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Persisting Long Term Benefits of Smoking Abstinence and Reduction in Asthmatic Smokers Who Have Switched to Electronic Cigarettes

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Abstract: *Background*. Improvements in asthma outcomes have been recently reported in asthmatic smokers who have substantially reduced their tobacco consumption by switching to ECs. Confirmation of these preliminary findings is necessary to reassure patients, healthcare professionals and policy makers. Here, we present findings from long term prospective assessment of objective and subjective asthma outcomes as well as safety and tolerability in this group of EC users with asthma. *Methods*. We prospectively re-evaluated respiratory symptoms, lung function, airway hyperresponsiveness, asthma control, asthma exacerbations and tobacco consumption in adult daily ECs users with asthma who were previously studied in a retrospective study. Measurements recorded at baseline prior to switching were compared with those at the follow-up visits at 6, 12, and 24 months. *Results*. Eighteen ECs users with mild to moderate asthma were followed up prospectively. Complete data was obtained from sixteen EC users and two relapsers. Significant and stable improvements in respiratory symptoms, lung function, AHR, ACQ, and tobacco consumption were observed in the 16 ECs users with asthma, but no significant changes in exacerbation rates were reported. Similar findings were found in the dual users. *Conclusion*. This prospective study confirms that EC use ameliorates objective and subjective asthma outcomes and shows that these beneficial effects may persist in the long term. EC use can reverse harm from tobacco smoking in asthma patients who smoke. The evidence-based notion that substitution of conventional cigarettes with EC is unlikely to raise significant respiratory concerns, can improve counseling between physicians and their asthmatic patients who are using or intend to use ECs.

Introduction

The asthmatic smoker represents a distinct disease phenotype with increased susceptibility of exacerbations and poor asthma-specific health status (Polosa and Thomson, 2013a; Eisner and Iribarren, 2007). Increased disease severity and marked impairment in asthma control is more frequently reported in asthmatic smokers who have smoked more than 20 pack years (Polosa *et al*., 2011). Most studies show an accelerated decline in lung function and increased airflow obstruction (Lange *et al*., 1998) and asthma patients who smoke appear to have an impaired response to the beneficial effects of antiasthma drugs compared to asthmatics who do not (Tomlinson *et al*., 2005; Chaudhuri *et al*., 2003). Nonetheless, quitting smoking can reverse the negative impact of tobacco smoke on asthma symptoms and lung function (Polosa *et al*., 2012).

Electronic cigarettes (EC) are battery-operated devices designed to vaporize nicotine without burning tobacco. The growing popularity of ECs proves that many adult smokers are keen in using an alternative to combustible cigarettes to reduce tobacco consumption or quit smoking and to relieve withdrawal symptoms (Caponnetto *et al*., 2013b). Data from internet surveys (Farsalinos *et al*., 2014a; Siegel and Tanwar, 2011; Etter and Bullen, 2014) and clinical trials (Caponnetto *et al*., 2013a; Bullen *et al*., 2013; Polosa *et al*., 2014a) have shown that ECs may help smokers quitting or reducing their tobacco consumption. Given that vapor toxicology - under normal condition of use - is by far less problematic than that of conventional cigarettes (Farsalinos and Polosa, 2014b), and exclusive ECs users have significantly lower urine levels of tobacco smoke toxicants and carcinogens compared to cigarette smokers (Hecht *et al*., 2014), switching to ECs use is likely to produce significant health benefits.

Only limited data is available regarding health effects of ECs use among vulnerable populations, including people with asthma. Moreover, it is unknown if regular "vaping" (the act of inhaling vapor from ECs) could result in improved or worsening asthma-related outcomes. In a recent retrospective study regular EC use was associated with objective and subjective improvements in asthma outcomes (Polosa *et al*., 2014b). In particular, significant improvement in Juniper's Asthma Control Questionnaire (ACQ), forced expiratory flow in 1 second (FEV1), forced vital capacity (FVC), forced expiratory flow at the middle half of the FVC (FEF25-75) and airways hyperresponsiveness (AHR) to inhaled methacholine were observed. Long term prospective assessment of objective and subjective asthma outcomes as well as safety and tolerability was undertaken in this group of asthmatic EC users and compared with earlier retrospective findings that have been published and presented before (Polosa *et al*., 2014b).

