UNIVERSITAT DE BARCELONA

# Environmental and bystanders' exposure to secondhand aerosols of electronic cigarettes in the European population

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# Environmental and bystanders' exposure to secondhand aerosols of electronic cigarettes in the European population


Doctoral thesis presented by

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Amb la present, els doctors **Esteve Fernández Muñoz** i **Marcela Fu Balboa**, directors de la tesis de la doctoranda **Beladenta Amalia** donen el seu vistiplau a la versió definitiva de la tesis doctoral *Environmental and bystanders' exposure to secondhand aerosols of electronic cigarettes in the European population* i n'autoritzen el dipòsit i la defensa sempre i que la Comissió de Doctorat així ho aprovi.

I, perquè consti i tingui els efectes que corresponguin, signen la present.

Beladenta Amalia
*Doctoranda*

Prof. Esteve Fernández Muñoz
*Director de la tesis*

Dra. Marcela Fu Balboa
*Directora de la tesis*

“

*Let this thesis be part of the tobacco control and human rights movements around the world. I would not stop keeping faith in those who fight for social justice by protecting the most vulnerable from one of the biggest public health catastrophes the world has ever faced, the tobacco epidemic.*

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# FUNDING

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# THESIS PRESENTATION

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This PhD thesis is the result of the three-year research I have conducted at the Tobacco Control Research Group, Catalan Institute of Oncology - Bellvitge Biomedical Research Institute (ICO-IDIBELL), Barcelona, Spain. The studies presented here have been conducted within the TackSHS project, a Horizon 2020 research project on secondhand tobacco smoke and electronic cigarettes, including assessing exposure to their secondhand aerosols. The TackSHS project has been coordinated by the ICO-IDIBELL research group.

This thesis consists of five manuscripts, four of which have been published in high-impact journals, and the fifth is under preparation for submission. All these manuscripts report studies that investigated exposure to secondhand aerosol from electronic cigarettes in the European population by means of personal, environmental, and population exposure assessment, as well as the policy-level analysis.

This thesis is structured into the following sections: introduction, hypotheses, aim, results, discussion, conclusions, and references. The annexes include the studies' questionnaires, ethical approval documents, *curriculum vitae*, and the list of publications by this thesis author during the development of this PhD thesis along with the list of scientific presentations which this thesis author has made in national and international conferences.

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# ABBREVIATIONS

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| | | |
|---|---|---|
| COPD | : | Chronic obstructive pulmonary disease |
| COVID-19 | : | Coronavirus disease 2019 |
| ENDS | : | Electronic Nicotine Delivery Systems |
| ENNDS | : | Electronic Non-nicotine Delivery Systems |
| EU | : | European Union |
| EVALI | : | Electronic cigarette, or vaping, product use-associated lung injury |
| FCTC | : | Framework Convention on Tobacco Control |
| HTPs | : | Heated tobacco products |
| MS | : | Member States |
| NNAL | : | 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol |
| NNK | : | Nicotine-derived nitrosamine ketone |
| NNN | : | N-nitrosonornicotine |
| PG | : | Propylene glycol |
| PM | : | Particulate matter |
| RASHA-E | : | Regulatory approaches to protect bystanders from exposure to SHA in European countries |
| SHA | : | Secondhand aerosol from electronic cigarettes |
| SHS | : | Secondhand smoke |
| TackSHS | : | Tackling secondhand tobacco smoke and e-cigarette emissions |
| TPD | : | Tobacco Products Directive |
| TSNAs | : | Tobacco-specific nitrosamines |
| UK | : | United Kingdom |
| US | : | United States |
| USD | : | United States Dollar |
| VOCs | : | Volatile organic compounds |
| WHO | : | World Health Organization |
| WP | : | Work-package |

# ABSTRACT

# ABSTRACT

**Introduction:** In the past few years, electronic cigarettes (e-cigarettes) have increased their popularity among youth and adults in many parts of the world, including Europe. The emerging body of evidence has shown that e-cigarettes' aerosols contain hazardous compounds, including fine particulate matter ($PM_{2.5}$), nicotine, and tobacco-specific nitrosamines (TSNAs), which threaten the health of users and bystanders. However, there was still limited research on secondhand exposure to e-cigarette aerosol (SHA) among bystanders, which was particularly important to justify whether e-cigarette use will result in net health benefits in the population.

**Objectives:** The overall objective of this thesis is to evaluate the exposure to SHA in the European population from a policy perspective, population level, and individual level. The thesis has the following specific objectives: 1) to examine the national and subnational legislations regulating the use of e-cigarettes in public and private places across the World Health Organization (WHO) European Region countries; 2) to assess the extent of the population's exposure to SHA in different public and private settings in European countries; 3) to characterise personal and environmental exposure to SHA in controlled confined settings that emulate real-life conditions; and lastly, 4) to characterise personal and environmental exposure to SHA in real-life conditions.

**Methods:** Five studies were performed to meet the objectives of this thesis. To achieve the first specific objective, a survey study among in-country health policy experts of multiple countries within the WHO European Region was conducted to collect data on national and subnational regulations surrounding e-cigarette use in public and private places. The second objective was accomplished by conducting two surveys in European countries to collect data on e-cigarette use in outdoor settings and the self-reported population's exposure to SHA. For the third objective, an experimental study was conducted in an enclosed controlled room and car to assess the airborne and biological markers of short-term SHA exposure in the indoor environment. Lastly, the fourth objective entailed an observational study in e-cigarette users' homes in multiple European countries to investigate the airborne markers of SHA exposure in indoor environments and biomarkers in non-users living in the homes.

**Results:** Twenty-eight out of 48 (58.3%) countries within the WHO European Region regulated e-cigarette use at national level, with European Union (EU) Member States (MS) having a significantly higher proportion (73.1%) of countries adopting e-cigarette use legislation at national level compared to their non-EU counterparts (40.9%). The number of places regulated by country's e-cigarette use legislation was associated with country's smoking prevalence and income level. Our survey in 11 European countries suggests that the outdoor setting with the highest visibility of e-cigarette use was the outdoor areas of hospitality venues (21.3% of venues). Although limited, e-cigarette use was observed in places frequented by children, such as school entrances (11.0% of entrances) and children's playgrounds (4.0% of playgrounds). Additionally, our population study shows that 16.0% of e-cigarette non-users in 12 European countries were exposed to SHA in any indoor setting at least weekly, with a median duration of exposure of 43 minutes/day. The prevalence of SHA exposure differed by country's e-cigarette use prevalence and geographic region in Europe. SHA exposure among non-users was more likely to occur in men, younger age groups, highly educated groups, e-cigarette past users, current smokers, those perceiving SHA as harmless, and living in countries with higher e-cigarette use prevalence. From our experiment study, we found that $PM_{2.5}$ concentration increased about two-fold during short-term (30 minutes) e-cigarette use compared to baseline in a controlled room and car, but the airborne nicotine remained low throughout the experiment. Although the levels of biomarkers of SHA exposure (i.e., nicotine, cotinine, 3'-OH-cotinine, nornicotine, TSNAs, PG, and glycerol) measured in saliva samples of bystanders were mostly below their limits of quantification after e-cigarette use in those settings, bystanders experienced acute irritation symptoms, including dry eyes, throat, and nose, after short-term SHA exposure. In contrast, our observational study shows that airborne nicotine concentration in e-cigarette users' homes was significantly higher than that was found in non-users' homes, while $PM_{2.5}$ concentration in e-cigarette users' homes was similar to non-users' homes. The concentrations of some biomarkers of SHA exposure, such as nicotine, cotinine, 3'-OH-cotinine, 1,2-PG in saliva, and cobalt in the urine sample of e-cigarette non-users living with the users were found to be higher than those living with non-users.

**Conclusions:** This thesis shows that personal and environmental exposure to SHA occurred, and it may risk the health of bystanders in the long run. Since SHA exposure at the population level in Europe was not negligible, and e-cigarette use legislation was not widely adopted in European countries, governments should make more efforts to protect bystanders, particularly vulnerable groups such as young people, by including e-cigarettes in the smoke-free policies.

# RESUMEN

# RESUMEN

**Introducción:** En los últimos años, los cigarrillos electrónicos han aumentado su popularidad entre los jóvenes y adultos en muchas partes del mundo, incluida Europa. La cada vez más creciente evidencia indica que los aerosoles de los cigarrillos electrónicos contienen compuestos peligrosos, que incluyen partículas finas ($PM_{2.5}$), nicotina y nitrosaminas específicas del tabaco (TSNAs), que amenazan la salud de los usuarios y de las personas expuestas pasivamente. Sin embargo, la investigación sobre la exposición pasiva al aerosol del cigarrillo electrónico (ACE) todavía es limitada, lo que es particularmente importante para justificar si el uso del cigarrillo electrónico genera beneficios netos para la salud de la población.

**Objetivos:** El objetivo general de esta tesis es evaluar la exposición al ACE en la población europea desde una perspectiva política, a nivel poblacional y a nivel individual. La tesis tiene los siguientes objetivos específicos: 1) examinar las legislaciones nacionales y subnacionales que regulan el uso de cigarrillos electrónicos en lugares públicos y privados en los países de la Región Europea de la Organización Mundial de la Salud (OMS); 2) evaluar el alcance de la exposición de la población al ACE en diferentes lugares públicos y privados en países europeos; 3) caracterizar la exposición personal y ambiental al ACE en entornos cerrados en condiciones controladas que simulan las condiciones de la vida real; y por último, 4) caracterizar la exposición personal y ambiental al ACE en condiciones de la vida real.

**Métodos:** Se realizaron cinco estudios para cumplir con los objetivos de esta tesis. Para lograr el primer objetivo específico, se realizó una encuesta entre expertos en políticas de salud de varios países de la Región de Europa de la OMS para recopilar datos sobre las regulaciones nacionales y subnacionales relacionadas con el uso de cigarrillos electrónicos en lugares públicos y privados. El segundo objetivo se logró mediante la realización de dos encuestas en países europeos para recopilar datos sobre el uso de cigarrillos electrónicos en lugares al aire libre y la exposición autoinformada de la población al ACE. Para el tercer objetivo, se llevó a cabo un estudio experimental controlado en una habitación y un automóvil cerrados para evaluar marcadores aéreos y biológicos de la exposición breve al ACE en ambientes interiores. Por último, el cuarto objetivo consistió en un estudio observacional en hogares de usuarios de cigarrillos electrónicos en varios países europeos para investigar los marcadores aéreos de exposición al ACE en ambientes interiores y biomarcadores en personas no usuarias que viven en estos hogares.

**Resultados:** Veintiocho de los 48 (58,3%) países de la Región de Europa de la OMS regulaban el uso de cigarrillos electrónicos a nivel nacional, y los Estados Miembros (EM) de la Unión Europea (UE) tenían una proporción significativamente mayor (73,1%) de países que habían adoptado una legislación sobre el uso de cigarrillos electrónicos a nivel nacional en comparación con otros Estados de fuera de la UE (40,9%). El número de lugares regulados por la legislación del país sobre el uso de cigarrillos electrónicos se asoció con la prevalencia de tabaquismo y el nivel de ingresos del país. Nuestra encuesta en 11 países europeos sugiere que el lugar al aire libre con mayor visibilidad de uso de cigarrillos electrónicos fueron las áreas al aire libre de los locales de restauración (21,3% de los locales). Aunque de manera limitada, se observaron personas usando cigarrillos electrónicos en lugares frecuentados por niños, como en entradas a escuelas (11,0% de las entradas) y en parques infantiles (4,0% de parques infantiles). Además, nuestro estudio poblacional muestra que el 16,0% de personas no usuarias de cigarrillos electrónicos en 12 países europeos estuvieron expuestas al ACE en cualquier espacio interior al menos una vez por semana, con una duración media de exposición de 43 minutos/día. La prevalencia de la exposición al ACE variaba según la prevalencia de uso de cigarrillos electrónicos en el país y según la región geográfica. La exposición al ACE entre las personas no usuarias de cigarrillos electrónicos ocurría con mayor probabilidad en hombres, en grupos de edad jóvenes, en grupos con mayor nivel educativo, exusuarios de cigarrillos electrónicos, fumadores actuales, aquellos que percibían el ACE como inofensivo y entre aquellos que vivían en países con una mayor prevalencia de uso de cigarrillos electrónicos. A partir de nuestro estudio experimental, encontramos que la concentración de $PM_{2.5}$ se multiplicó aproximadamente por dos durante el uso de cigarrillos electrónicos durante un período breve (30 minutos) en comparación con el nivel basal en una habitación y en un automóvil en condiciones controladas, pero la concentración de nicotina en el aire permaneció baja durante todo el experimento. Aunque las concentraciones de biomarcadores de exposición al ACE (es decir, nicotina, cotinina, 3'-OH-cotinina, nornicotina, TSNAs, PG y glicerol) medidos en muestras de saliva de personas no usuarias de cigarrillos electrónicos estuvieron en su mayoría por debajo de sus límites de cuantificación después del uso de cigarrillos electrónicos en esos lugares, estas personas refirieron experimentar síntomas de irritación aguda, como sequedad de ojos, garganta y nariz, luego de la exposición breve al ACE. Por otra parte, nuestro estudio observacional muestra que la concentración de nicotina en el aire de los hogares de usuarios de cigarrillos electrónicos fue significativamente más alta que la encontrada en hogares donde no se usaban cigarrillos electrónicos, mientras que la concentración de $PM_{2.5}$ fue similar en ambos tipos de hogares. Asimismo, se encontró que las concentraciones de algunos biomarcadores de exposición al ACE, como nicotina, cotinina, 3'-OH-cotinina, 1,2-PG en saliva y cobalto en muestras de orina de personas no usuarias de cigarrillos electrónicos que vivían con los usuarios era superior a las concentraciones observadas en los participantes que vivían en hogares donde no se usaban cigarrillos electrónicos.

**Conclusiones:** Esta tesis muestra que el uso de cigarrillos electrónicos conlleva cierta exposición ambiental y personal al ACE, y puede poner en riesgo la salud de los expuestos a largo plazo. Dado que la exposición al ACE a nivel poblacional en Europa no fue insignificante, y que no se ha adoptado una legislación amplia sobre el uso de cigarrillos electrónicos en los países europeos, los gobiernos deberían hacer más esfuerzos para proteger a las personas expuestas involuntariamente, en particular a grupos vulnerables como los jóvenes, mediante la inclusión de los cigarrillos electrónicos en las políticas libres de humo.

# INTRODUCTION

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## Definition of Electronic Cigarettes

Electronic cigarette, also known as e-cigarette or vape, is a type of battery-powered electronic nicotine delivery systems (ENDS) or electronic non-nicotine delivery systems (ENNDS) that vaporise a liquid (also called e-liquid) into an aerosol (1). Unlike conventional cigarettes, e-cigarettes use does not generate any combustion process. Instead, it heats the e-liquid containing nicotine and flavours to create an aerosol inhaled by the user (1). E-cigarettes also differ from heated tobacco products (HTPs) as the former do not heat tobacco as HTPs do (2), although most e-cigarettes also emit tobacco-related components, such as nicotine and tobacco-specific nitrosamines (TSNAs).

The invention of modern e-cigarette has been often credited to Chinese pharmacist Hon Lik in 2003, but the development of e-cigarette systems has been carried out by tobacco companies since at least 1963 (3). Generally, an e-cigarette device consists of a battery and a cartridge containing an atomizer to heat the e-liquid (Figure 1). Since entering the market, e-cigarettes have been evolving into different types. Figure 2 shows the development of the first three e-cigarette types. The earliest type, called the first generation, resembles a combustible cigarette and is not rechargeable or refillable, while the newer versions (the second and third generations) have rechargeable batteries and refillable reservoirs (tanks) that allow users to purchase and mix different e-liquids, even with illicit drugs, including cannabis, ecstasy, and cocaine (1,4). The last type of e-cigarettes entering the market (the fourth generation, Figure 3), which resembles USB sticks, is called “pod”. The surge of these pod-based e-cigarettes (e.g., JUUL), especially the disposable devices (e.g., Puff Bar, Figure 4), has been concerning given their attractiveness to youth (5–8).

