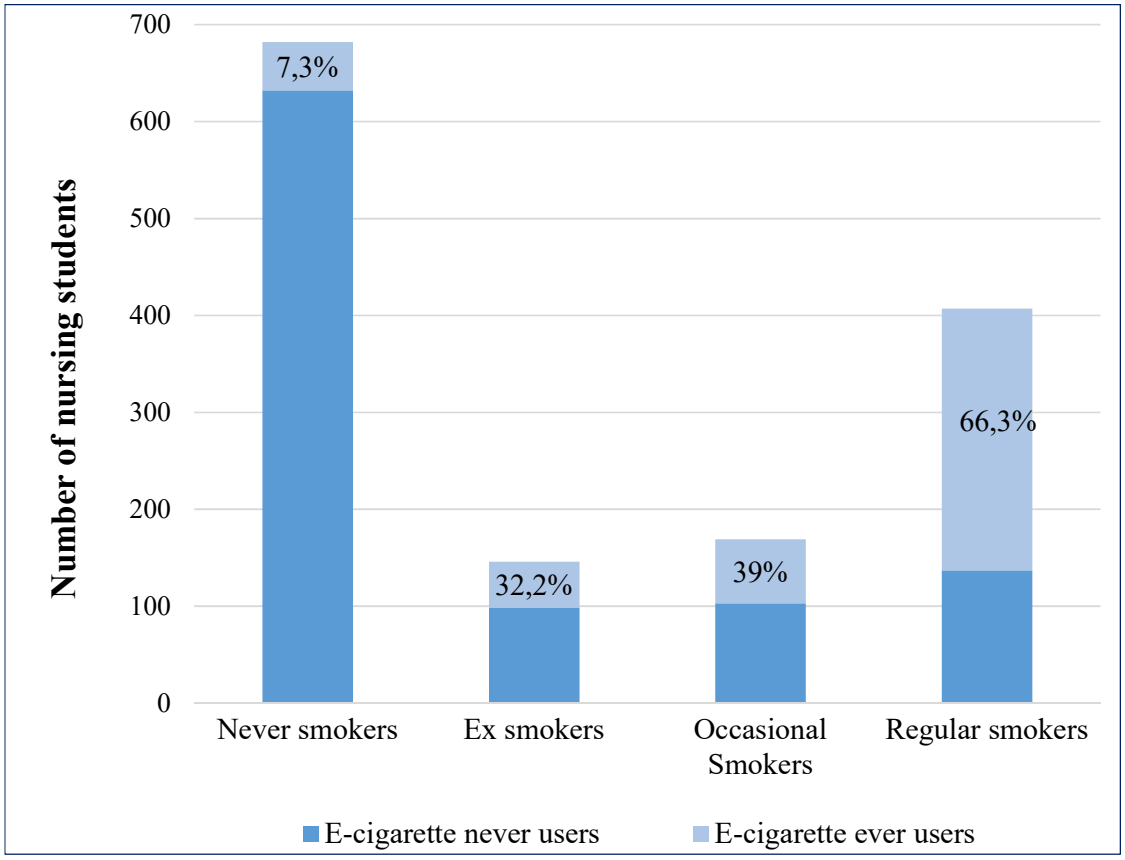


Figure 4. Association between ever use of e-cigarette and tobacco smoking habits.

Although the use of e-cigarette in the last month was 10-fold more rare than ever use in the lifespan, it presented a similar pattern with respect to tobacco smoking, being reported by 0.6% (5/851) of non-smokers and by 4.4% (26/584) of current smokers ($p<0.001$). In detail, e-cigarette current use was nearly absent among never tobacco smokers, being reported by just one subject out of 682 (0.2%), it became detectable among ex-smokers (4/146=2.7%) and occasional smokers (3/167=1.8%), and peaked to 5.5% (22/402) among regular smokers (chi-square for trend: $p<0.001$).

In multivariable analysis the risk of e-cigarette ever use significantly increased with incremental use of tobacco smoking: compared to never tobacco smokers, the Odds Ratio

(OR) of ever using e-cigarette was 5.97 (95% CI 3.46-10.33), 7.75 (5.07-11.85), 24.6 (16.62-36.50), respectively, in ex-smokers, occasional smokers and regular smokers. The risk of ever using e-cigarette was more than doubled (OR=2.54, 95% IC 1.15-5.59) in students living with housemates who used e-cigarettes with respect to students whose housemates smoked neither tobacco nor e-cigarettes. Female gender, as well as living in centres located in Alpine valleys, appeared to be protective factors for e-cigarette ever use (Table 8).