Methods

Patient population

Patients in the current study belong to an asthma cohort of adult daily EC users that were identified from medical records. Details of this patient population have been presented elsewhere (Polosa *et al*., 2014b). In the current study, eighteen daily ECs users with mild to moderate asthma were prospectively followed up for one additional year. This study was approved by the local institutional ERB and informed consent was obtained from each patient.

Study design and assessments

In the preliminary study (Polosa *et al*., 2014b), patients' medical records were reviewed twice over one year, at 6 ±1 (follow-up visit 1; F/up 1) and 12 ±2 (follow-up visit 2; F/up 2) months) from baseline (when they first reported EC use) to acquire details about respiratory symptoms, asthma outcomes and tobacco consumption. We also included data from the clinic visit immediately prior to the baseline visit (pre-baseline visit). Pre-baseline data were acquired 6-12 months prior to the baseline visit; comparison of pre-baseline study outcomes with those obtained at baseline was used to demonstrate disease stability.

In the present study, the same daily EC users with asthma were prospectively re-evaluated for changes in respiratory symptoms, asthma outcomes and tobacco consumption for an additional year from October 2013 to January 2015 (follow-up visit 3; F/up 3). Re-evaluation also included (i) Juniper's Asthma Control Questionnaire (ACQ) score; (ii) number of exacerbations from the previous follow up visit (an asthma exacerbation was defined as an increase in respiratory symptoms requiring a short course of oral or parenteral corticosteroids); (iii) simple spirometry with parameters of forced expiratory flow in 1 second (FEV1), forced vital capacity (FVC), and forced expiratory flow at the middle half of the FVC (FEF25-75); and (iv) in some subjects bronchial provocation tests assessing airway hyperresponsiveness (AHR) with methacholine were also conducted as previously described (Piccillo *et al*., 2008). Daily cigarette consumption, (biochemically verified by exhaled breath carbon monoxide

- eCO monitoring), and review of EC use were also included in the re-evaluation. Findings obtained at F/up 3 were compared with those from baseline and from F/up 1 and 2.

Smoking/Vaping status

Smoking abstinence was defined as complete self-reported abstinence from tobacco smoking (not even a puff) since the previous study visit. This was also biochemically verified at F/up 3 by eCO levels of ≤7 ppm. Asthmatic EC users in this category are classified as Quitters (Single users).

Smoking reduction was defined as sustained self-reported reduction (at least >50%) in the number of cig/day from baseline. Asthmatic EC users in this category are classified as Reducers (Dual users).

EC users who were not categorized in the above categories were classified as Relapsers.

Analyses

Table 1. Patients characteristics at pre-baseline and baseline (before switching to electronic cigarettes).

All data obtained at the various time points were expressed as mean (±standard deviation (SD)) except for methacholine PC20 values expressed as geometric mean (data range). We also delineated data for single (exclusive EC use) and dual users (combined EC use with conventional cigarettes). Statistical comparisons of parameters assessed were carried out using student's T-test and Wilcoxon-signed rank test depending on whether the data was parametric or not, respectively. Missing measurements were not included in the analyses. A two-tailed p value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with the Statistical Package for Social Science (SPSS for windows version 18.0, Chicago, IL, USA).

Results

Characteristics of the patients and their EC use

Patient details are listed on **Table 1**. Of the starting 18 (11 male, 7 females) asthmatic EC users identified and evaluated in the preliminary study (Polosa *et al*., 2014b), two (1 dual user and, 1 single user) relapsed to exclusive tobacco smoking by the final follow up visit at 24 months. Of note, one dual user became single user by the end of the study. Thus, by the end of the follow-up we analyzed data from 10 single and 6 dual users. Dual users smoked less than 6 conventional cigarettes/day already at F/up 1, and less than 4 at F/up 2 and F/up 3.

Table 2. Changes in objective and subjective asthma parameters measured at baseline and at subsequent follow-up visits.

There were no significant differences in the measured parameters of lung function, methacholine PC20, number of respiratory exacerbations, or ACQ scores between the pre-baseline and baseline visits (except for a small but significant change in FEF25-75) (Table 1). All patients remained on a stable dose of ICS, LABA as well as on-demand SABA throughout the study.