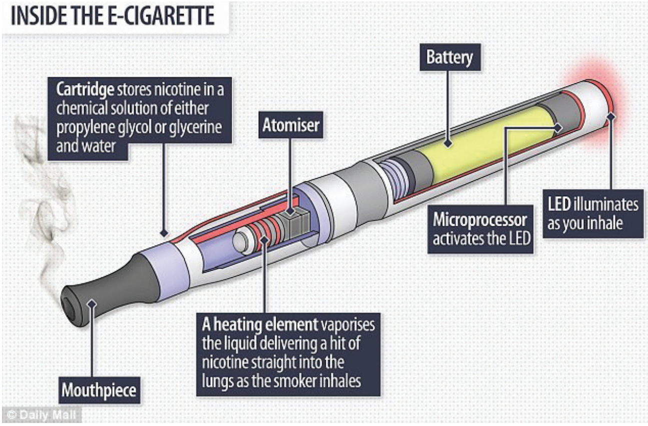


Figure 1. Parts of an electronic cigarette. Image source: Daily Mail Online (9)

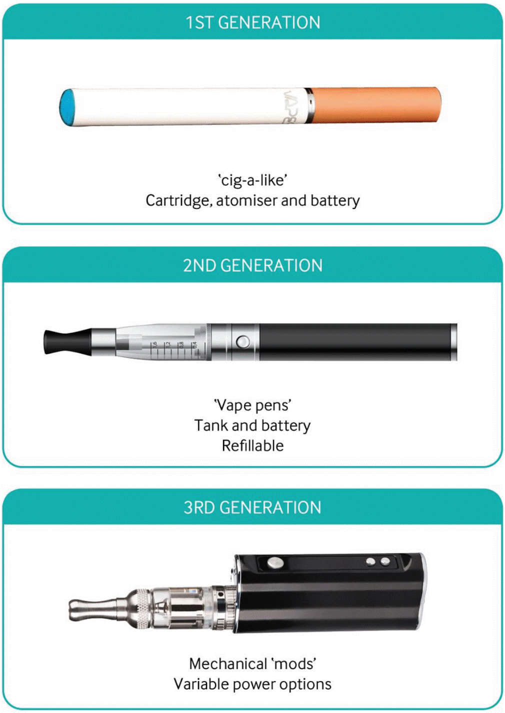


Figure 2. The first, second, and third generations of electronic cigarettes. Image source: BMJ (10)


Figure 3. JUUL, the most popular brand of electronic cigarette fourth generation.
Image source: NEJM (7)


Figure 4. Puff Bars with their attractive flavours and appearances.
Image source: Tobacco Control (8)

E-liquids contain a wide variety of chemicals already identified in combustible cigarette smoke and are considered harmful constituents. A review study identified 60 compounds present in e-liquids, including benzene, diacetyl, formaldehyde, metal elements, propylene glycol (PG), glycerine, nicotine, N-nitrosonornicotine (NNN), nicotine-derived nitrosamine ketone (NNK) and flavouring agents (11). Although e-liquids without nicotine are available, most of the products in the market contain nicotine (12,13). The nicotine content of commercially available e-liquids varies from low to high, commonly ranged from 12 to 18 mg/ml, but may reach as high as 60 mg/ml, depending on the locations of purchase made (14–16). However, the inaccuracy in nicotine labelling has been widely found. A systematic review of 20 studies on nicotine concentration analysis in e-liquid samples worldwide has shown that 48.3% of samples were deviated more than 10% above or below the labelled nicotine. Even among those labelled as nicotine-free (0 mg/ml), 50.9% actually contained detectable nicotine up to 23.9 mg/ml (17). Some concerns over inadvertent nicotine exposure among youth have risen as more than a third of adolescents were unaware of the nicotine concentration in their e-liquid, as shown by a study in the United States (US) (18). However, it is important to note that low nicotine concentrations in e-liquid may not be translated into less harm for users and bystanders. The users of lower nicotine content engaged in compensatory behaviour, such as a higher number and duration of puff, thus, consumed more e-liquid, and consequently, users had a stronger urge to use the e-cigarette than those using higher nicotine levels (19,20). The use of salt-based nicotine (benzoic acid added) in the e-liquid of many pod-based e-cigarettes, including JUUL, can boost the addictiveness of the e-cigarettes with low concentration given the ability of nicotine salt formulations to deliver nicotine dose without aversive user experiences, such as harshness and bitterness (7). Consumption of lower nicotine concentration also exposes users to carcinogenic compounds, such as formaldehyde and acetaldehyde (19,21).

High variability of e-liquid contents, product characteristics, and functioning are available as e-cigarette types and systems are rapidly evolving (22,23). By 2014, 466 brands of e-cigarettes and 7764 unique flavours in e-liquids were identified in online retailers worldwide, which expanded to over 15,000 flavours by 2017, according to a website survey (24,25). Flavours in e-liquids, which predominantly are tobacco, menthol/mint, fruit, dessert/candy flavours, are an important factor in e-cigarette use as they are associated with topography patterns, widely appealing to consumers, especially to young people, and being the reasons for using e-cigarettes (26,27). This rapid evolution of e-cigarette and e-liquid products may affect the actual chemical and particle emission in the aerosols and add the complexities of the product regulation.

# Electronic cigarette use

The global market of e-cigarettes has grown massively in the past few years and is estimated to worth 37.4 billion USD by 2025 (28). The immense growth of the e-cigarette market is mainly due to the rising popularity of e-cigarettes around the world with the increasing use both in youth and adults. In the US, an epidemic of e-cigarette use in youth has occurred as the prevalence substantially increased by 78% from 2017 to 2018 (29,30). Even from 2017 to 2019, the prevalence of 30-day nicotine e-cigarette use among youth in the country was doubled (31). An upward trend was also observed among youth in Canada, where more than 70% increase occurred within a year from 2017 to 2018 (32). A recent Eurobarometer report shows that the prevalence of people aged ≥ 15 years who have at least tried these products in 27 European Union (EU) Member States (MS) and the United Kingdom (UK) increased from 12% in 2014 to 14% in 2020, and more than half of e-cigarette users used the products, with or without nicotine, every day (33). The report also reveals a higher proportion of younger people who have at least tried e-cigarettes than the older counterparts. Indeed, e-cigarette use among youth aged 13-15 years in some European countries was shown to increase markedly over the years, according to the latest report from Global Youth Tobacco Survey (30). The report reveals that in Italy, the prevalence of current e-cigarette use increased from 8.4% in 2014 to 17.5% in 2018, and in Georgia from 5.7% in 2014 to 13.2% in 2017, while in Latvia, it was 9.1% in 2011 and 18% in 2019. Another data from the UK shows that the current e-cigarette use among adolescents has more than doubled from 2014 to 2018 (34).

In Europe, e-cigarette use has been frequently observed in indoor places where smoking is typically banned, such as workplaces, bars, restaurants, and train and metro stations (35–37). Even in workplaces with smoke-free policies but permitted e-cigarette use, the rate of cigarette smoking was higher than that was found in workplaces with comprehensive policies that included e-cigarette use ban, as has been shown by a study in Japan (38). Evading smoke-free regulation has been reported by e-cigarette users as one of the main reasons for the use of e-cigarettes (39–41). Indeed, the levels of support for the ban of e-cigarette use in public places in the EU were lower among those who used e-cigarettes to circumvent smoke-free regulations (42).

# Consequences of electronic cigarette use on users and the exposed population

Similar to e-liquids, e-cigarette aerosol consists of a vast array of constituents, such as particulate matter (PM), toxic chemicals, including nicotine, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (NNN, NNK), and metals, which are associated with harmful effects in humans (11,21,43). The number of chemicals identified in e-cigarette aerosol reaches up to 47 compounds, 22 of which are also present in e-liquids (11). Some of them, such as nicotine and metals, have been even identified at comparable or higher levels than those found in combustible cigarettes (44–46). The smaller particle size of e-cigarette aerosol may penetrate deeper into the lungs and generate more severe disease (47,48). Thus, e-cigarettes are not harmless and not necessarily safer than combustible cigarettes. Nevertheless, e-cigarette aerosol has been often claimed as “water vapour” making it perceived as benign (49).

Many studies have documented the adverse health effects of e-cigarette use among users. The use of e-cigarettes, with or without nicotine, may impair the primary human airway epithelial cells of young, healthy non-smokers that made them prone to respiratory virus infection (50). The findings are in line with subsequent studies on respiratory effects of e-cigarettes, which suggest that there are measurable adverse biologic effects on organ and cellular health in vitro, in animals, and humans (51–53).

A recent review and cohort studies showed that health effects related to e-cigarette use include respiratory conditions such as acute lung injury syndrome, chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis, and asthma, as well as non-respiratory diseases such as acute intoxication, traumatic and thermal injuries (53–56). In users who also smoked combustible cigarettes (dual users), e-cigarette use has been found to cause immediate respiratory mechanical, and inflammatory consequences, with more severe effects in asthmatic smokers (57). Even after controlling for cigarette smoking, marijuana use, and other confounding factors, ever and current e-cigarette use was still significantly associated with asthma in US adolescents (58). Given the presence of nicotine in most e-liquids, even in some e-liquids labelled without nicotine ingredient, e-cigarette use results in symptoms of dependence that may be more addictive than combustible cigarettes (23,59) and may impair brain function in young users (60).

Apart from the health risks for individual users, e-cigarettes may also have some impact on tobacco use. E-cigarette use has been associated with an increased risk of cigarette smoking relapse among recent and long-term former smokers in the US (61), leading to dual-using with combustible cigarettes, with more detrimental effects to health (53), and renormalisation of tobacco smoking (62). Evidence shows that e-cigarette use might undermine the long-term efforts to denormalise smoking as a gateway to tobacco smoking and lead to other substance use among youth by leading them to initiate alcohol and marijuana use (63–65).

The phenomenon highlights the potential threat that e-cigarettes pose to vulnerable population groups such as young users. Youth have been rapidly adopting e-cigarettes because of the devices' novelty and thousands of flavours (27). The compact design of the latest model of e-cigarettes (e.g., pod-based e-cigarettes) enables stealth use of the devices, even in prohibited areas such as school classrooms (66). The popularity of e-cigarettes among young people, despite evidence showing they are addictive and harmful to developing brains and contain toxic chemicals, was related to the controversial e-cigarette industry marketing tactics that appeal to young audience (67,68) and have led to many e-cigarette lawsuits filed by mostly parents of underage consumers who were unaware of the side effects of e-cigarette use (69).

E-cigarette use has been deemed to be closely related to the recent health crisis. In 2019, there was an outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI) in the US. As of 18$^{th}$ February 2020, a total of 2,807 were hospitalised for EVALI cases across the US, 68 of which died. More than half (52%) of the EVALI hospitalised patients were under 25 years old, according to a report per 14$^{th}$ January 2020 (70). Vitamin E acetate used as a diluent in tetrahydrocannabinol e-liquid has been found to be the primary aetiology of EVALI (70). Yet, a subsequent study in an animal model suggests that EVALI-like condition occurred after the use of e-cigarettes at high power, without tetrahydrocannabinol, vitamin E, or nicotine (71). In the context of the current coronavirus disease 2019 (COVID-19) pandemic, a study conducted among adolescents and young adults in the US has found that e-cigarette use was a significant risk factor for the disease (72). Another data from the country shows that a higher state-wide e-cigarette use prevalence was significantly associated with higher COVID-19 cases and death on a state level (73). The evidence was in accordance with prior preclinical data, which suggests that e-cigarette aerosol, independent of nicotine, disrupts alveolar surfactant homeostasis and provokes lung inflammation, which may predispose e-cigarette users to poor COVID-19 outcomes (74).

The widespread use of e-cigarettes may be partly explained by the strong claims embraced by proponents of e-cigarettes, who suggested the devices as a safer alternative to conventional cigarettes and, hence, as a tobacco harm reduction strategy (34). The harm reduction approach to curb tobacco smoking has been widely discussed, especially since a report commissioned by Public Health England in 2015 asserted that e-cigarettes are 95% less harmful than combustible cigarettes (34). However, the estimate, which has been cited very often by e-cigarette advocates and media, was mainly based on a hard evidence-lacking study in 2013 where a group of experts assigned the relative harms of nicotine-containing products and concluded that e-cigarettes were substantially less harmful than combustible cigarettes (75). At that time, there was limited evidence for the harms of e-cigarettes, which the authors of the article acknowledged as a limitation of the study (75). The problematic oft-cited evidence of the relative harms of e-cigarettes has been refuted by other researchers, given the accumulating evidence of the increased prevalence of e-cigarette use and potential harms of e-cigarettes (76).

There has also been a claim suggesting that e-cigarettes can help smokers quit smoking. However, recent evidence do not support the claim had e-cigarettes were used as consumer products, which is currently the actual pattern of use in the real world (77). Under medical supervision, as shown in a randomised clinical trial study, e-cigarettes were slightly more effective than nicotine replacement therapy for smoking cessation, but a majority (80%) of e-cigarette users remained using e-cigarette for a year, which raises concern over the long-term addiction and safety of the devices (78). Furthermore, some studies assert that adults were trying and using e-cigarettes not only because they deemed the devices a safer alternative to combustible cigarettes, but also to evade the smoke-free laws conveniently (37,38).

# Secondhand exposure to aerosol from e-cigarettes

Secondhand exposure to aerosol from e-cigarettes (SHA) originates from the exhaled aerosol emitted by e-cigarette use. Unlike secondhand smoke (SHS), which is also generated from the side-stream of tobacco smoking, SHA only comes from the exhaled aerosol since activated e-cigarette produces little to no side-stream emissions (79). However, SHA is known to contain toxicants that were also present in e-cigarette aerosol inhaled by the users, such as nicotine, PM (ultrafine particles, particles with diameter size of 2.5 μm or less [$PM_{2.5}$], and 10 μm or less [$PM_{10}$]), VOCs, PG, vegetable glycerine or glycerol, metals, TSNAs, and flavourings (23,80–83).

There is solid evidence showing that e-cigarette use deteriorates indoor air quality by emitting some pollutants. Airborne nicotine concentration, for instance, was found to increase after e-cigarette use sessions during an experimental study in a room (80,84) and in some observational studies inside homes of e-cigarette users (85), e-cigarette convention events (86,87), vape shops (88,89), and even their neighbouring businesses (89). The concentration of $PM_{2.5}$ also markedly increased during e-cigarette use in settings such as office rooms (83,84,90), homes (81,91), cars (91), e-cigarette events (86,92), and vape shops (88,89,93) and may travel to their neighbouring spaces (89). The chemicals present in SHA in the indoor environment, such as formaldehyde, could be taken up by bystanders through inhalation and dermal exposure with the worst estimation of 5.7% and 6.4% of exhaled formaldehyde, respectively (94). It has been shown that bystanders absorbed nicotine from the e-cigarette's aerosol at the same level as those absorbed from SHS (85). While particles' diameters inhaled by active e-cigarette users were commonly reported to be larger than 150 nm, the diameters of aerosols in SHA were mainly ultrafine particles (smaller than 100 nm), with a unimodal peak around 30-40 nm. Most of them will deposit in the lower airways (alveolar), causing potential health effects on bystanders passively exposed (95).

Therefore, e-cigarette use may have harmful effects not only on users but also on bystanders. Some studies found that short-term exposure to SHA may cause headache, dry mouth, ocular, nasal, and airway irritation symptoms, a reduced respiratory function, induce nicotine's systemic effects, such as increased heart rate and systolic blood pressure, and increase risk of tumours in upper respiratory tract of e-cigarette non-users (80,96,97). Exposure to SHA may worsen the asthma symptoms in youth with asthma and even was associated with higher odds of asthma symptoms among adolescents who were not using e-cigarette and not smoking tobacco products (98,99). Although there is still a lack of evidence on the long-term health effects of SHA, the constituents of e-cigarettes have been known to cause adverse health effects. For instance, PM can induce cardiovascular, respiratory diseases (100), diabetes, and cancers (101), and exposure to nicotine may cause nicotine-related diseases, like cardiovascular diseases and impaired brain function (60,85,102,103). Moreover, TSNAs, such as NNN and NNK, and carbonyl compounds, such as formaldehyde and acetaldehyde, which were identified in e-cigarette aerosol (21,104), are carcinogenic (105–108). The solvents in e-liquids, PG and glycerol, were found to form formaldehyde and aldehyde by heating process regardless of the e-cigarette device attributes, which, thus, may also contribute to the adverse health effects of those carbonyl compounds (109–112).