Table 8. Risk factors for e-cigarette ever use.

Risk factors	OR of e-cigarette ever use (95%IC)	p-value
Smoking Habits		
Never Smokers	1	
Ex-Smokers	**5.97 (3.46 – 10.33)**	**<0.001**
Occasional Smokers	**7.75 (5.07 – 11.85)**	**<0.001**
Regular Smoker	**24.6 (16.62 – 36.50)**	**<0.001**
Sex		
Male	1	
Female	**0.45 (0.32 – 0.63)**	**<0.001**
Family history of smoking		
None	1	
Relative who smoked e-cigarettes	0.68 (0.37 – 1.25)	0.219
Relative who smoked tobacco	1.19 (0.92 – 1.53)	0.178
Housemates currently smoking		
None	1	
Housemates smoking e-cigarettes	**2.54 (1.15 – 5.59)**	**0.021**
Housemates smoking tobacco	1.16 (0.94 – 1.43)	0.163
Centre		
Verona	1	
Vicenza	**1.12 (1.01 - 1.24)**	**0.027**
Legnago	**0.89 (0.85 – 0.94)**	**<0.001**
Trento	**0.82 (0.73 – 0.91)**	**<0.001**
Bolzano	**0.66 (0.63 – 0.69)**	**<0.001**
University class		
1st year	1	
2st year	1.01 (0.73 – 1.41)	0.939
3st year	0.79 (0.56 – 1.11)	0.173

OR (Odds Ratio), 95% IC, *P*-values were computed by logistic regression model. Significant results were highlighted in bold.

In the multivariable analyses focused on either smoking initiation or cessation, e-cigarette ever use emerged as the strongest predictor, among all factors considered. The odds of being ever tobacco smoker was one order of magnitude higher among e-cigarette ever users than never users, who in turn had a three times higher odds of having quitted smoking if ever tobacco smokers (Table 9). Moreover, the risk of smoking initiation was not affected by family history of smoking, while being significantly higher among students living with currently smoking housemates. The risk of smoking cessation among ever smokers tended to increase with increasing university class, and was the highest in Legnago, a centre with well-established long-lasting anti-smoking interventions (Table 9).

Seventeen of 26 dual users (students declaring to currently use both electronic and tobacco cigarettes) provided their motivations to use e-cigarette: tobacco cessation, decrease of tobacco consumption and reduction of harmful health effects were reported respectively by 11 (65%), 3 (18%) and 3 (18%) nursing students. Of note, only three students reported to have completely stopped smoking thanks to e-cigarette and only one of these was a current vaper.

Table 9. Effect of e-cigarette ever-use on smoking initiation and cessation.

	Smoking initiation		**Smoking cessation**	
Risk factors	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
E-cigarette: ever vs never users	**13.45 (9.26-19.55)**	**<0.001**	**0.33 (0.20-0.53)**	**<0.001**
Sex (women *vs* men)	0.90 (0.76-1.06)	0.215	0.73 (0.44-1.22)	0.235
Family history of smoking				
None	1		1	
Users of e-cigarettes	1.32 (0.89-1.95)	0.162	1.05 (0.69-1.60)	0.820
Users of tobacco cigarettes	0.93 (0.73-1.19)	0.562	1.20 (0.58-2.50)	0.617
Housemates currently smoking				
None	1		**1**	
Users of *e-cigarettes*	0.99 (0.72-1.37)	0.975	0.87 (0.62-1.21)	0.416
Users of *tobacco cigarettes*	**2.55 (1.66-3.91)**	**<0.001**	0.55 (0.26-1.16)	0.116
Centre				
Verona	1		1	
Vicenza	1.02 (0.99-1.05)	0.200	0.95 (0.86-1.05)	0.331
Legnago	**1.11 (1.08-1.14)**	**<0.001**	**1.44 (1.27-1.63)**	**<0.001**
Trento	0.97 (0.91-1.04)	0.423	**1.29 (1.03-1.62)**	**0.028**
Bolzano	**1.41 (1.37-1.45)**	**<0.001**	**1.38 (1.20-1.59)**	**<0.001**
University class				
1st year	1		**1**	
2nd year	1.12 (0.92-1.37)	0.269	**2.31 (1.04-5.11)**	**0.039**
3rd year	1.35 (0.97-1.86)	0.072	1.47 (0.76-2.86)	0.254

ORs (95% CI) and p values were computed by logistic regression models, controlling for centre, sex, family history of smoking habits, smoking habits among current housemates, and university class. significant results were highlighted in bold.