Smoking consumption

Overall, there was a marked reduction in conventional cigarette use amongst EC users, the mean cigarette/day consumption of 21.9 at baseline decreasing to 2.3 at F/up 1 ($p<0.001$), 1.9 at F/up 2 ($p<0.001$), and 1.5 at F/up 3 ($p<0.001$) respectively (**Table 2**). Substantial reduction in conventional cigarette use was also observed in dual users; their mean cigarette/day consumption at baseline decreasing from 20.7 to 5.3 at F/up 1 ($p<0.001$), 3.7 at F/up 2 ($p<0.001$), and 3.5 at F/up 3 ($p<0.001$), respectively (Table 2). Importantly, 10 out of 16 asthmatics were still exclusively using EC at 24 months and not smoking conventional cigarettes throughout the study (single users).

ECs pattern of use

For all patients, first-time purchase was a "cig-alike" EC model, but the majority went on to adopt refillable "pen-like" ECs. Duration of regular EC use ranged from 20 to 26 months, with ten patients using them for at least 2 years. All participants were using standard refillable ECs by the end the study. The preferred nicotine strength of their e-liquid was 9 mg/ml and 18 mg/ml, which was consumed by 62.5% (10/16) and 18.8% (3/16) of EC users respectively. Most of the participants consistently preferred tobacco flavors over other flavors at final follow up visit.

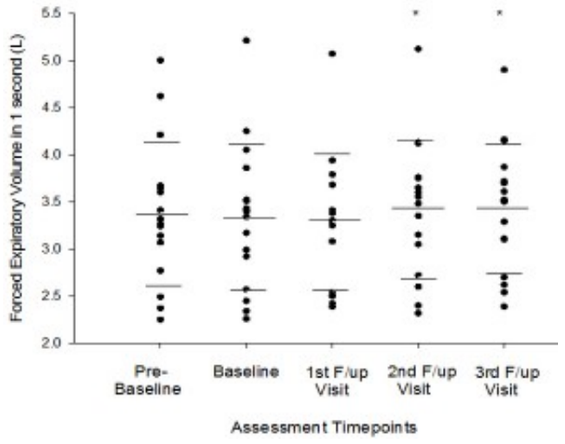

Figure 1A. Dot plots representation of individual forced expiratory volume (FEV1) at the four timepoints of assessment for 16 EC users with asthma. The line in the figure shows the mean. * p≤0.05; ** p≤0.01; *** p≤0.001 compared to baseline.

Changes in lung function, methacholine PC20 and ACQ scores

Compared to baseline, at F/up 1 there were significant improvements in ACQ scores (Table 2; **Figure 2**); at F/up 2 and F/up 3 significant improvements were observed on ACQ scores, and all lung function parameters including methacholine PC20 (Table 2; **Figures 1-3**). Improvements detected at 12 months were still present at 24 months.

Similar improvements were also observed in the dual users (Table 2). At F/up 1, there were significant improvements in ACQ scores and FEF25-75. At F/up 2 and F/up 3 significant improvements from baseline (except for FVC at F/up 3) were observed on ACQ scores, lung function parameters, and methacholine PC20 (Table 2).

Of note, deterioration in objective and subjective asthma outcomes was noted in the two patients who relapsed to exclusive tobacco smoking. The normal FEV1/FVC of 79.5% at 12 months (F/up 2) decreased to 71.0% at 24 months (F/up 3), which indicates worsening obstructive disease. Their methacholine PC20 was reduced three-fold from 2.95 mg/ml to 1.05 mg/ml and their ACQ score increased substantially from 1.45 to 2.3.

Asthma exacerbations

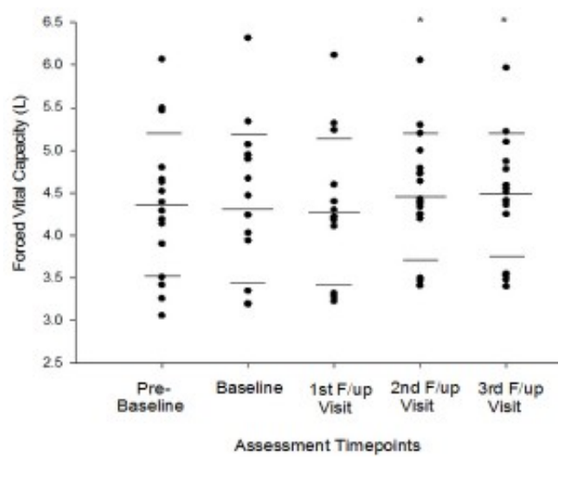

Figure 1B. Dot plots representation of individual forced vital capacity (FVC) at the four timepoints of assessment for 16 EC users with asthma. The line in the figure shows the mean. * p≤0.05; ** p≤0.01; *** p≤0.001 compared to baseline. Abbreviations: F/up, follow-up; L, liters.