Unfortunately, the latest evidence shows that the extent of the population's exposure to the SHA is not negligible. In the US, for example, exposure to SHA in indoor or outdoor public places was reported by nearly one in three (33.2%) middle and high-school students in 2018, rising by 7.5% in just one year (113). Thirty-seven percent of smokers, who were e-cigarette non-users, were exposed to SHA in six European countries in 2016, ranging from 18% in Spain to 63% in Greece (35).

Similar to e-cigarette use, exposure to SHA might influence social perception towards nicotine product use, which may hamper the progress in tobacco control. Seeing e-cigarette use or being exposed to SHA in public places has been found to renormalise smoking among youth (113,114). Even among adolescents not susceptible to future cigarette smoking, exposure to SHA in indoor or outdoor public places was associated with susceptibility to using e-cigarettes (115). The public misperception about the harms of e-cigarette use and SHA may encourage the uptake of e-cigarettes and their use in places where children are likely to be present (114,116,117).

# Regulation of electronic cigarette use

While regulation of e-cigarettes is complex because it depends on its definition as a product, the above evidence suggests that regulatory approaches are needed to prevent involuntary exposure to SHA. Studies in the US demonstrate that e-cigarette use restrictions, either at states (118,119) or at the household level (120), may effectively reduce e-cigarette use prevalence among adults and youth. Workplaces that exempted e-cigarettes in their smoke-free indoor environment policies were not only associated with higher rates of e-cigarette use but also tobacco smoking and HTPs use (38). A complete e-cigarette use ban at workplaces has been found to lower the risk of exposure to SHA among non-users in such locations (120).

Unlike tobacco smoking, e-cigarette use in the presence of bystanders is still deemed socially acceptable. The majority of e-cigarette users surveyed by an online questionnaire reported unrestricted use of their e-cigarettes in places where smoking was typically banned (121), and most of the e-cigarette users surveyed among smokers in six European countries felt comfortable or neutral to use their devices around others (35). However, e-cigarette use prohibition, especially in smoke-free places, was highly supported by the general public, with around 70-85% support from US adults and EU non-smokers (42,122,123). Even among current and former smokers in the EU, e-cigarette use ban in public places was supported by 45.7% and 63.1% of each group, respectively (42).

The World Health Organization (WHO) recommends to Parties of the Framework Convention on Tobacco Control (FCTC) to regulate e-cigarettes, including banning the use of e-cigarettes in places where combustible cigarettes use is prohibited as an effort to protect bystanders from exposure to SHA (124). In Europe, Article 20 in the EU Tobacco Products Directive (EU TPD) 2014/40/EU stipulates provisions on the safety and quality specifications for e-cigarettes, which address the concern over the diversity of the product characteristics sold in the EU market (125). Nevertheless, the EU TPD did not include any e-cigarette use measures; the power to regulate e-cigarette use was given to the EU MS. However, the European Commission has recently considered updating the EU recommendations on smoke-free environments by 2023 to extend the coverage of smoke-free environments policy to novel tobacco products, including e-cigarettes, as part of a strategy to reduce smoking prevalence across the region to 5% by 2040 (126). It means the recommendations will call on EU MS to forbid e-cigarette use in public places and workplaces. The latest available study shows that there had been 25 countries globally enacting e-cigarette use legislation at the national level in 2014-2016 (127). In England, e-cigarette use indoors was prohibited in all acute non-specialist public-funded health centres (i.e., NHS Trusts), and all except one higher education institution, but permitted its use in outdoor areas of the health centres and 75% of higher education institutions (128).

# Justification of the investigation

Bystanders, especially the vulnerable groups such as children and people with comorbidities, are important consideration factors while making a policy for e-cigarette use (129). That is because the short- and long-term effects that e-cigarette use has on bystanders may implicate in overall population's health. Using a simulation of population model, a study predicted that even with very optimistic assumptions about the effects of e-cigarettes on smoking cessation and a 95% reduction in risk associated with e-cigarette use compared to smoking conventional cigarettes, the availability of e-cigarettes is still associated with net population harm in the US: 1.5 million years of life lost based on e-cigarette use patterns in 2014 (130). However, the study did not take into account the effects of exposure to SHA among bystanders, given the limited evidence available at that time. That further justifies the need to investigate the effects of SHA on bystanders to answer the big question of whether e-cigarette use will result in net health benefit or harm in the population.

Despite the growing body of evidence showing that SHA chemicals are not harmless and, hence, pose a new challenge to public health, research on SHA is a considerably emerging study area. At the time of completing this doctoral thesis, there was limited evidence on personal and environmental exposure to SHA. As noted in the previous section, past studies on SHA exposure were vastly based on the measurement of indoor air quality and biomarkers that were conducted by using either machine-generated aerosol, in highly controlled conditions at a laboratory, in a real-world setting but poorly controlled, or in an extreme scenario such as e-cigarette events and vape shops that did not represent common use in real life. A study to better characterise the bystander's exposure to SHA in confined settings was needed. On the other hand, a further study on exposure to SHA under real-life conditions was also warranted. There was also a need to quantify such exposure in the population. However, there was no study on exposure to SHA among the general population in Europe. Data from European countries on this issue will allow a better understanding of the problem's magnitude in the European population.

It is also important to assess the regulation surrounding e-cigarette use in public and private places in Europe because it will enable us to analyse the extent of the harm from SHA perceived by the government of the respective countries. Moreover, since there was no common regulation on e-cigarette use in Europe, a comparison across countries about restrictions in e-cigarette use in public and private places was needed by which we might understand the similarities and differences of the regulations and factors driving such phenomenon. However, only a few studies have examined specific national regulations dedicated to protecting bystanders from exposure to SHA.

This thesis may contribute to the adoption and implementation of tobacco control and overall public health strategy in Europe, as countries in the WHO European region, including EU MS, are committed to achieving the targets in Sustainable Development Goal 3.4 by reducing one-third of premature mortality from non-communicable diseases, and promoting mental health and well-being by 2030 (131,132). To provide evidence-based recommendations for e-cigarette products in Europe, this thesis produced several studies that assessed the SHA exposure in bystanders in the region from a policy perspective to the ground reality as they are keys to see the holistic picture of the problem. This thesis linked the findings from the different studies altogether with a focus on bystanders' end.

# HYPOTHESES

# HYPOTHESES

The hypotheses of this PhD thesis are:

1. There is a significant difference in the adoption status of e-cigarette use legislations among countries within the WHO European Region according to country-specific factors.
2. Country-specific factors, such as country's EU membership status, income level, smoking prevalence, and tobacco control performance, are all associated with the number of places regulated by country's e-cigarette use legislation.
3. E-cigarette use in locations frequented by minors (i.e., children) is less visible than in other public places.
4. Population groups with a lower socioeconomic status in European countries have a higher prevalence of exposure to SHA.
5. SHA in controlled confined settings significantly increases the concentrations of $PM_{2.5}$ and airborne nicotine.
6. SHA in controlled confined settings significantly increases the concentrations of biomarkers of SHA exposure among bystanders.
7. SHA in a real-life condition significantly increases the concentrations of $PM_{2.5}$ and airborne nicotine.
8. SHA in a real-life condition significantly increases the concentrations of biomarkers of SHA exposure among bystanders.

AIM

# AIM

This thesis aims to evaluate the exposure to SHA in the European population from a policy perspective, population level, and individual level. To meet the aim, this doctoral thesis had four main objectives with their corresponding specific objectives:

1. To examine the national and subnational legislations regulating the use of e-cigarettes in public and private places across the WHO European Region countries.
   a. To describe and compare the legislations regarding e-cigarette use restrictions in public and private places.
   b. To identify country-specific factors that correlate to the adoption of the legislations.
   c. To evaluate the alignment of the legislations with the recommendations by the WHO FCTC on the regulation of e-cigarette use in enclosed settings.

2. To assess the extent of the population's exposure to SHA in different public and private settings in European countries.
   a. To identify the prevalence of exposure to SHA among e-cigarette non-users in different indoor settings across European countries.
   b. To assess the relationship between sociodemographic factors at individual and country-level and exposure to SHA in different indoor settings across European countries.
   c. To identify the spread of e-cigarette use in different outdoor settings in European countries.

3. To characterise personal and environmental exposure to SHA in controlled confined settings that emulate real-life conditions.
   a. To assess the environmental exposure to SHA, by measuring the $PM_{2.5}$ and airborne nicotine concentrations before, during, and after short-term use of an e-cigarette in a room and car.
   b. To assess the personal exposure to SHA, by measuring the concentrations of various biomarkers of SHA exposure among bystanders before and after short-term use of an e-cigarette in a room and car.
   c. To investigate the health symptoms that occurred in bystanders before and after short-term exposure to SHA.

4. To characterise personal and environmental exposure to SHA in real-life conditions.
    a. To measure the concentrations of $PM_{2.5}$ and airborne nicotine in e-cigarette users' homes in four European countries.
    b. To analyse the differences in the concentrations of $PM_{2.5}$ and airborne nicotine in e-cigarette users' homes according to the pattern of e-cigarette use at homes in four European countries.
    c. To measure the biomarkers of SHA exposure concentrations among bystanders living with e-cigarette users in four European countries.

# METHODS

# METHODS

## Study designs

Five studies were performed to achieve the aim of this thesis. Four of them were observational studies conducted in multiple European countries from 2017 to 2019, while another one was an experimental study performed in Barcelona (Catalonia, Spain) in 2019. All of the studies were developed in the context of the TackSHS Project ("Tackling secondhand tobacco smoke and e-cigarette emissions: exposure assessment, novel interventions, impact on lung diseases and economic burden in diverse European populations"; www.tackshs.eu), which comprehensively assessed the impact of SHS and SHA on European population (133).

# Data sources

This thesis mainly used primary data collected from the TackSHS project, including survey studies among tobacco-related product users, e-cigarette users, and non-users, and field studies collecting data of environmental and biological markers of SHS and SHA in room, car, and home settings. Data from an *ad hoc* survey among in-country health policy experts of multiple European countries was also collected to complete this thesis. Additionally, this thesis utilised secondary data from reports, such as the 2016 Tobacco Control Scale (134), 2017 WHO Report on the Global Tobacco Epidemic (135), and 2015 Global Burden of Disease Study (136), and publicly accessible countries' national laws.

## Regulatory approaches to protect bystanders from exposure to SHA in European countries (RASHA-E): a survey to in-country informants

RASHA-E was a cross-sectional study with the general aim to assess regulations surrounding e-cigarette use in countries belonging to the WHO European Region. To meet the objective, a survey was performed to in-country health policy experts from 53 countries of the WHO European Region, comprising 28 EU MS and 25 non-EU countries. Data was collected from May to July 2018, using an online self-administered questionnaire (Annex 1) developed *ad-hoc* by a research team at the Catalan Institute of Oncology (Spain) and WHO European Region Office (Denmark). The questionnaire, which was available in English and Russian, collected information on the classification of e-cigarettes in the national regulation, national and subnational legislation of e-cigarette use in indoor and outdoor places, transposition status of Article 20 of TPD 2014/40/EU, challenges in adopting the regulation and the level of compliance.

This thesis used the data from the RASHA-E study that focused on e-cigarette use legislation at the national and sub-national level, applied to 27 public and private places, both indoors and outdoors, such as educational facilities, hospital or healthcare facilities, workplaces, private vehicles, and homes. Information on levels of difficulties in adopting the legislation, public support and compliance to the legislation was also analysed in this thesis.

## TackSHS Project

The overall aim of the TackSHS project was to comprehensively investigate the impact that SHS and SHA have on the respiratory health of the European population and how the impact varies according to socioeconomic and other characteristics (133). The 4-year project was coordinated by a research team from the Catalan Institute of Oncology - Bellvitge Biomedical Research Institute (ICO-IDIBELL) in Spain and involved 11 work-packages (WPs). Each WP had specific objectives and approaches. This thesis used data from three WPs of the TackSHS project: an environmental assessment of SHS exposure in private and outdoor settings in Europe (WP2), a pan-European population survey on SHS and SHA exposure (WP3), and an assessment of environmental and bystanders' exposure to SHA in controlled settings and in real-life conditions (WP8).

### Environmental assessment of SHS exposure in private and outdoor settings in Europe (WP2)

WP2 was a cross-sectional study led by the Public Health Agency of Barcelona (ASPB, Spain), in which the overall objective was to evaluate SHS exposure in private and outdoor settings in Europe (133). WP2 was performed from March 2017 to October 2018 in major cities of 11 European countries (Bulgaria, England, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Romania, and Spain), representing geographical, legislative, and cultural variations across the EU. Around 1,000 environmental measurements were collected, including 180 measurements from homes in 9 countries and 660 measurements in outdoor settings in the 11 countries involved; and 120 environmental measurements were collected in cars in two countries. The assessment under this WP involved airborne nicotine measurement and direct observation of tobacco-related or nicotine product use, including e-cigarette use, in the included settings.

From this WP, we used data to describe e-cigarette use outdoors, such as in children's playgrounds, schools' entrances, and terraces of hospitality venues, in the 11 European countries. The three settings were chosen as they represent outdoor locations where children are likely to present or occupied by large numbers of people. The data collection form used is presented in Annex 2.

### Pan-European survey on SHS and SHA exposure (WP3)

This WP was a cross-sectional study, led by Mario Negri Institute for Pharmacological Research - IRCCS (Italy), with the primary objective of assessing the prevalence and determinants of smoking, e-cigarette use, and exposure to SHS and SHA across Europe (133). WP3 fieldwork was started in November 2016 with the pilot study in Italy, and the main fieldwork took place between June 2017 and

October 2018 using a face-to-face survey method among approximately 12,000 individuals aged 15 years and older from 12 European countries (Bulgaria, England, France, Germany, Greece, Ireland, Italy, Latvia, Poland, Portugal, Romania, and Spain), representing the general adult population in the countries. An *ad-hoc* questionnaire was developed from existing validated questionnaires to collect information on cigarette smoking, use of e-cigarettes and HTPs, exposure to SHS and SHA in different indoor and outdoor settings, and attitudes and perceptions towards various tobacco control policies. The questionnaire is provided in Annex 3.

From this WP, we obtained data to investigate the prevalence of bystanders' exposure to SHA in public and private indoor settings, including home, workplace, public transportation, private transportation, and other indoor places (e.g., cafeterias, bars, restaurants, leisure facilities) across the 12 European countries, and its relationship with sociodemographic characteristics at individual and national level.

### Assessment of environmental and bystanders' exposure to SHA in controlled and real-life conditions (WP8)

WP8 aimed to comprehensively examine the bystanders' and environmental exposure to SHA through three sub-studies: 1) a systematic review of publications on exposure to SHA; 2) an experimental study that assessed environmental and personal exposure to SHA in controlled conditions in a car and a room; 3) an observational study to assess the environmental and personal exposure to SHA in real-life conditions at homes in four European countries (Greece, Italy, Spain, and the UK) (133). WP8 was led by the Catalan Institute of Oncology (Spain) and conducted between June to September 2019. We present data from the 2$^{nd}$ and 3$^{rd}$ sub-studies from this WP, in which environmental exposure was assessed by measuring the airborne nicotine and $PM_{2.5}$, while a wide range of biomarkers, such as nicotine, cotinine, TSNAs, PG, and glycerol, in biological samples of e-cigarette non-users and users were measured as a proxy of personal exposure assessment. WP8 also collected data on e-cigarette use and SHA patterns at homes using an *ad-hoc* questionnaire and personal diary card (see Annexes 4 and 5).