Discussion

The main results of this third study were:

- in the Nursing School of Verona and nearby towns, one third of students had ever tried e-cigarettes, but very few (2.1%) had become regular vaper;

- on the contrary, nursing students presented a rather high prevalence of current tobacco smokers, similar to the prevalence recorded in the general Italian population samples of the same age [Verlato et al, 2014], but remarkably higher than the prevalence observed in Italian physicians specializing in Public Health [La Torre et al., 2014];

- e-cigarette ever use was cross-sectionally associated with a higher risk to start smoking and to a lower risk of quitting smoking. Of note, only a trivial proportion of nursing students reported to have stopped smoking thanks to e-cigarette use.

Prevalence of users of e-cigarettes and conventional cigarettes

Awareness of e-cigarettes was nearly identical in the present survey (94.7%) and in a national sample of the same age (15-24 years) (94.8%) [Gallus, 2014], as well as the prevalence of current e-cigarette users (2.1% and 2.4% respectively). At variance, the prevalence of ever use of e-cigarettes were three times higher in nursing students from Northern-Eastern Italy (30.3%) than in the national sample of the same age (15-24 years) (11.6%) [Gallus, 2014], although it is noteworthy that the second prevalence referred to two-years previous data. In the present study both ever and current use of e-cigarette was higher among men (43.8% and 3.7%, respectively) than women (26.3% and 1.7%, respectively), in agreement with the current literature [Gallus 2014].

The proportion of e-cigarette ever use, reported by Italian nursing students (30.3%), was comparable to the proportion recorded in other academic settings, which ranged from 24-28% in American college students [Franks et al., 2017, Kenne et al., 2016] to 36% among French military nursing students [Guillet et al., 2015]. As regards current e-cigarette use, vapers were rare both in the present study (2.1%) and among medical students from New York (1.6%) [Zhou et al., 2015], while a much larger proportion was recorded among French military nursing students (25%) [Guillet et al., 2015] and Arkansas health professional students (20.6%) [Franks et al., 2017].

As regards tobacco smoking, the proportion of current smokers was similar among nursing students from North-Eastern Italy (28.2%) and in coevals from the same area (27.9%), as recorded in a previous study [Verlato 2014]. It should be reminded that the definition of current smoking slightly differed between the two surveys: it was defined as "having smoked several times per week in the last 30 days" in the present survey and as "having smoked at least one cigarette per day per one year and also in the last month" in the general population study [Verlato, 2014]. When considering both occasional and regular smokers, the proportion of current smokers (40.9%) became similar to that reported by French military nurses (40%) [Guillet et al., 2015]. Of note, a lower proportion of current smokers had been recorded in 2015 in the general Italian population: 21.3%, 27.6%, 33.5% in men aged 18-19, 20-24, 25-34 years respectively and 16.4%, 19.9%, 19.1% in women [Istat, 2018].

On the other hand the prevalence of tobacco smoking, recorded in the present survey, was similar to that previously recorded in nursing students in Europe (34.3% in men and 27.5% in women) [Sreeramareddy et al., 2018] and Greece (30.5% and 30.6%) [Barbouni et al., 2012], and in health professional students in the US (27.8% overall) [Franks et al., 2017]. A larger prevalence (40%) was recorded in French military nursing

students and instructors [Guillet et al., 2015]. Prevalence was lower in medical students from New York (3.9% smoking cigarettes and 2.1% cigars) [Zhou et al., 2015], in mostly undergraduates students from Midwestern university (16.3%) [Kenne et al., 2016] and in Italian post-graduate students attending the School of Public Health (26.2% in men and 16.2% in women) [La Torre et al., 2014]. Current smoking was particularly rare among Chinese medical/health professional students, with an overall prevalence of only 7% [Yang et al., 2015].

In addition e-cigarette ever use, as well as conventional smoking initiation, was affected by housemates' smoking habits, but not by family history of smoking. A pro e-cigarette social environment, such as housemates currently smoking e-cigarette, represented a very important incentive to start using e-cigarette in agreement with the current literature [Barrington-Trimis et al., 2016; Suftin 2015].