There were no significant differences in number of respiratory exacerbations throughout the study (Table 2). The average number of exacerbations at baseline of 1.13 not being significantly different from 0.93 exacerbations at F/up 1, 0.87 exacerbations at F/up 2, and 0.81 exacerbations at F/up 3, respectively. Of note, exacerbation rate increased from 0 at 12 months (F/up 2) to 2 at 24 months (F/up 3) in the two patients who relapsed to exclusive tobacco smoking.

Safety and tolerability

No severe adverse reactions or acute exacerbation of asthma symptoms (i.e., cough, wheeze) were noted during period of observation with EC use and none of the patients in the study cohort had a hospital or intensive care unit admission. EC use appears to be well tolerated in these asthmatic patients with dry mouth and throat irritation being occasionally reported.

Discussion

The negative impact of tobacco smoke on asthma symptoms and lung function has been thoroughly documented (Polosa and Thomson, 2013a; Eisner and Iribarren, 2007; Polosa *et al*., 2011). Emerging evidence now indicates that asthmatic smokers who quit or reduce substantially tobacco consumption by switching to ECs use are likely to gain significant health benefits. In a recent retrospective study, regular EC use was associated with significant improvement in lung function and asthma symptom scores (Polosa *et al*., 2014b). However, standard issues associated with retrospective studies do not allow establishing a causal relationship. Therefore, we followed up this group of EC users with asthma in the course of their regular visits at the outpatient clinic in order to document changes in asthma outcomes prospectively. Here we confirm that regular EC use ameliorates asthma outcomes and shows that these beneficial effects may persist in the long term. Moreover, it was shown that similar benefits could be also noted in the dual users and that regular EC use was well tolerated.

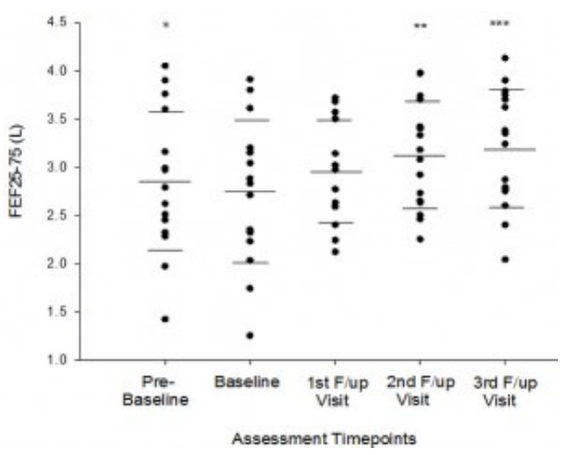

Figure 1C. Dot plots representation of individual forced expiratory flow at

the middle half of the FVC (FEF25-75) at the four timepoints of assessment for 16 EC users with asthma. The line in the figure shows the mean. * p≤0.05; ** p≤0.01; *** p≤0.001 compared to baseline. Abbreviations: F/up, follow-up; L/sec, liters/second.

These confirmatory findings are of great importance considering that many asthmatic patients continue to smoke and seem uninterested in quitting (Polosa and Thomson, 2013a; Polosa *et al*., 2012), a paradox that may be explained by the highly addictive nature of tobacco smoking and the remitting clinical nature of asthma, particularly in its mild-to-moderate forms. The success in reducing cigarette consumption or quitting smoking with EC in these asthmatic patients may be explained by the combined compensatory effect at both physical and behavioral level (Caponnetto *et al*., 2013b). In agreement with this, nicotine-free plastic inhalators can improve quit rates only in smokers for whom cigarette handling and manipulation play a key role in their smoking ritual (Caponnetto *et al*., 2011).

This study confirms that lung function of smokers with asthma may improve when stopping smoking for a sufficient period of time. The improvement reported persisted in the long-term prospective follow up. These findings are in agreement with the positive results of prospective studies looking at the effect of stopping smoking on lung function in asthma (Tønnesen *et al*., 2005; Chaudhuri *et al*., 2006). Taken together, the evidence suggests that the harmful effects of smoking on the asthmatic airways can be reversed. It is plausible that the attenuation in pro-inflammatory effects of cigarette smoke on the airways after reducing smoking consumption by switching to EC use might have caused overall improvement in lung function (Polosa and Thomson, 2013; Chalmers *et al*., 2001).