# Ethical aspects

The thesis project has received ethical approval from the Bioethical Committee of the University of Barcelona (Institutional Review Board: IRB 00003099; Annex 6). The overall TackSHS project has been approved by the Research Ethics Committee of the Hospital Universitari de Bellvitge (PR341/15; Annex 6). All of the study protocols under the project were approved by the Ethics Committee of the WP2, WP3, and WP8 coordinating centres (Annex 6) and by the national Ethics Committees in each of the participating countries. The RASHA-E study was approved by the Research Ethics Committee of the Hospital Universitari de Bellvitge (PR200/18; Annex 6). Moreover, all the studies were registered at www.ClinicalTrials.gov (NCT03150186 for WP2; NCT02928536 for WP3; NCT04140617 for WP8 experimental study; and NCT04140630 for WP8 observational study) according to the Horizon 2020 ethics guidelines (http://tackshs.eu/ethics/).

# RESULTS

# RESULTS

Table 1 shows the summary of the five scientific publications included in this PhD thesis, four of which have been published in high-impact international journals.

Table 1 Summary of publications.

| No. | Authors and title | Journal and reference | Journal IF[a] (2019) | Category, Journal rank | Cita-tions[b] |
|---|---|---|---|---|---|
| 1 | **Amalia B**, Fu M, Feliu A, Tigova O, Fayokun R, Mauer-Stender K, Fernández E. Regulation of electronic cigarette use in public and private areas in 48 countries within the WHO European Region: a survey to in-country informants | J Epidemiol. 2020; JE20200332. doi: 10.2188/jea.JE20200332 | 3.691 | Public, environmental, and occupational health, Q1 | 1 |
| 2 | **Amalia B**, Rodríguez A, Henderson E, Fu M, Continente X, Tigova O, Semple S, Clancy L, Gallus S, Fernández E. How widespread is electronic cigarette use in outdoor settings? A field check from the TackSHS project in 11 European countries | Environ Res. 2021;193:110571 | 5.715 | Public, environmental, and occupational health, Q1 (D1) | 0 |
| 3 | **Amalia B**, Liu X, Lugo A, Fu M, Odone A, van den Brandt PA, Semple S, Clancy L, Soriano JB, Fernández E, Gallus S. Exposure to secondhand aerosol of electronic cigarettes in indoor settings in 12 European countries: data from the TackSHS survey | Tob Control. 2021;30:49-56 | 6.726 | Public, environmental, and occupational health, Q1 (D1) | 8 |
| 4 | **Amalia B**, Fu M, Tigova O, Ballbé M, Castellano Y, Semple S, Clancy L, Vardavas C, López MJ, Cortés N, Pérez-Ortuño R, Pascual JA, Fernández E. Environmental and individual exposure to secondhand aerosol of electronic cigarettes in confined spaces: Results from the TackSHS Project | Indoor Air. 2021; ina.12841. doi: 10.1111/ina.12841 | 4.739 | Public, environmental, and occupational health, Q1 (D1) | 0 |

| | | | | | |
|---|---|---|---|---|---|
| 5 | **Amalia B**, Fu M, Tigova O, Ballbé M, Castillo BP, Pérez-Ortuño R, Pascual JA, Vardavas C, Vyzikidou VK, Gil F, Olmedo P, Soriano JB, López MJ, Cortés N, Boffi R, Veronese C, Gallus S, Lugo A, O'Donnell R, Dobson R, Semple S, Fernández E. Exposure to secondhand aerosol from electronic cigarettes at home: a real-life study in four European countries | In preparation | - | - | - |

[a] InCites Journal Citation Reports 2019 by Web of Science
[b] Number of articles citing the corresponding publications, up to 27 April 2021

# PAPER 1

## Regulation of electronic cigarette use in public and private areas in 48 countries within the WHO European Region: a survey to in-country informants

Beladenta Amalia, Marcela Fu, Ariadna Feliu, Olena Tigova, Ranti Fayokun, Kristina Mauer-Stender, Esteve Fernández.

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Original Article

J Epidemiol 2021

# Regulation of Electronic Cigarette Use in Public and Private Areas in 48 Countries Within the WHO European Region: A Survey to In-country Informants

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## ABSTRACT

**Background:** The objective of this study is to describe the legislation regulating the use of electronic cigarettes (e-cigarettes) in various places in European countries.

**Methods:** A survey among experts from all countries of the World Health Organization (WHO) European Region was conducted in 2018. We collected and described data on legislation regulating e-cigarette use indoors and outdoors in public and private places, the level of difficulties in adopting the legislation, and the public support and compliance. Factors associated with the legislation adoption were identified with Poisson and linear regression analyses.

**Results:** Out of 48 countries, 58.3% had legislation on e-cigarette use at the national level. Education facilities were the most regulated place (58.3% of countries), while private areas (eg, homes, cars) were the least regulated ones (39.6%). A third of countries regulated e-cigarette use indoors. Difficulty and support in adopting the national legislation and its compliance were all at a moderate level. Countries' smoking prevalence and income levels were linked to legislation adoption.

**Conclusions:** Although most WHO European Region countries had introduced e-cigarette use legislation at the national level, only a few of the legislation protect bystanders in indoor settings.

**Key words:** e-cigarettes; ENDS/ENNDS; secondhand exposure; legislation; FCTC



## INTRODUCTION

Electronic cigarettes (e-cigarettes) have gained popularity in Europe in recent years, with an increase in the prevalence of adults who have at least tried these products in the European Union (EU) Member States (MSs), from 12% in 2014 to 15% in 2017; two-thirds of them use the products every day.[1] Recent surveys in Italy and the United Kingdom have shown marked increases in current e-cigarette use amongst youth.[2,3] Moreover, 16% of non-users in European countries reported being exposed to secondhand aerosol (SHA) from e-cigarettes in indoor settings at least weekly.[4]

E-cigarette use might potentially harm e-cigarette users and bystanders, as its aerosol increases airborne concentrations of particulate matters and nicotine in indoor environments compared to background levels; also, it contains carcinogens and other substances, such as volatile organic compounds, polycyclic aromatic hydrocarbons, and metals.[5–7] Thus, exposure to SHA from e-cigarettes is not risk-free, and appropriate regulation on e-cigarette use is needed, especially to protect bystanders. Banning the use of e-cigarettes in indoor settings or, at least, where tobacco smoking is already prohibited, has been advised by The Seventh Session of Conference of the Parties (COP7) to the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) in 2016 and by the largest non-governmental tobacco control organization in Europe, the European Network for Smoking and Tobacco Prevention (ENSP).[8,9]

Studies assessing regulation on e-cigarette use in specific places are still scarce. A previous study in 2014 included very few European countries (France and the United Kingdom).[10] Thus, a broader perspective around e-cigarette use regulation in specific places is needed as it will present the opportunity to better understand the extent of the population's protection from exposure to SHA of e-cigarettes in the European countries, where such regulation is available.

Using information from in-country experts, this study aimed to assess legislation regulating the use of e-cigarettes in different

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places in WHO European Region countries, identify barriers and promoters for the adoption of the legislation, and evaluate their alignment with the regulatory option described at COP7 (FCTC/COP7/11) on the regulation of e-cigarette use in enclosed settings.

## METHODS

### Study population

Country is the unit of analysis in this ecological cross-sectional study. A survey was conducted in May–July of 2018 among in-country health policy experts (informants) from all countries of the WHO European Region, consisting of 28 EU MSs and 25 non-EU countries at that time.[11] The use of informants was determined to be appropriate to meet the objectives in assessing the level of challenge and support for passing the legislation, and its level of compliance, going beyond information about the legislation on paper.

### Questionnaire and data collection

An online questionnaire was developed and was available in English and in Russian, given that Russian-speaking countries were the most common non-English speaking countries in the WHO European Region (11 out of 50 non-English speaking countries). There were 49 questions gathering information on national and subnational legislation of e-cigarette use in several places, on challenges in adopting the legislation and its level of compliance. We sought to identify legislation as written by asking factual questions, and legislation in practice by obtaining information on specific aspects of its implementation. To test the quality and feasibility of the questionnaire, a pilot survey was conducted with informants from five countries (Denmark, Italy, Spain, Turkey, and Ukraine) that represented different geographic, demographic, and economic characteristics. Responses received from the pilot survey were validated and included in the final analysis.

At least two informants per country were provided by the ENSP and the WHO Regional Office for Europe, giving priority to representatives of non-governmental bodies in the field of tobacco control to avoid biased responses. Each informant was invited by e-mail to complete the online questionnaire within 2 weeks. If there were any discrepancies in factual questions between informants' answers from the same country, we reviewed the official legislation documents provided by informants, re-contacted them, or sought an opinion from another informant from the same country.

This study received ethical approval from the Clinical Research Ethics Committee of the Bellvitge University Hospital (Reference number: PR200/18). All informants received detailed information about the study before they provided their consent to participate.

### Measures

Countries were grouped according to the six United Nations (UN) regional groups: North Europe, West Europe, South Europe, East Europe, West Asia, and Central Asia; and to the three World Bank's income-groups: High, Upper-middle, and Lower-middle.[12]

We refer to e-cigarette use legislation as any law and written regulation regarding e-cigarette use in specific places. The availability of e-cigarette use legislation at the national and subnational levels was determined by binary questions (yes/no) and was not mutually exclusive, as countries might have e-cigarette use legislation in both levels or in either of them. We gathered information about e-cigarette use legislation separately for nicotine-containing and nicotine-free types, according to the allowance of the use of these devices with or without nicotine. Unless stated otherwise, we refer to legislation that encompasses the use of any type of e-cigarette (either nicotine-containing or nicotine-free).

We explored e-cigarette use legislation applied to a total of 27 public and private places, both indoors and outdoors, that were grouped into eight main sectors as done in a previous study[13]: health and social care; education; public places (enclosed public places, parks, children playgrounds); workplaces; hospitality venues (hotels, restaurants, bars); public transportation; private places (private vehicles and homes) and other places (eg, tunnels, sporting facilities, elevators, markets). We categorised e-cigarette use legislation into "partial ban", referring to ban with exceptions (eg, e-cigarette use in designated place only), and "total ban", meaning no exceptions to the ban.

Informants were asked to score (on a 0–5 scale) the level of difficulties encountered in adopting the e-cigarette use legislation in their country, regardless of the enactment status of the national legislation; while the scores for their perception of the level of public support and compliance with the legislation were asked only to informants from countries with legislation on e-cigarette use at the national level. For the level of difficulty variable, a higher score means more challenges experienced in the respective countries. For the level of public support and compliance, a higher score implies better support and compliance with the legislation. Informants could express the underlying reasons for the score they assigned.

To study the determinants of the adoption of e-cigarette use legislation in a country, we used the MPOWER composite score from the 2017 WHO Report on the Global Tobacco Epidemic, representing the country's tobacco control policy performance.[14] The MPOWER composite score was calculated by adding up the six scores of each MPOWER measure; thus the possible range of this score is from 6 (1 in each of the six scores) to 29 (4 in 'M' score and 5 in 'P', 'O', 'W', 'E' and 'R' scores).[15,16] We also used the national age-adjusted smoking prevalence obtained from the 2015 Global Burden of Disease Study as a predictor factor, given the strong relationship between conventional cigarette and e-cigarette use.[17]

### Data analysis

The proportion (%) of each measure within groups of countries and across all countries was estimated. Median values and their associated interquartile range (IQR) were used to estimate the number of places covered by the e-cigarette use legislation per group of countries. Mean values were calculated as an aggregated level of difficulties, public support, and compliance measure for each group of countries.

We conducted a Poisson regression analysis to identify the association of the number of places regulated by e-cigarette use legislation (dependent variable) with smoking prevalence, MPOWER score, EU membership status, and the country's income level (independent variables). A multiple linear regression analysis was performed to estimate the association between the score of the difficulties in legislation's adoption (dependent variable) and the aforementioned independent variables. Statistical significance was set at $P < 0.05$. All analyses were conducted using STATA 14.0 (StataCorp, College Station, TX, USA).

## RESULTS

Informants from 48 countries (10 Russian-speaking countries) completed the questionnaire; among them, 26 were EU MSs and 22 non-EU countries. For 26 countries, we only had one informant (eTable 1). Potential Informants from five countries (Turkmenistan, Latvia, Slovakia, Monaco, and San Marino) did not respond to the survey. No discrepancies in answers to factual questions were found among informants from the same country.

### Countries regulating e-cigarette use

Table 1 shows 28 (58.3%) countries regulated e-cigarette use at national level, and five (10.4%) countries adopted the legislation at the subnational level, two of which had no national legislation in place. EU MSs group had a significantly higher proportion of countries adopting e-cigarette use legislation at national level compared to non-EU countries (73.1% vs 40.9%). High-income countries' group had the highest proportion of countries with e-cigarette use legislation (67.9%; $P = 0.074$). There were nine (18.7%) countries prohibiting e-cigarette use regardless of the place of use (total ban); most of them were EU MSs and also high-income countries (eTable 1).

By UN regions, West Asia, East Europe, and South Europe had the highest proportions (around 60%) of countries with national legislation on e-cigarette use. E-cigarette use legislation did not significantly vary by income-level or regional group.

### E-cigarette use legislation by places

More indoor than outdoor areas were covered by national e-cigarette use legislation (31.2% vs 18.7%; $P = 0.157$), with 53.9% of the EU MSs restricting e-cigarette use in indoor settings of primary and secondary schools (Figure 1). EU MSs had a significantly higher proportion of countries restricting e-cigarette use in both indoor ($P < 0.001$) and outdoor ($P = 0.011$) areas than non-EU countries.

Education facilities were the most protected places, with almost six out of 10 countries (58.3%) having either partial or total ban on using e-cigarettes in these places, indoors or outdoors (Figure 2). Twenty-seven out of 48 countries (56.3%) regulated e-cigarette use in public transport, and 26 countries (54.2%) regulated e-cigarette use in health and social care facilities, public places, and workplaces. Apart from "other" places, private areas were the places that had the lowest coverage (39.6%) by national legislation on e-cigarette use.

**Table 1.** Countries in the World Health Organization European Region adopting legislation on electronic cigarette (e-cigarette) use[a] at the national and/or subnational level[b] according to their European Union membership status, income level, and United Nations regional group, 2018

| | E-cigarette use legislation at national level | | E-cigarette use legislation at subnational level | |
|---|---|---|---|---|
| | *n* (%) | *P*-value[c] | *n* (%) | *P*-value[c] |
| Total ($N = 48$) | 28 (58.3) | | 5 (10.4) | |
| **EU Membership** | | | | |
| EU ($N = 26$) | 19 (73.1) | 0.024 | 4 (15.4) | 0.357 |
| NON-EU ($N = 22$) | 9 (40.9) | | 1 (4.55) | |
| **Income Level** | | | | |
| H ($N = 28$) | 19 (67.9) | 0.074 | 4 (14.3) | 0.826 |
| UM ($N = 13$) | 4 (30.8) | | 1 (7.7) | |
| LM ($N = 7$) | 5 (71.4) | | 0 (0.0) | |
| **UN Regional Group** | | | | |
| WA ($N = 5$) | 3 (60.0) | 1.000 | 0 (0.0) | 0.387 |
| CA ($N = 4$) | 2 (50.0) | | 0 (0.0) | |
| NE ($N = 9$) | 5 (55.6) | | 2 (22.2) | |
| WE ($N = 7$) | 4 (57.1) | | 1 (14.3) | |
| EE ($N = 10$) | 6 (60.0) | | 2 (20.0) | |
| SE ($N = 13$) | 8 (61.5) | | 0 (0.0) | |

CA, Central Asia; EE, East Europe; EU, European Union; H, High; LM, Lower-Middle; NE, North Europe; SE, South Europe; UM, Upper-Middle; UN, United Nations; WA, West Asia; WE, West Europe.

[a]Applied for the use of any type of e-cigarettes (nicotine-containing or nicotine-free).