Although nursing students of North-Eastern Italy had been trained about risk factors and health promotion, they did not present a healthier lifestyle with respect to their coevals from the general population, having the same proportion of current smokers and a higher proportion of e-cigarette ever users. At variance, a substantial reduction in smoking habits was observed among Italian physicians specializing in Public Health, whose proportion of current smokers was 20.9% [La Torre 2014]. Of note, the prevalence of tobacco smoking tended to decrease from the first class to subsequent classes; moreover, smoking cessation was the highest in a centre (Legnago) with active anti-smoking interventions. This suggests that the knowledge acquired within the nursing curriculum also improves awareness of risk factors, and promotes a healthy lifestyle.

Relation between conventional tobacco smoking and e-cigarette use

E-cigarette and tobacco smoking were strongly related in the present study on Italian nursing students, in agreement with the current literature. Indeed the prevalence of e-cigarette ever use (7.3%, 32.2% and 57.2% respectively among never, past and current tobacco smokers) was similar to values found out in French military nursing students (21.9% and 57% among non-smokers and current tobacco smokers) [Guillet 2015] and in American college students (13.9%, 45%, 74.2% among never, past and current tobacco smokers) [Kenne, 2016].

A fundamental public health question is if e-cigarette could be a gateway to nicotine addiction and consequently to tobacco smoking initiation. The cross-sectional design of the present does not allow addressing the cause-effect relation between e-cigarettes use and tobacco smoking. With this limitation in mind, in the present study e-cigarette ever use was cross-sectionally associated with a higher risk to start smoking, with respect to never users. This association was particularly strong, the OR being 13.5 for smoking initiation. Accordingly, many literature data, from meta-analysis to longitudinal and cross-sectional studies, support the notion that e-cigarette use among adolescents/young adults increased the probability for future use of traditional cigarettes [Soneji et al., 2017; Doran et al., 2017; Trinidad et al., 2017; McCabe et al., 2017; Barrington-Trimis et al., 2016]. In a cross-sectional survey on French university students, the 20% of current smokers declared to have started smoking conventional cigarettes after using e-cigarettes [Rakotozandry et al., 2016]. Nicotine contained into e-cigarettes could contribute to its addiction and represent a gateway to tobacco smoking. Furthermore, e-cigarette use could even induce adolescents/young adults to use other substances, including marijuana [Westling et al, 2017].

As regards smoking cessation, the probability to become an ex-smoker among ever smokers was three times lower for e-cigarette ever users with respect to never users (OR=0.33). This finding was supported by a longitudinal study on current smokers enrolled in American colleges, where trying e-cigarettes more than doubled the risk to retain smoking habits after a three year follow-up [Sutfin 2015]. Furthermore, a survey on French university students found that, even if 12.6% of cigarette ever smokers had given up smoking thanks to a e-cigarettes, a higher proportion (20%) had begun to smoke conventional cigarettes after using e-cigarettes [Rakotozandry et al., 2016]. Nevertheless, e-cigarettes could be useful in promoting a reduction in daily cigarette consumption in persisting smokers [Rakotozandry et al., 2016]; nearly half of French military nurses reported an average decrease of 5-10 cigarettes smoked per day after e-cigarettes initiation [Guillet et al., 2015]. Accordingly, some studies indicated that e-cigarette could relieve smoking abstinence symptoms [Perkins et al., 2017] and help the ex-smokers to remain abstinent from nicotine [Manzoli et al., 2017].

Limitations

Some limitations of the present study should be acknowledged. Firstly, the low number of students reporting current use of e-cigarette (n=31) limited the possibility to evaluate the determinants of this condition. Secondly, the cross-sectional design did not allow investigating the direction of the association between e-cigarettes use and conventional tobacco smoking. Finally, smoking habits were assessed by questionnaire; however, a good agreement (Cohen's k = 0.93) between self-reported smoking consumption and serum cotinine levels had been found among young adults of Verona [Olivieri et al., 2002].

Conclusions

The use of e-cigarette seemed to be rather rare among Italian nursing students, and mainly restricted to current smokers. One third of students had ever tried e-cigarette, but only 2% had become regular vapers. E-cigarette ever use was as low as 7% among never smokers and peaked to 66% among regular smokers. E-cigarette did not appear to be as an instrument to stop smoking among nursing students. Moreover, the present study points also out the importance of school-based prevention programs in order to correct respiratory health habits, given the alarming high prevalence (40.9%) of tobacco smoking among nursing students. Indeed health professional students will play an essential role in promoting healthy habits and counselling the general population about smoking cessation.

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