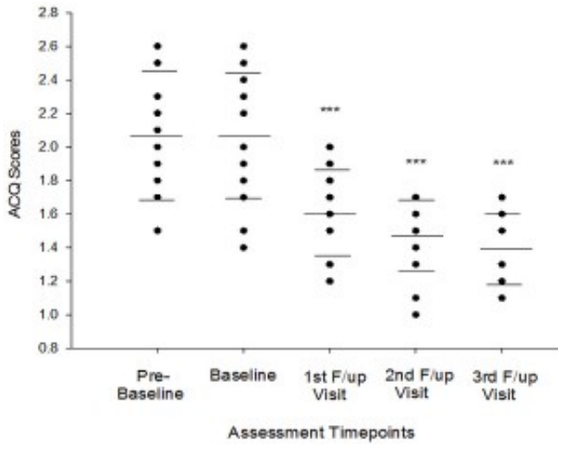

Figure 2. Dot plots representation of individual Juniper's Asthma Control Questionnaire (ACQ) score at the four timepoints of assessment for 16 EC users with asthma. The line in the figure shows the mean. * p≤0.05; ** p≤0.01; *** p≤0.001 compared to baseline. Abbreviations: F/up, follow-up.

Given the close relationship between airway inflammation and airway hyperresponsiveness (AHR) in asthma (Joos *et al*., 2003) it is not surprising to observe significant and persistent improvements in methacholine PC20 in the asthmatic smokers who had been abstinent or reduced their tobacco consumption. The reported changes in methacholine PC20 are consistent with the results of prospective studies in allergic smokers for whom an objective proof of cessation was documented (Piccillo *et al*., 2008). The observed improvement in AHR may have important clinical implications because it is a risk factor for asthma symptoms and attenuated pulmonary function levels (Sparrow *et al*., 1987; Tashkin *et al*., 1996). Thus, improvement AHR is likely to confer some clinical benefit as documented by the early and stable reduction in asthma symptoms (i.e., ACQ scores). In support of this view, deterioration in methacholine PC20, lung function, and ACQ scores was noted in the two patients who relapsed to exclusive tobacco smoking.

In spite of significant improvement in lung function, AHR and asthma control, no significant change in disease exacerbations was observed. This discrepancy can be explained by the low baseline values for exacerbations in our mild-to-moderate asthmatic patient cohort (hence it is possible that scope for further improvement was limited). Nonetheless, EC use in this vulnerable population did not trigger any acute exacerbation of asthma symptoms.

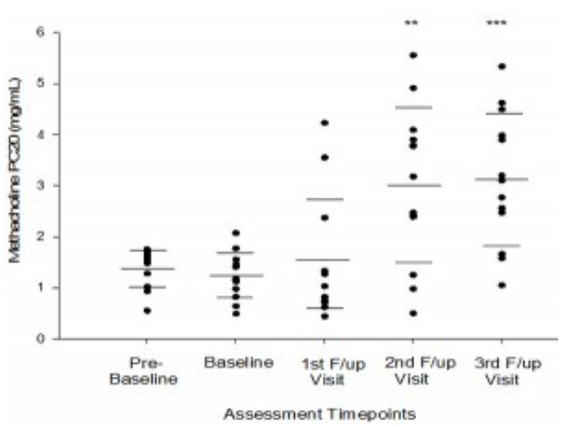

Figure 3. Dot plots representation of individual Methacholine PC20 at the four timepoints of assessment for a group of EC users with asthma. The line in the figure shows the geometric mean. * p≤0.05; ** p≤0.01; *** p≤0.001 compared to baseline. Abbreviation: F/up, follow-up.

Consistent improvements in subjective and objective asthma outcomes were also observed in dual users with no real difference in dual compared to single users by the end of the follow up. This could be due to the fact that dual users in this study substantially reduced their daily tobacco consumption by 70-80% (i.e., heavy reducers).

The observed positive findings in asthma patients who have become regular ECs users are consistent with results from a large internet survey of EC users diagnosed with asthma (Farsalinos *et al*., 2014a). An improvement in symptoms of asthma after switching was reported in 65.4% of the respondents. Although improved asthma symptoms were more often noted in exclusive EC users, improvement was also often reported by dual users. Worsening after switching was only reported in 1.1% of the asthmatics. Taken together, these findings provide emerging evidence that EC use can reverse harm from tobacco smoking in exclusive EC users as well as in dual users when their level of reduction in cigarette consumption is substantial (i.e., heavy reducers).