[b]Existence of national and subnational level legislation on e-cigarette use are not mutually exclusive; countries might have e-cigarette use legislation in both levels or in either of them.

[c]Estimated by chi-squared test or Fisher's exact test whenever appropriate.

### Number of places covered by the national legislation on e-cigarette use

Figure 3 maps a varied coverage level of national e-cigarette use legislation across WHO European Region countries. As shown in Table 2, out of 27 total places assessed, a median of 21.5 (IQR, 14.5–27.0) and 18.0 (IQR, 13.0–27.0) indoor and outdoor places were covered by national e-cigarette use legislation for e-cigarettes with and without nicotine, respectively. For both types of e-cigarettes, there were no significant differences in the median number of places according to EU membership or income level.

### Barriers, support, and compliance with the e-cigarette use legislation

On average, the level of difficulties perceived in adopting the national legislation on e-cigarette use was 2.8 (95% CI, 2.4–3.2), on a scale from 0 to 5 (Table 2). Non-EU countries reported a significantly higher level of difficulties compared to their EU counterparts (mean score of 3.4 vs 2.2, $P = 0.002$). Likewise, upper- and lower-middle income countries had the highest scores for difficulties in adopting the national e-cigarette use legislation (means: 3.3 and 3.4, respectively; $P = 0.042$). Some of the difficulties mentioned by informants were opposition from vaping "front-groups", "lobby of importers of e-cigarettes", "lack of political will", and "unclear scientific knowledge" regarding e-cigarettes at the time of legislation adoption.

The mean score of public support among countries with national legislation in place was 3.7 (95% CI, 3.3–4.1). Non-EU countries reported a significantly higher score than EU MSs (4.3 vs 3.4, $P = 0.025$). However, both groups of countries had a similar score on the compliance level (3.4 vs 3.5, $P = 0.749$). The overall score for the compliance level was moderate, at 3.5 (95% CI, 3.0–4.0).

### Factors associated with e-cigarette use legislation

After adjusting for all predictor factors measured, the number of places regulated by e-cigarette legislation in a country had a positive association with smoking prevalence in a country, while a negative association was evident with the country's income levels (Table 3). Every 1% increase in smoking prevalence in a country was significantly associated with 3% more places covered by the legislation. Compared to low-middle income countries, high-income countries had fewer regulated places ($P < 0.05$). Our adjusted model has shown that difficulties in legislation adoption by countries were not associated with any of the factors listed.

See eTable 1, eTable 2, eTable 3, and eTable 4 for the individual country results.

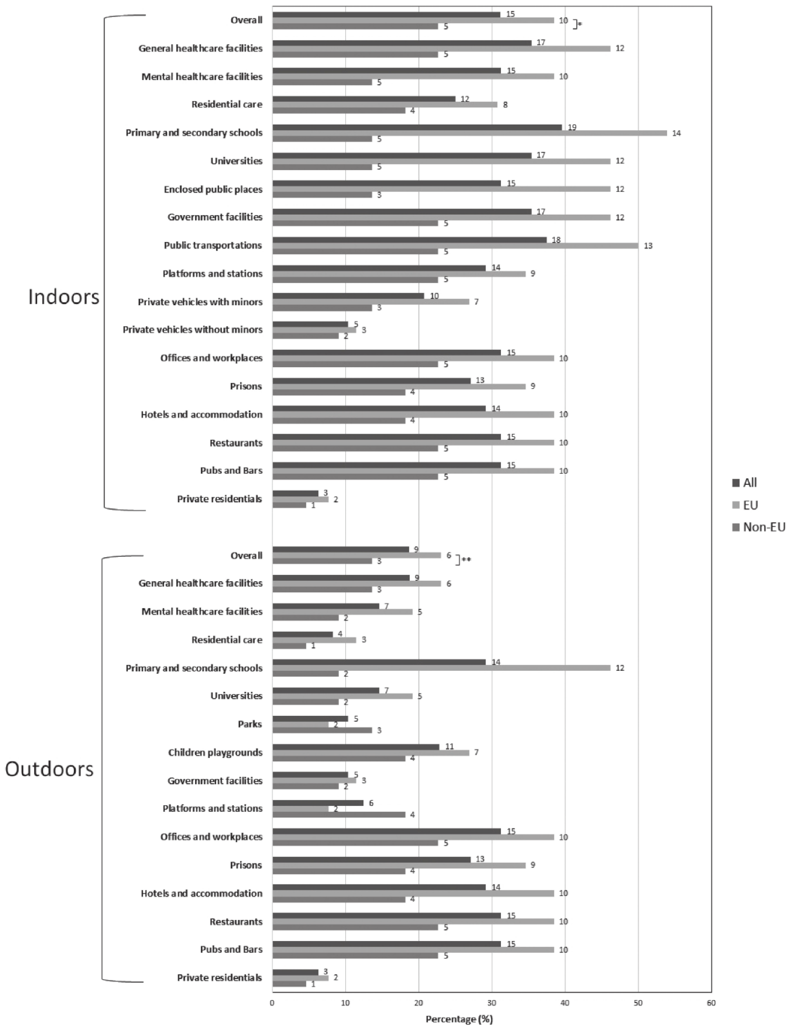


**Figure 1.** Proportion and number of countries within the World Health Organization European Region[a] restricting the use of electronic cigarettes (e-cigarettes) in indoor and outdoor places, 2018. EU, European Union. [a]Among all countries (Total $n = 48$; EU $n = 26$; Non-EU $n = 22$). Either partial or total ban for the use of any type of e-cigarettes (with or without nicotine). *EU vs Non-EU, indoors; $P < 0.001$; estimated using Kruskal-Wallis post-hoc test. **EU vs Non-EU, outdoors; $P = 0.011$; estimated using Kruskal-Wallis post-hoc test. Absolute numbers of countries are shown on the right side of each bar.

## DISCUSSION

Our data showed that there were around 60% of the 48 WHO European Region countries having any legislation on e-cigarette use, despite the growing evidence about the potential harms of SHA to bystanders and the increasing number of e-cigarette users among EU citizens.[1,5,7] We found three more countries in the Region that had enacted national e-cigarette use legislation than the 25 identified in the policy scan study in 2014–2016.[18] The discrepancy observed might be due to additional countries introducing e-cigarette use measures in their legislation within two years after the policy scan. There is also a difference in the

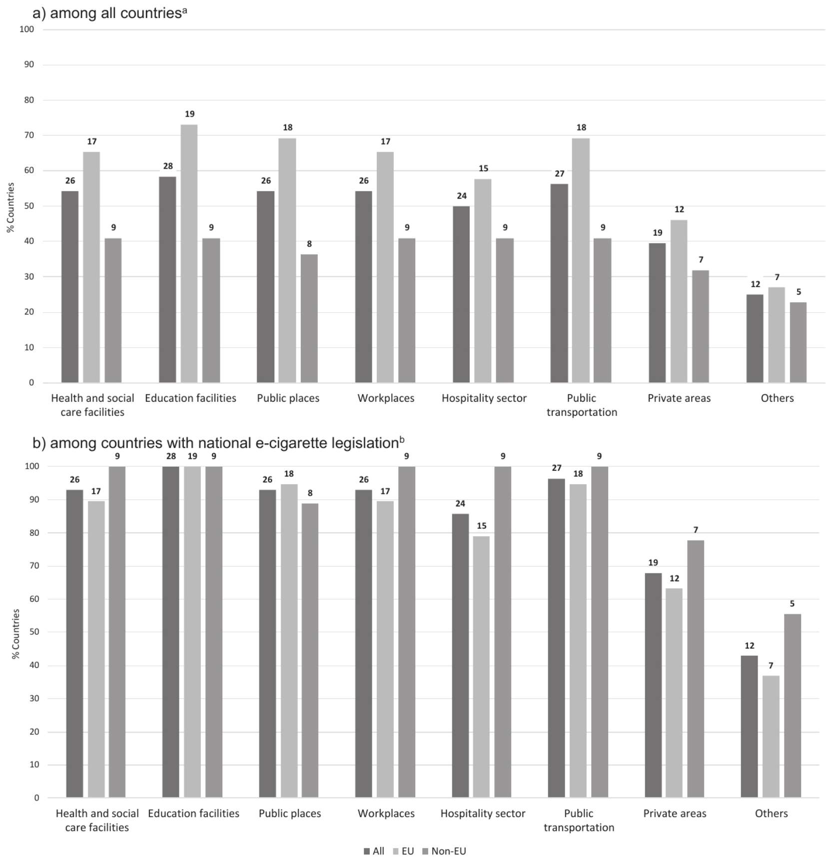


**Figure 2.** Proportion and number of countries within the World Health Organization European Region restricting the use of electronic cigarettes (e-cigarettes)[c] in various places (a) among all countries[a] and (b) only among countries with national e-cigarette legislation in place[b], 2018. [a]Among all countries (Total $n = 48$; EU $n = 26$; Non-EU $n = 22$). [b]Among countries with the national legislation on e-cigarette use (Total $n = 28$; EU $n = 19$; Non-EU $n = 9$). [c]Either partial or total ban for the use of any type of e-cigarettes (with or without nicotine). Absolute numbers of countries are shown on top of each bar. "Others" includes places such as tunnels, sporting facilities, elevators, and markets.

research methods, as the policy scan used policy documents as the main data source.

The supranational policy environment might have played a key role in the disparity between EU and non-EU countries. All EU MSs were obliged to transpose Article 20 of EU Tobacco Products Directive (TPD) 2014/40/EU, which stipulates provisions on the safety and quality specifications for e-cigarettes to their national legislation.[19] Although none of the provisions in the Article restricts the use of e-cigarettes, the EU TPD might have motivated MSs to go beyond the Article's provisions and advance their e-cigarette law-making, including introducing e-cigarette-free areas.

Only five countries (France, Poland, Lithuania, the United Kingdom, and Russia) enacted subnational legislation on e-cigarette use, of which two countries, the United Kingdom and Russia, had no national legislation. In line with the diffusion of smoking bans, where the legislation is developed at the local level and spread to the neighbouring regions and the national level, we may expect that e-cigarette legislation will follow the bottom-up rules.[20,21] However, the spatially uneven pattern for the diffusion policy found in this study is in line with a study in the United States, which showed an inconsistent patchwork of e-cigarette use bans across states.[22]

This study shows that e-cigarette use was mostly forbidden in educational premises, public transports, healthcare facilities, public places, and workplaces, as already observed with smoking regulation.[13] Although e-cigarette use in private areas had been frequently reported, as evident in more than half of users in some

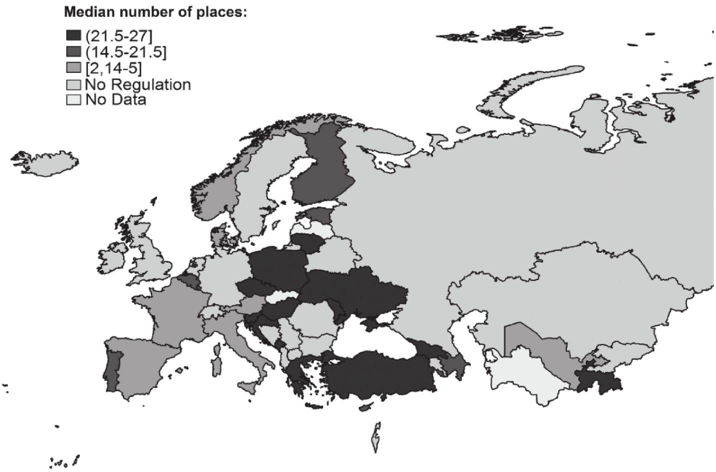


**Figure 3.** Median number of places covered by national legislation on e-cigarette use in the countries of the World Health Organization European Region, 2018

**Table 2.** Median number of places (and interquartile range, IQR) covered by national legislation on electronic cigarette (e-cigarette) use, and mean score (in a 0–5 scale) of the level of barriers, support, and compliance with the legislation according to the European Union membership status and income-level group within the countries of the World Health Organization European Region, 2018

| | Number of places[a] regulated | | | | Score in barriers, support and compliance with the legislation | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Nicotine-containing e-cigarettes | | Nicotine-free e-cigarettes | | Difficulties | | Public support | | Compliance | |
| | Median[b] (IQR) | *P*-value[c] | Median[b] (IQR) | *P*-value[c] | Mean[d] (95% CI) | *P*-value[e] | Mean[f] (95% CI) | *P*-value[e] | Mean[f] (95% CI) | *P*-value[e] |
| **All** | 21.5 (14.5–27.0) | | 18.0 (13.0–27.0) | | 2.8 (2.4–3.2) | | 3.7 (3.3–4.1) | | 3.5 (3.0–4.0) | |
| **EU membership** | | | | | | | | | | |
| EU | 17.0 (14.0–27.0) | 0.176 | 17.0 (12.0–27.0) | 0.861 | 2.2 (1.7–2.7) | 0.002 | 3.4 (2.9–3.9) | 0.025 | 3.5 (3.0–4.1) | 0.749 |
| Non-EU | 26.0 (21.0–27.0) | | 21.0 (14.0–27.0) | | 3.4 (2.9–4.0) | | 4.3 (3.9–4.6) | | 3.4 (2.3–4.4) | |
| **Income level** | | | | | | | | | | |
| H | 17.0 (14.0–24.0) | 0.063 | 16.0 (12.0–24.0) | 0.127 | 2.4 (1.8–2.9) | 0.042 | 3.6 (3.3–3.9) | 0.242 | 3.7 (3.2–4.2) | 0.084 |
| UM | 27.0 (24.0–27.0) | | 27.0 (24.0–27.0) | | 3.3 (2.5–4.2) | | 3.2 (1.0–5.8) | | 2.2 (0.1–5.5) | |
| LM | 26.0 (23.0–27.0) | | 14.0 (0.0–27.0) | | 3.4 (2.1–4.8) | | 4.3 (3.7–4.8) | | 3.6 (2.9–4.3) | |

CI, Confidence Interval; EU, European Union; H, High; IQR, Interquartile range; LM, Lower-Middle; UM, Upper-Middle; UN, United Nations.
[a]Either indoors or outdoors.
[b]Among countries with national e-cigarette use legislation in place. The number of places ranges 0–27 (incl. "others", such as tunnels, sporting facilities, elevators, and markets). Whenever a country bans the use of e-cigarettes regardless of the place of usage, a score of 27 was assigned. The median calculation did not include countries without the national legislation on e-cigarette use.
[c]Estimated by Mann-Whitney or Kruskal-Wallis test as appropriate.
[d]Range of score: 0–5; among all countries.
[e]Estimated by *t*-test or one-way ANOVA test as appropriate.
[f]Range of score: 0–5; among countries with national e-cigarette use legislation in place.

populations,[23,24] this study found that private areas remained the least protected place from SHA, as it is also the case for tobacco smoke-free regulation.[25] This might be due to the reluctance of legislators to interfere with individual behaviours in a private domain which is often deemed as a "liberty violation".[26] Only half of the countries in the WHO European Region restricted e-cigarette use in hospitality premises, although recent studies showed the frequent use of e-cigarettes in those places, ranging from 18% in clubs to 69% in restaurants.[23,27]

Regarding the alignment with COP7 WHO FCTC recommendation, there were just over a third of countries in the WHO European Region that prohibited the use of e-cigarettes indoors. This is despite the fact that almost two out of 10 smokers in six European countries observed people using e-cigarettes in indoor places where smoking is banned, and 16% of e-cigarette non-users in 12 European countries were exposed to SHA at least weekly in enclosed settings.[4,28]

This study shows that both country's smoking prevalence and income level were significantly associated with the number of places regulated under national legislation. Although it is still unknown why countries with higher smoking prevalence had more extensive places covered by their legislation, the ability of governments to bring e-cigarettes under existing smoking bans have been reported based on how existing regulations defined

**Table 3.** Unadjusted and adjusted estimates of the factors associated with the number of places regulated by electronic cigarette (e-cigarette) use legislation in countries within the World Health Organization European Region; and mean score (in a 0–5 scale) of difficulties in the adoption of the legislation, 2018

| Independent variables | Outcomes | | | |
|---|---|---|---|---|
| | Unadjusted | | Adjusted[a] | |
| | Ratio number of places[b] | Score of difficulties[c] | Ratio number of places[b] | Score of difficulties[c] |
| **Smoking prevalence** | 1.03* | 0.01 | 1.03* | 0.02 |
| **MPOWER score** | 1.00 | −0.13 | 1.01 | −0.06 |
| **EU membership** | | | | |
| Non-EU | REF | REF | REF | REF |
| EU | 0.80 | −1.20* | 0.98 | −0.87 |
| **Income level** | | | | |
| LM | REF | REF | REF | REF |
| UM | 1.09 | −0.08 | 0.82* | 0.08 |
| H | 0.75* | −1.07 | 0.63* | −0.29 |

EU, European Union; H, High income level; LM, Low-middle; MPOWER, Overall score for Monitor tobacco use, Protect people from tobacco smoke, Offer help to quit smoking, Warn about the dangers of tobacco, Enforce bans on tobacco advertising, promotion, and sponsorship, Raise taxes on tobacco—the possible range of this score is from 6 (1 in each of the six scores) to 29 (4 in 'M' score and 5 in 'P', 'O', 'W', 'E' and 'R' scores); UM, Upper-middle.
*$P < 0.05$.
[a]Adjusted for all independent variables listed.
[b]Calculated using Poisson regression model, including countries with national e-cigarette use legislation ($n = 28$).
[c]Calculated using a linear regression model, including all countries ($n = 48$).

"smoking". A broader definition of "smoking" often successfully eases the application of a smoking ban to e-cigarettes.[29] Moreover, the variety in the enactment status of the e-cigarette legislation may be explained by diverse harm perception of e-cigarettes across countries. In a previous study, the presence or absence of opportunity narratives around e-cigarette use appears to have influenced the policy outcome, such as the number of restricted places for e-cigarette use.[30]

Although the current study is unable to identify factors that may assist or hinder e-cigarette use legislation, there was moderately high support for the enforcement of the legislation (3.7 out of 5 points) within the WHO European Region. Similarly, high support for e-cigarette use bans in smoke-free areas was expressed by either the general population, former and current tobacco smokers in EU populations.[1,31]

Some countries reported "vaping front-groups" and "lobbyists" as underlying barriers in passing e-cigarette use legislation. The proponents of e-cigarette use argued that such a ban may inhibit smokers from switching to e-cigarettes and deter smoking cessation efforts.[32] Both arguments, however, are not supported by sufficient evidence nor directly relevant to protecting the health of bystanders, the main aim of promoting such bans.[33,34] On the other hand, enforcement of smoking bans while allowing e-cigarette use would be complicated, confusing, and challenging.[35]

This study might be limited by the source of the data, which was primarily obtained from the view of the informants, not the legislation documents themselves. Nevertheless, apart from the aforementioned rationale of choosing this method, the informants provided updated information regarding the enactment and enforcement of the legislation along with the information about compliance, support, and barriers, which goes beyond the information provided by the sole legislation documents. For some countries ($n = 26$), responses were received from only one informant. Yet, subjective answers were minimised by cross-checking them with the legislation whenever it was provided by the informants. As informants unlinked to regulators were prioritised, potential self-complacency bias when reporting the information should have been mitigated. Additionally, this paper focuses on e-cigarette use legislation that has passed at subnational and national level; thus, information on pre-emption was not available. More appropriate study design, using a qualitative design, would be helpful to investigate such matter. While this study was unable to collect data from five countries, it achieved very high participation, with over 90% of countries in the WHO European Region, covering more than 98% of its population.

This study benefitted from the first analysis of the regulatory approach in restricting e-cigarette use in various indoor and outdoor places across the WHO European Region. Information from in-country experts offers some insights about barriers and support for the legislation and level of compliance. Additionally, standardised questions have allowed us to make comparisons among countries.

In conclusion, almost 60% of 48 countries in the WHO European Region regulated e-cigarette use at the national level, and only a third of countries followed the WHO FCTC recommendation in prohibiting the use of e-cigarettes indoors by July 2018. Future research needs to systematically evaluate the implementation and compliance of e-cigarette use regulation in the European Region and how it affects different populations. Countries may need assistance in building capacity and on dealing with the issues encountered while enacting and enforcing e-cigarette use regulations.

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Contributions of authorships: EF had the original idea for the study; All co-authors participated in the protocol preparation; BA, MF, EF, and OT developed the questionnaire; BA collected the data of the study; BA prepared the database with the results; BA carried out the statistical analysis with the supervision of EF and MF; BA wrote the first draft of the manuscript in collaboration with all co-authors; All authors reviewed the manuscript, made substantial contributions to conception, design and interpretation of data; All co-authors approved the final version of the manuscript.

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Conflicts of interest: None declared.

## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.2188/jea.JE20200332.

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# PAPER 2

## How widespread is electronic cigarette use in outdoor settings? A field check from the TackSHS project in 11 European countries

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Short communication

# How widespread is electronic cigarette use in outdoor settings? A field check from the TackSHS project in 11 European countries

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ABSTRACT

Exposure to secondhand aerosol from electronic cigarettes (e-cigarettes) may pose harms to bystanders, but they are used in many indoor settings. Less evidence exists on e-cigarette use in outdoor settings. This study aims to assess the use of e-cigarettes in outdoor settings in Europe. A cross-sectional study was conducted at the entrances of primary schools (N = 200), children's playgrounds (N = 200), and outdoor hospitality venues (N = 220) during 2017–2018 in major cities of 11 European countries. We performed 30-min observations and recorded e-cigarette use at three-time points: at 0 min, 15 min, and 30 min. We described the number and proportion of settings with e-cigarette use observed at any of the three-time points according to country and other contextual variables. Results showed that there were 22 (11.0%) school entrances, eight (4.0%) playgrounds, and 47 (21.3%) outdoor hospitality venues where e-cigarette use was observed at any time point. School entrances and outdoor hospitality venues with observed e-cigarette use were more frequently found in countries with a higher prevalence (≥1.4%) of e-cigarette use (school entrances: 18.0% vs. 4.0%; p = 0.002, outdoor hospitality venues: 26.7% vs. 15.0%, p = 0.036). In conclusion, the outdoor setting with the highest visibility of e-cigarette use was outdoor areas of hospitality venues. Although still limited, e-cigarettes were also used in outdoor settings frequented by children. Governments should consider measures to restrict e-cigarette use outdoors to protect the health of bystanders, particularly in areas where children may be present.

## 1. Introduction

Electronic cigarettes (e-cigarettes) have become popular in many parts of Europe; their use among adults increased from 12% in 2014 to 15% in 2017 (Comission, 2017). However, many toxic substances are present in e-cigarette aerosol (Stratton et al., 2018), posing potential risks to the health of users (Bozier et al., 2020) and non-users passively exposed to its secondhand aerosol (SHA) (Bayly et al., 2019). Consequently, their use has been regulated in some indoor areas where the use of conventional tobacco products is already forbidden. Despite this, e-cigarette use has been observed in some smoke-free spaces in the United States (US) (Dunbar et al., 2020), even where their use has been

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explicitly prohibited (Yingst et al., 2019). In outdoor spaces of dining areas and children's playgrounds in an Australian city, where tobacco smoking was forbidden, e-cigarette use was reported by 36.8% and 8.7% of e-cigarette users, respectively (Twyman et al., 2018).

As e-cigarette use has been widespread, exposure to SHA among bystanders merits some attention. About 16% of adults in the general population and 37% of adult smokers in Europe reported being exposed to SHA, mostly occurring in indoor areas of bars or restaurants and workplaces or educational venues (Amalia et al., 2020; Tigova et al., 2019). In the US, SHA exposure in indoor and outdoor public places among middle and high school students surged, from 25.6% in 2017 to 33.2% in 2018 (Dai, 2020). In Europe, younger bystanders and those who live in countries with prevalent e-cigarette use were more likely to be exposed to SHA (Amalia et al., 2020). Furthermore, seeing e-cigarette use in public places might renormalise smoking among youth (Agaku et al., 2020).

Given the increasing prohibitions of tobacco smoking outdoors and the bans on use of e-cigarette indoors, e-cigarette use might be shifted to outdoor venues (Patel et al., 2016). Furthermore, some of the health issues related to e-cigarette use indoors may also apply to outdoor areas, particularly where people are close together. Thus, an assessment of the extent of e-cigarette use outdoors is warranted; however, the evidence is absent in Europe.

This study aims to describe e-cigarette use in outdoor settings frequented by children or by large numbers of people, namely, school entrances, children's playgrounds, and outdoor hospitality venues in 11 European countries.

## 2. Materials and methods

This cross-sectional study, conducted within the framework of the TackSHS Project (Fernández et al., 2020), aimed to describe e-cigarette use outdoors in primary schools entrances, children's playgrounds, and outdoor hospitality venues, from March 2017 to October 2018, in major cities of 11 European countries: Bulgaria, France, Germany, Greece, Ireland, Italy, Poland, Portugal, Romania, Spain, and the United Kingdom (UK). The TackSHS project was approved by the Clinical Research Ethics Committee of the Bellvitge University Hospital (PR341/15), and the protocol of this study was approved by all the countries' local Research Ethics Committees.

Detailed methods have been reported elsewhere (Henderson et al., 2020). In brief, we selected densely populated urban areas in Bulgaria (Sofia), France (Paris), Germany (Mannheim, Heidelberg), Greece (Athens), Ireland (Dublin), Italy (Milano, Varese), Poland (Ciechanow, Warsaw), Portugal (Braga), Romania (Bucharest), Spain (Barcelona), and the United Kingdom (Edinburgh) based on opportunistic criteria, considering feasibility. From these cities, we conveniently selected 20 sites for each of the three types of outdoor settings in each country, except for France, where e-cigarette use data was only collected in outdoor hospitality venues. The selection of the sites considered neighbourhoods from different socioeconomic status (SES), which was assessed using local ecological synthetic indexes. When these synthetic indexes were not available, as was the case for Bulgaria, France, Greece, Poland, and Romania, other socioeconomic indicators were used, such as the cost of housing or the rate of poverty, among others. For each setting, half of the observations were made in the lowest SES neighbourhoods (<20th percentile of the SES distribution) and the other half in the highest (>80th percentile of the SES distribution). We visited a total of 200 school entrances, 200 children's playgrounds, and 220 outdoor hospitality venues across all countries.

Observations in school entrances and children's playgrounds were performed before the start or at the end of school hours. In outdoor hospitality venues (i.e., cafeterias, bars, and night pubs), half of the observations were made at any daytime and the other half after dinnertime during the weekdays and weekends. All observations started when at least five people, adults and/or children, were present in each setting.

The use of any type of electronic nicotine/non-nicotine delivery systems that vaporise liquid, hence, not heated tobacco products (e.g., iQOS), was recorded. A trained data collector recorded if e-cigarettes were used in each setting at the beginning (0 min), at 15 min, and at the end (30 min) of the observation period. We determined that an e-cigarette was used if data collectors visually noticed at least one person using e-cigarette at any of the three observation time points.

We reported the overall number and proportion (%) of settings in which e-cigarettes were used, stratified by country, neighbourhood's SES, the country's tobacco control performance according to the Tobacco Control Scale score (Joossens and Raw, 2017), country's smoking prevalence (Gallus et al., 2020), country's e-cigarette use prevalence (Fernández et al., 2020), and existence of national e-cigarette use regulation at the setting (obtained from different sources; see the footnote of Table 1). Chi-squared test was conducted to determine differences in proportions between subgroups at the 0.05 significance level. All analyses were performed with the statistical package Stata 15.

## 3. Results

Overall, there were 22 out of 200 (11.0%) school entrances in which e-cigarette use was observed (Table 1). While Greece had the highest proportion (n = 8; 40.0%), e-cigarette use was not observed at school entrances in Poland, Portugal, or Spain. School entrances with e-cigarette use were observed four times (18.0% vs. 4.0%; $p = 0.002$) more frequently in countries with higher (≥1.4%) national prevalence of e-cigarette use than in countries with lower prevalence.

Table 1 also shows that e-cigarette use was observed in 8 out of 200 (4.0%) children's playgrounds. Most of the venues were found in Ireland (3 playgrounds, 15.0%), while e-cigarette use was not observed in five countries (Bulgaria, Poland, Portugal, Spain, and the UK). No differences were found according to the studied contextual variables.

Finally, e-cigarette use was observed in 47 out of 220 (21.3%) outdoor hospitality venues (Table 1), mainly in Greece and Portugal, in 9 (45.0%) outdoor hospitality venues in each country. In contrast, e-cigarette use was not observed in any of the venues in Spain. Outdoor hospitality venues with e-cigarette use were more frequently observed in countries with a higher national prevalence of e-cigarette use (26.7% vs. 15.0%, $p = 0.036$).

## 4. Discussion

Our findings show that e-cigarette use was observed in the three outdoor settings studied, even those frequented by children, with diversity across European countries. Some contextual factors at the national level can partly contribute to the intercountry differences observed. Country's e-cigarette prevalence, for example, was associated with observed e-cigarette use in school entrances and outdoor hospitality venues. Indeed, Greece, the UK, and Ireland, the countries with the highest proportion of school entrances with observed e-cigarette use, are countries with higher national e-cigarette use prevalence.

Our findings also indicate that e-cigarette use outdoors may happen regardless of the neighbourhood SES and the country's tobacco control performance. Previous studies suggested that e-cigarette use is not associated with individual's place of residence or SES (Vardavas et al., 2015; Friedman and Horn, 2019). Socioeconomic factors might play differently in e-cigarette use compared to tobacco smoking depending on attitudes and policies with regard to e-cigarette usage.