In theory, EC use might induce people to introduce higher nicotine doses than those from tobacco cigarettes. However, there is no evidence to suggest that EC promotes higher nicotine consumption. In fact, the opposite is true because ECs are generally much less efficient than conventional cigarettes at delivering nicotine to the body (Nides *et al*., 2014; Dawkins *et al*., 2014; Farsalinos *et al*., 2014). Although compensatory puffing behaviors may contribute to higher nicotine intake both in exclusive EC users and in dual (combined cigarette smoking and vaping) users, overall level of plasma nicotine/cotinine (cotinine is a stable metabolite of nicotine) is comparable (not

higher) to that of their previous smoking behavior (Behar *et al*., 2015; Pacifici *et al*., 2015). Nonetheless, nicotine is a powerful psychoactive substance and EC use may perpetuate an addictive behavior. However, there is increasing evidence that ECs may reduce measures of nicotine dependence (Etter *et al*., 2015; Foulds *et al*., 2015). Moreover, it is a common trend among EC users to reduce the nicotine strength of their e-liquid over time (Farsalinos *et al*., 2013; Polosa *et al*., 2015), suggesting that regular EC use may reduce nicotine dependence in the long term.

By substantially reducing the number of cigarettes smoked per day and exposure to their numerous hazardous toxicants, e-Cigarettes may not only improve asthma symptoms and pulmonary function but may also confer an overall health advantage in smokers with asthma (Polosa *et al*., 2013b). Therefore, e-Cigarette use in asthmatic smokers who are unable or unwilling to quit should be exploited as a safer alternative approach to harm-reversal (i.e., specific reversal of asthma-related outcomes) and, in general, to harm-reduction (i.e., overall reduction of smoke-related diseases).

There are some limitations in this study. Firstly, this is a small uncontrolled study, hence results must be interpreted with caution. Nonetheless, despite being a small study, the beneficial effects were consistently documented for each and every asthma outcomes throughout the final follow up visit. Secondly, it is likely that patients in this study represent a self-selected sample, which is not representative of all asthmatic smokers who switch to ECs. Lastly, assessment of symptoms may be liable to recall bias and the good tolerability reported by these patients should be considered with prudence.

The present study confirms that regular EC use ameliorates objective and subjective disease outcomes in asthma and shows that these beneficial effects may persist in the long term. Large controlled studies are now warranted to elucidate the emerging role of the e-vapor category for smoking cessation and/or reversal of harm in asthma patients who smoke. Nonetheless, the notion that substitution of conventional cigarettes with EC is unlikely to raise significant respiratory concerns, can improve counseling between physicians and their asthmatic patients who are using or intend to use ECs.

Disclosure

R.P. has received grant support from anti-asthma drug manufacturers including CV Therapeutics, NeuroSearch A/S, Sandoz, Merck Sharp & Dohme, and Boehringer-Ingelheim; has served as a speaker for CV Therapeutics, Novartis, Merck Sharp & Dohme, Roche, and GlaxoSmithKline; has served as a consultant for CV Therapeutics, Duska Therapeutics, NeuroSearch A/S, Boehringer-Ingelheim, and Forest Laboratories; and has received payment for developing educational presentations from Merck Sharp & Dohme, Novartis, and Almirall.

R.P. has also received lecture fees and research funding from GlaxoSmithKline and Pfizer, manufacturers of stop smoking medications; he has also served as a consultant for Pfizer and Arbi Group Srl, an Italian e-cigarettes distributor. R.P.'s research on e-cigarettes, smoking, and asthma is supported by Lega Italiana AntiFumo (LIAF).

J.B.M. has received honoraria for speaking and financial support to attend meetings/advisory boards from anti-asthma drug manufacturers including Wyeth, Chiesi, Pfizer, Merck Sharp & Dohme, Boehringer-Ingelheim, Teva, GlaxoSmithKline/Allen & Hanburys, Napp, Almirall, and Novartis.

P.C., M.C., D.C., M.D.A., G.C., C.R., and A.F. have no relevant conflicts of interest to declare in relation to this work.

Author Contribution

R.P. and J.B.M. contributed equally to this article.

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