Since our study included areas frequented by adults and children, it suggests that the formulation of a comprehensive smoke-free policy should entail consideration of the impact of e-cigarette use on the perception of bystanders, in both population groups. There is evidence that SHA, including visibility of e-cigarette use, among adults may renormalise tobacco smoking, trigger relapse to smoking among quitters, and promote initiation of e-cigarette use and, thus, put current

**Table 1**
Number and proportion* of outdoor settings where electronic cigarette (e-cigarette) use was identified at any observation time (Comission, 2017) according to contextual variables in 11 European countries. TackSHS project, 2017–2018.

| | SCHOOL ENTRANCES (N = 200) | | CHILDREN'S PLAYGROUNDS (N = 200) | | OUTDOOR HOSPITALITY VENUES (N = 220) | |
|---|---|---|---|---|---|---|
| | n (%) | p – value[2] | n (%) | p – value[2] | n (%) | p – value[2] |
| All | 22 (11.0) | | 8 (4.0) | | 47 (21.3) | |
| Country | | – | | – | | – |
| Bulgaria | 1 (5.0) | | 0 (0.0) | | 1 (5.0) | |
| France | – | | – | | 6 (30.0) | |
| Germany | 1 (5.0) | | 1 (5.0) | | 1 (5.0) | |
| Greece | 8 (40.0) | | 1 (5.0) | | 9 (45.0) | |
| Italy | 3 (15.0) | | 1 (5.0) | | 2 (10.0) | |
| Ireland | 4 (20.0) | | 3 (15.0) | | 6 (30.0) | |
| Poland | 0 (0.0) | | 0 (0.0) | | 3 (15.0) | |
| Portugal | 0 (0.0) | | 0 (0.0) | | 9 (45.0) | |
| Romania | 1 (5.0) | | 2 (10.0) | | 6 (30.0) | |
| Spain | 0 (0.0) | | 0 (0.0) | | 0 (0.0) | |
| United Kingdom | 4 (20.0) | | 0 (0.0) | | 4 (20.0) | |
| Neighbourhood socioeconomic status | | 0.175 | | 0.141 | | 0.173 |
| High | 8 (8.0) | | 2 (2.0) | | 27 (25.2) | |
| Low | 14 (14.0) | | 6 (6.1) | | 20 (17.7) | |
| Country's Tobacco Control Scale overall score (2016)[3] | | 0.094 | | 0.753 | | 0.502 |
| <50 | 10 (16.6) | | 2 (3.3) | | 11 (18.3) | |
| ≥50 | 12 (8.5) | | 6 (4.3) | | 36 (22.5) | |
| Country's tobacco smoking prevalence (%)[4] | | 0.651 | | 0.470 | | 0.076 |
| <31.0 | 12 (12.0) | | 5 (5.0) | | 16 (16.0) | |
| ≥31.0 | 10 (10.0) | | 3 (3.0) | | 31 (25.8) | |
| Country's e-cigarette use prevalence (%)[5] | | 0.002 | | 0.149 | | 0.036 |
| <1.4 | 4 (4.0) | | 2 (2.0) | | 215 (15.0) | |
| ≥1.4 | 18 (18.0) | | 6 (6.0) | | 32 (26.7) | |
| E-cigarette use regulation exists in the setting at the national-level[6] | | 0.076 | | 0.059 | | – |
| Yes | 3 (5.0) | | 0 (0.0) | | – | |
| No | 19 (13.6) | | 8 (5.7) | | 47 (21.4) | |

*Proportion was reported as a percentage among total observation in the corresponding contextual variable (by row).
[1]E-cigarette use data was collected over 30 min at three-time points: minute 0′, 15′, and 30’.
[2] Chi-squared test.
[3] Tobacco Control Scale 2016 Ranking: <50 (Bulgaria, Germany, Greece) ≥50 (France, Italy, Ireland, Poland, Portugal, Romania, Spain, UK).
[4] Current tobacco smoking prevalence (2017–2018, TackSHS survey data): <31.0% (Germany, Ireland, Italy, Poland, and the United Kingdom) and ≥31.0% (Bulgaria, France, Greece, Portugal, Romania, and Spain). Cut-off was set at the median of total population current tobacco smoking prevalence across the listed countries (31.0%).
[5] Current e-cigarette use prevalence (2017–2018, TackSHS survey data): <1.4% (Germany, Italy, Poland, Portugal, and Spain) and ≥1.4% (Bulgaria, France, Greece, Ireland, Romania, and the United Kingdom). Cut-off was set at the median of total population e-cigarette use prevalence across the listed countries (1.4%).
[6] Tobaccocontrollaws.org (accessed May 20, 2020), Globaltobaccocontrol.org (accessed May 20, 2020), and countries' national laws. Countries with e-cigarette use regulation in place for (a) School entrances: France, Italy, Poland, and Portugal; (b) Children's playgrounds: Poland, Portugal, and Spain; (c) Outdoor hospitality venues: none.

smokers at risk of being dual users as they might start using e-cigarette (King et al., 2015, 2016; Mirbolouk et al., 2019). A previous study has revealed that e-cigarette non-users who were current smokers or former e-cigarette users were more likely to be exposed by SHA (Amalia et al., 2020). Among youth, seeing e-cigarette use may normalise the use of nicotine-containing products, resulting in an increased risk of starting the use of e-cigarettes and tobacco products in the future (Dai, 2020; Agaku et al., 2020). Even among adolescents not susceptible to future cigarette smoking, exposure to the smell from e-cigarette use in indoor or outdoor public places was associated with susceptibility to using e-cigarettes (Kowitt et al., 2018). As most of the current tobacco control policies tend not to restrict e-cigarette use outdoors, it is advisable that their use is included in outdoor smoking restrictions, especially in areas where children may be present.

The scarcity of e-cigarette use observed in designated areas for children compared to outdoor hospitality venues, as also evident in the outdoor secondhand tobacco smoke exposure in 12 European countries, might be explained by the commonly perceived harms of SHA exposure for children (Nguyen et al., 2017). However, the finding is likely to change over time with the increasing take-up of e-cigarettes, particularly to circumvent smoke-free regulations (Patel et al., 2016). Having the same e-cigarette use rules as for smoking in outdoor settings might provide simplicity in communication and implementation of the regulations.

The World Health Organization has advised countries to outlaw e-cigarette use in smoke-free places, including smoke-free areas outdoors, to protect non-users from SHA exposure (World Health Organization, 2020). Interestingly, we still observed some e-cigarette use activities in three school entrances where e-cigarette use was actually banned. The violation of the law highlights the importance of law enforcement.

Our study was limited by the convenience sampling of the settings selected and, thus, these results are not generalisable. Nevertheless, we monitored the main cities of 11 European countries, representative of different socio-cultural and socioeconomic characteristics. As the e-cigarette users in high SES areas can come from low SES areas, or vice versa, the stratification of settings by neighbourhood SES in this study should not be interpreted as the SES of e-cigarette users. Additionally, the difficult identification of e-cigarette use because of its similarity to other handheld items might influence our estimates. However, our data collectors were moving around the areas to maximise the observations. Given the limited duration of observation, our results might underestimate the real e-cigarette use in these settings; a longer observation period in future studies is warranted. Notwithstanding the limitations, this is the first multi-country study describing e-cigarette use in outdoor settings that considered different contextual determinants using a standardised protocol.

## 5. Conclusions

Our results show that e-cigarette use was observed in outdoor settings, including those frequented by children, across 11 European countries. Governments should consider strengthening their tobacco control policy by extending the smoke-free laws to cover e-cigarette use in outdoor places, especially those where children are present and people are close together, as well as effectively enforcing the laws.

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## Authors contribution

Beladenta Amalia: Data curation, Writing – original draft. Alejandro Rodríguez: Investigation, Writing – review & editing. Elisabet Henderson: Resources, Writing – review & editing. Marcela Fu: Writing – review & editing. Xavier Continente: Conceptualisation, Formal analysis, Writing – review & editing. Olena Tigova: Writing – review & editing. Sean Semple: Writing – review & editing. Luke Clancy: Writing – review & editing. Silvano Gallus: Writing – review & editing. Esteve Fernández: Conceptualisation, Supervision, Writing – review & editing. Maria J. López: Conceptualisation, Supervision, Writing – review & editing.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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# PAPER 3

## Exposure to secondhand aerosol of electronic cigarettes in indoor settings in 12 European countries: data from the TackSHS survey

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# Exposure to secondhand aerosol of electronic cigarettes in indoor settings in 12 European countries: data from the TackSHS survey

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## ABSTRACT

**Introduction** Exposure to secondhand aerosol from e-cigarette (SHA) may pose harmful effects to bystanders. This study aims to investigate the prevalence, duration and determinants of SHA exposure in various indoor settings in 12 European countries.

**Methods** In 2017–2018, we conducted a cross-sectional study, the TackSHS survey, on a representative sample of the population aged ≥15 years in 12 European countries (Bulgaria, England, France, Germany, Greece, Ireland, Italy, Latvia, Poland, Portugal, Romania and Spain). We described the prevalence and duration of exposure to SHA in several indoor settings among 11 604 e-cigarette non-users. Individual-level and country-level characteristics associated with SHA exposure were also explored using multilevel logistic regression analyses.

**Results** Overall, 16.0% of e-cigarette non-users were exposed to SHA in any indoor setting at least weekly, ranging from 4.3% in Spain to 29.6% in England. The median duration of SHA exposure among those who were exposed was 43 min/day. 'Other indoor settings' (eg, bar and restaurant) was reported as the place where most of e-cigarette non-users were exposed (8.3%), followed by workplace/educational venues (6.4%), home (5.8%), public transportation (3.5%) and private transportation (2.7%). SHA exposure was more likely to occur in certain groups of non-users: men, younger age groups, those with higher level of education, e-cigarette past users, current smokers, those perceiving SHA harmless and living in countries with a higher e-cigarette use prevalence.

**Conclusions** We found inequalities of SHA exposure across and within European countries. Governments should consider extending their tobacco smoke-free legislation to e-cigarettes to protect bystanders, particularly vulnerable populations such as young people.

**Trial registration number** NCT02928536.

## INTRODUCTION

Electronic cigarette (e-cigarette) use has increased in many parts of the world. In the USA, with Juul's extraordinary growth and marketing strategy, e-cigarette use has been declared as an epidemic in youth by the US Surgeon General as it substantially increased by 78% from 2017 to 2018.[1 2] According to the Eurobarometer surveys, the prevalence of adults who had at least tried e-cigarettes in 28 European countries has grown from 12% in 2014 to 15% in 2017.[3]

The growing use of e-cigarettes has raised concerns as the product is potentially harmful both to users and bystanders.[4 5] While some studies showed that e-cigarettes emit lower levels of some toxic chemicals compared with smoke from conventional cigarettes, other studies revealed that e-cigarette aerosol contains comparable or higher levels of other harmful constituents, such as nicotine and metals.[6–9] It has been also shown that bystanders absorb nicotine from e-cigarette aerosol at levels comparable with secondhand tobacco smoke (SHS).[10] Additionally, e-cigarette aerosol may expose non-users to toxic chemicals, including particulate matter and carcinogens, such as volatile organic compounds, polycyclic aromatic hydrocarbons, formaldehyde, acetaldehyde and tobacco-specific nitrosamines.[11–14] Secondhand aerosol (SHA) from e-cigarettes has been found to cause acute reduced lung function and associated with higher odds of asthma exacerbations, which might reflect more adverse health effects with longer period of exposure.[15 16] Exposure to SHA from e-cigarette may renormalise tobacco smoking, induce relapse to smoking for those who have quit smoking and trigger initiation of e-cigarette use among non-smokers, particularly young people.[17–21] The above evidence suggests that appropriate regulations are needed to prevent involuntary exposure to SHA.

The WHO recommends to Parties of the Framework Convention on Tobacco Control to consider the prohibition of e-cigarette use in indoor settings or at least in those places where smoking is already banned.[22] In Europe, e-cigarette use has been frequently observed in indoor places where smoking is normally banned, such as workplaces, bars, restaurants and train and metro stations.[23–25] Evading smoke-free regulation has been reported by e-cigarette users as one of the main reasons for the use of e-cigarettes.[26–28] To the best of our knowledge, to date there have been 28 European countries regulating the use of e-cigarettes, but mostly in selected public places only.[29]

While public debate about the risks and benefits of e-cigarette use continues to arise, evidence on the extent of the population's exposure to the SHA has been documented.[30] According to the 2015

National Youth Tobacco Survey data, exposure to SHA in indoor or outdoor public places was reported by one in four middle-school and high-school students in the USA, including 4.4 million who were e-cigarette non-users and one million not exposed to SHS.[31] Recent data from six European countries indicated that 37% of smokers (e-cigarette non-users) were exposed to SHA, ranging from 18% in Spain to 63% in Greece.[23] However, there has been no study on exposure to SHA from e-cigarettes among the general population in Europe.

This paper aims to assess the prevalence and duration of exposure to SHA from e-cigarettes in various indoor settings among e-cigarette non-users aged 15 years or older in 12 European countries. We also explored the sociodemographic factors at the individual and country level that were associated with SHA exposure.

## METHODS

### Data source

This is a questionnaire-based cross-sectional study using data from the TackSHS survey, conducted in 12 selected European countries (Bulgaria, England, France, Germany, Greece, Ireland, Italy, Latvia, Poland, Portugal, Romania and Spain). The detailed methods of the TackSHS survey, including the questionnaire development, have been explained elsewhere.[32 33] Sampling methods varied across countries, including multistage sampling (in Bulgaria, Greece, Italy, Latvia, Poland and Romania), cluster sampling with quotas (in England and France) and stratified random sampling (in Germany, Ireland, Portugal and Spain). In each country, we sampled around 1000 people representative of the general population in terms of age, sex, geographical area, and in most of countries, socioeconomic characteristics. In total, the survey included 11 902 subjects aged 15 years or older from 12 European countries, representing 79.2% of the whole EU population. A pilot study was conducted in Italy in November 2016 while the fieldwork in other countries was conducted between June 2017 (in Romania) and October 2018 (in Latvia), using the same questionnaire administered with computer-assisted personal interviewing in all 12 countries. The questionnaire included information on socioeconomic and demographic characteristics, cigarette smoking, e-cigarette use, SHS and SHA exposures in various indoor and outdoor settings, and attitudes and perception towards SHS and SHA exposures.[33]

For the purpose of this study, only e-cigarette non-users were included. Thus, the total sample size in this study was 11 604 subjects.

### Measures

Respondents who reported that they had never used e-cigarette during their lifetime or had stopped using it at least for 30 days before the time of the survey were considered as e-cigarette non-users (ie, never and ex-users). From a question ‘On average, how much time per day do you think you are exposed to e-cigarette aerosol in each of the following sites?’, interviewees indicated one or more of the indoor settings where they experienced SHA exposure. Five indoor settings were considered: home, workplace (or educational venues for students), public transportation (eg, train, tram, bus and subway), private transportation and ‘other indoor places’ (eg, cafeterias, bars, restaurants and leisure facilities). For each indoor setting, e-cigarette non-users reported the average exposure time (in min/day) during a working and non-working day. An e-cigarette non-user was defined as exposed to SHA in a certain setting, if (s)he was exposed in that setting at least 1 min per day in a working and/or non-working day. The prevalence (%) of exposure (at least weekly) was computed for each setting and overall. Duration of SHA exposure was computed as the weighted daily average minutes of exposure in working and non-working days among subjects exposed to SHA in each setting.

Ever smokers were defined as respondents who reported smoking at least 100 cigarettes (including hand-rolled cigarettes) during their lifetime. Among ever smokers, current smokers were participants who reported current smoking at the time they participated in this survey, while ex-smokers were those who had stopped smoking by the time they participated in this survey.[34]

Information on harm perception from SHA exposure was obtained by asking respondents ‘Do you agree or disagree with the following sentence? Exposure to e-cigarette vapour is harmful to my health, with five possible answer options: (1) strongly agree; (2) moderately agree; (3) moderately disagree; (4) strongly disagree; (5) does not know or does not answer’. Options 1 and 2 were categorised as ‘harmful’, whereas options 3 and 4 were categorised as ‘harmless’.

Level of education was constructed by taking country-specific tertiles of schooling years as low, intermediate and high. The 12 countries were classified by their geographical area into Northern Europe, Western Europe, Southern Europe and Eastern Europe according to United Nations M49 Standard,[35] by the World Bank GDP per capita,[36] by their score in the 2016 Tobacco Control Scale,[37] by country’s smoking prevalence and by country’s e-cigarette use prevalence. The latter two were estimated from the TackSHS survey data.

### Statistical analysis

We reported proportion, and median estimates of the SHA exposure among e-cigarette non-users across countries and sociodemographic subpopulations. We used the median of the minutes exposed as point of estimates for the duration of SHA due to extremely right-skewed distribution of the data.

A multilevel logistic regression model, allowing for clustering of observations at the country level was fitted to examine the relationship between SHA exposure status (as a binary dependent variable) and sociodemographic characteristics at individual and country levels (independent variables). Adjusted OR (aOR) and their corresponding 95% CI were estimated after adjusting for sex, age, level of education, e-cigarette use status and smoking status.

Statistical weights were used to generate representative estimates of the general population of each country (individual weight). To calculate results for the entire sample, we applied ‘country weights’, which combined individual weights with an additional weighting factor, with each country contributing in proportion to its population aged 15 years or over, obtained by Eurostat.[38] Analyses were performed with STATA V.14.0.

## RESULTS

The sample sociodemographic characteristics are presented in online supplementary table 1. Among 11 604 e-cigarette non-users, 16.0% (95% CI: 15.3% to 16.7%) were exposed at least weekly to SHA from e-cigarettes in any indoor setting, and ranged from 4.3% (95% CI: 3.2 to 5.7) in Spain to 29.6% (95% CI: 26.7 to 32.6) in England, with significant differences among men and women (17.2% vs 15.0%, $p<0.001$) for the 12 countries combined (table 1). The highest prevalence of at least weekly SHA exposure was reported in England for both men and women (31.8% and 27.8%, respectively). Overall, the median duration of SHA exposure for e-cigarette non-users who had

**Table 1** Country-specific prevalence (%) of e-cigarette secondhand aerosol (SHA) exposure (at least weekly), overall and by sex in e-cigarette non-users of the European population aged ≥15 years.* TackSHS survey, 2017–2018

| | | % exposure to SHA from e-cigarettes (95% CI) | | |
|---|---|---|---|---|
| Country | N† | Total | Men | Women |
| Bulgaria | 1035 | 14.9 (12.8 to 17.2) | 14.3 (11.4 to 17.6) | 15.4 (12.6 to 18.7) |
| England | 940 | 29.6 (26.7 to 32.6) | 31.8 (27.5 to 36.3) | 27.8 (24.1 to 31.8) |
| France | 974 | 26.3 (23.6 to 29.1) | 27.5 (23.6 to 31.7) | 25.2 (21.6 to 29.2) |
| Germany | 1000 | 11.1 (9.2 to 13.2) | 12.6 (10.0 to 15.9) | 9.5 (7.3 to 12.4) |
| Greece | 959 | 28.9 (26.1 to 31.8) | 30.3 (26.4 to 34.6) | 27.4 (23.6 to 31.6) |
| Ireland | 916 | 22.1 (19.6 to 24.9) | 24.6 (20.8 to 28.8) | 19.8 (16.4 to 23.7) |
| Italy | 1045 | 12.8 (10.9 to 15.0) | 15.7 (12.8 to 19.2) | 10.1 (7.9 to 13.0) |
| Latvia | 1009 | 5.6 (4.4 to 7.2) | 6.7 (4.8 to 9.3) | 4.7 (3.2 to 6.8) |
| Poland | 718 | 12.3 (10.1 to 14.9) | 13.9 (10.5 to 18.1) | 11.0 (8.2 to 14.5) |
| Portugal | 991 | 11.4 (9.6 to 13.5) | 12.5 (9.8 to 15.8) | 10.5 (8.1 to 13.4) |
| Romania | 999 | 10.0 (8.3 to 12.0) | 10.9 (8.5 to 14.0) | 9.2 (6.9 to 12.0) |
| Spain | 1018 | 4.3 (3.2 to 5.7) | 2.2 (1.2 to 3.9) | 6.3 (4.5 to 8.7) |
| Total | 11 604 | 16.0 (15.3 to 16.7) | 17.2 (16.2 to 18.2) | 15.0 (14.1 to 15.9) |

*Individual-level weight was applied to all estimates. For total estimates of the entire sample, country-level weight was applied with each country contributing in proportion to its population aged 15 years or over.[38]
† Sample size (N) is the unweighted country-specific number of e-cigarette non-users.

been exposed to SHA was 43 min/day (Q1–Q3: 14–130). The duration of SHA exposure ranged from 2 min/day (Q1–Q3: 1–7) in Spain to 103 min/day (Q1–Q3: 21–240) in Italy (figure 1).

Table 2 shows the country-specific prevalence and duration of SHA exposure in various indoor settings. SHA exposure among e-cigarette non-users mostly occurred in 'other indoor settings' (8.3%), followed by workplace/educational venues (6.4%), home (5.8%), public transportation (3.5%) and private transportation (2.7%). France had the highest prevalence of SHA exposure at home (12.0%), workplace/educational venues (13.2%) and private vehicles (5.9%) compared with other countries, while the highest prevalence of SHA exposure in public transportation was in England (7.9%) and in 'other indoor settings' in Greece (19.0%). The longest median duration of SHA exposure was 43 min/day taking place at home and workplace, while the shortest one was in public transportation with a median exposure of 14 min/day. Despite the low prevalence of SHA exposure (1.8%) among Latvian e-cigarette non-users in 'other indoor places', they reported a 2-hour-per-day of SHA exposure in these venues.

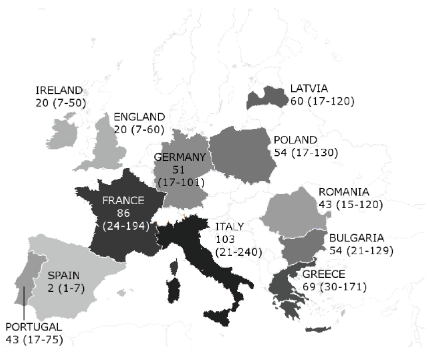


**Figure 1** Median (Q1-Q3) duration of exposure to SHA (minutes/day) from e-cigarettes.TackSHS survey, 2017-2018. Median estimates were calculated among e-cigarette non-users who had been exposed to SHA at any indoor setting. Q1, first quartile; Q3, third quartile.

Table 3 shows the proportion of SHA exposure and the corresponding aOR according to selected individual-level characteristics. At least weekly SHA exposure was more frequent in men (aOR: 1.13; 95% CI: 1.01 to 1.25) than in women and in the young (aOR for <25 vs ≥65 years: 3.15; 95% CI: 2.52 to 3.94; p for trend <0.001). The higher the level of education, the more likely e-cigarette non-users were exposed to SHA (aORs for intermediate level of education: 1.19; 95% CI: 1.05 to 1.35, and for high-level of education: 1.26; 95% CI: 1.10 to 1.44; p for trend <0.001). Higher odds of SHA exposure were related with being an e-cigarette past user (compared with never users aOR: 1.49; 95% CI: 1.14 to 1.95) and being a current smoker (compared with never smokers, aOR: 1.54; 95% CI: 1.36 to 1.74). Those who perceived SHA exposure as harmful were less likely to be exposed to SHA (vs harmless; aOR: 0.69; 95% CI: 0.61 to 0.78).

Compared with Northern Europe, SHA exposure was lower among e-cigarette non-users living in Southern (aOR: 0.27; 95% CI: 0.11 to 0.68) and Eastern Europe (aOR: 0.35; 95% CI: 0.13 to 0.94) (table 4). E-cigarette non-users living in countries with higher prevalence of e-cigarette use were more likely to be exposed to SHA (vs <1% e-cigarette use prevalence; aOR for 1%–4% group: 1.64, 95% CI : 1.05 to 2.56; aOR for >4% group: 4.35, 95% CI: 2.72 to 6.96; p for trend <0.001).

## DISCUSSION

Sixteen percent of e-cigarette non-users in 12 European countries were exposed to SHA at least weekly in any indoor setting, reporting a median of 43 min/day of exposure. Most of their exposure took place in 'other indoor settings' that include restaurants and bars, but, importantly, the exposure of longest duration occurred at home and workplace (43 min/day). It is also evident that variability in SHA exposure exists across countries and among different sociodemographic groups—men, the youngest, highly educated, past e-cigarette users, current smokers, those perceiving SHA as harmless and living in a country with high e-cigarette use prevalence were among individuals who were more likely to be exposed to SHA.

The highest prevalence of SHA exposure (more than one in four non-users, England) does not correspond to the longest duration of SHA exposure (103 min/day, Italy). The discrepancy might be partly due to lower time-sensitisation towards duration of SHA exposure among bystanders in countries where SHA exposure was more common; they perceived shorter duration of SHA exposure because they had already accustomed to it. However, the discrepancy highlights the importance of monitoring both measures, prevalence and duration of SHA exposure, in a population. There is no evidence on the safety levels of SHA exposure, while for SHS, there has been established evidence showing that there is no risk-free level of SHS.[39–41] However, it has been shown that 2 hours/day of exposure to exhaled aerosol of e-cigarettes for a week may significantly increase urinary and salivary cotinine among bystanders living in homes with e-cigarette users.[10] Another study also found that after an SHA exposure of 1 hour, the serum cotinine concentrations increased at similar levels as in subjects exposed to SHS.[42] That indicates bystanders may systematically absorb the nicotine from acute exposure to SHA.

**Table 2** Country-specific prevalence (%) and duration (minutes/day) of e-cigarette secondhand aerosol (SHA) exposure in selected indoor settings among e-cigarette non-users of the European population aged ≥15 years.* TackSHS survey, 2017–2018

| | | Home | | Workplace/educational venues | | Public transportation | | Private transportation | | Other indoor places | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Country | N† | % | Median‡ (min/day) | % | Median‡ (min/day) | % | Median‡ (min/day) | % | Median‡ (min/day) | % | Median‡ (min/day) |
| Bulgaria | 1035 | 4.6 | 64 | 4.6 | 43 | 2.8 | 17 | 1.3 | 43 | 10.8 | 43 |
| England | 940 | 7.6 | 30 | 10.9 | 14 | 7.9 | 7 | 5.1 | 12 | 14.2 | 17 |
| France | 974 | 12.0 | 34 | 13.2 | 48 | 5.1 | 24 | 5.9 | 17 | 14.2 | 48 |
| Germany | 1000 | 2.3 | 34 | 2.8 | 43 | 2.6 | 30 | 1.4 | 27 | 8.0 | 26 |
| Greece | 959 | 8.1 | 60 | 10.8 | 46 | 3.4 | 43 | 1.6 | 60 | 19.0 | 60.0 |
| Ireland | 916 | 8.8 | 31 | 9.4 | 14 | 3.8 | 7 | 2.3 | 10 | 11.6 | 10 |
| Italy | 1045 | 5.6 | 60 | 6.3 | 43 | 3.3 | 60 | 3.0 | 60 | 5.1 | 60 |
| Latvia | 1009 | 2.1 | 60 | 2.4 | 43 | 0.3 | 21 | 0.3 | 14 | 1.8 | 120 |
| Poland | 718 | 6.6 | 69 | 4.8 | 21 | 2.9 | 14 | 0.9 | 19 | 3.7 | 33 |
| Portugal | 991 | 4.4 | 60 | 4.2 | 21 | 0.3 | 6 | 2.3 | 17 | 6.8 | 18 |
| Romania | 999 | 4.1 | 60 | 4.4 | 43 | 1.4 | 15 | 2.5 | 21 | 3.4 | 24 |
| Spain | 1018 | 1.5 | 10 | 0.5 | 4 | 0.9 | 1 | 0.0 | 0 | 1.9 | 2 |
| Total | 11 604 | 5.8 | 43 | 6.4 | 43 | 3.5 | 14 | 2.7 | 21 | 8.3 | 33 |

*Individual weight was applied to all estimates in each country. For total estimates of the entire sample, country weight are applied with each country contributing in proportion to its population aged 15 years or over.[38]

†Sample size (N) is the unweighted, country-specific number of e-cigarette non-users.

‡Median estimates were calculated among e-cigarette non-users who had been exposed to SHA at the corresponding indoor setting.

A previous study, conducted among smokers in six European countries (Germany, Greece, Hungary, Poland, Romania and Spain) from June to September 2016, also identified differences in SHA exposure prevalence across countries, with Spain having the lowest exposure (18%) and Greece having the highest one (63%).[23] The variation of SHA exposure across countries may reflect a diverse country's e-cigarette use prevalence in Europe. Spain, for instance, was within the lowest e-cigarette use prevalence group (<1%) and had the lowest SHA exposure among others (4.3%). Indeed, the higher odds of SHA exposure in countries with higher e-cigarette use prevalence were evident from our regression analysis as we would expect, especially, if the use of the device is unregulated. The regression analysis revealed that country's e-cigarette use prevalence was an independent factor of SHA exposure among e-cigarette non-users, suggesting the need for countries to restrict the place of e-cigarette use. The policy for e-cigarette use restriction can be included in the country's current tobacco control strategy as, our study has shown, the current score of Tobacco Control Scale was still irrelevant to SHA exposure status. Moreover, a strong association found between SHA exposure and geographical area of the 12 countries might be attributable to the widespread 'vape-free' policy from one country to the neighbouring countries, as has been shown in the policy diffusion theory for local and national smoking ban regulations.[43 44]

Similar to what has been described with SHS exposure, each country's regulatory environment may also affect the differences in SHA exposure among countries.[45–48] Among the 12 countries included in this study, only Greece had introduced a 'vape-free' policy in all indoor settings by the time this study was conducted.[29] Despite the extensive coverage of 'vape-free' policy in Greece, non-users in the country were still markedly more exposed to SHA in indoor settings compared with other countries without any national 'vape-free' policy, like Bulgaria, Germany, Latvia and Romania.[29] In workplaces, including school and university, France, a country which already banned e-cigarette use in such settings, had the highest prevalence of SHA exposure.[29] This finding underscores the importance of implementing and enforcing existing policies on e-cigarette use in indoor places. Most of the SHA exposure occurred in 'other indoor settings', which include bars and restaurants where smoking, but not e-cigarette use is prohibited in all the 12 countries examined.[49] A previous European study indicated a 20% prevalence of e-cigarette use in indoor places where smoking was banned.[23] The greater opportunity of using e-cigarette compared with smoking conventional cigarettes in enclosed spaces, including pubs, bars and restaurants, has been mentioned as one of the motivations of using e-cigarettes in such settings.[27 50] That opportunity may encourage e-cigarette users, most of whom are dual users, to use e-cigarettes as an alternative to smoking in places where smoking is banned, as it is the case in 'other indoor settings'.[3 27 50] Moreover, the already prevalent social norm of smoking in certain recreational facilities, including bars and restaurants, could also drive e-cigarette use in these settings.[51] Thus, they are important factors to be considered in future public policies.

E-cigarette use in homes and private vehicles is a source of involuntary exposure to SHA for vulnerable populations, especially children. Despite the low prevalence of SHA exposure in homes shown in this study, an intense SHA exposure (43 min/day) occurred in such setting. In the UK, less than 10% of e-cigarette users forbid e-cigarette use in their homes, while a study in the USA indicates that about one in five e-cigarette users reported banning e-cigarette use inside their homes and cars.[52] We also identified sociodemographic discrepancies in SHA exposure. Men, young, highly educated, current smokers and e-cigarette past users were more likely to be exposed to SHA in indoor settings. These determinants of SHA exposure were also true for smokers as has been shown in a study among six European countries.[23] Being in the youngest age groups or the higher educational level were also positive determinants for e-cigarette use and awareness about e-cigarettes.[53–55] This peculiarity might be explained by the diffusion of innovation theory which states that early adopters of new behaviours tend to be males and those from higher socioeconomic status.[56] Accordingly, our data also found that SHA exposure was associated with highly educated

**Table 3** Proportion (%) and adjusted OR (aOR) for at least weekly exposure to e-cigarette secondhand aerosol (SHA) and corresponding 95% CI according to selected individual-level characteristics among e-cigarette non-users of European population aged ≥15 years.* TackSHS survey, 2017–2018

| Individual-level characteristics | N† | At least weekly exposed to SHA from e-cigarettes % | aOR (95% CI‡) |
|---|---|---|---|
| Sex | | | |
| Women | 6122 | 15.0 | 1§ |
| Men | 5482 | 17.2 | **1.13 (1.01 to 1.25)** |
| Age group (years) | | | |
| <25 | 1401 | 20.9 | **3.15 (2.52 to 3.94)** |
| 25–44 | 3955 | 19.3 | **2.69 (2.20 to 3.30)** |
| 45–64 | 4218 | 16.4 | **2.23 (1.83 to 2.73)** |
| ≥65 | 2030 | 6.2 | 1§ |
| *P for trend* | | | ***<0.001*** |
| Level of education¶ | | | |
| Low | 4381 | 13.4 | 1§ |
| Intermediate | 4064 | 17.5 | **1.19 (1.05 to 1.35)** |
| High | 3156 | 17.8 | **1.26 (1.10 to 1.44)** |
| *P for trend* | | | ***0.001*** |
| E-cigarette use status | | | |
| Never user | 11 299 | 15.6 | 1§ |
| Past user | 305 | 32.9 | **1.49 (1.14 to 1.95)** |
| Smoking status | | | |
| Never smoker | 6478 | 14.2 | 1§ |
| Former smoker | 1943 | 15.2 | 1.12 (0.96 to 1.31) |
| Current smoker | 3183 | 20.9 | **1.54 (1.36 to 1.74)** |
| Perception of SHA exposure harm¶ | | | |
| Harmless | 2104 | 22.8 | 1§ |
| Harmful | 7662 | 14.6 | **0.69 (0.61 to 0.78)** |

*Country weightwas applied with each country contributing in proportion to its population aged 15 years or over.[38]
†Sample size (N) is the unweighted number of e-cigarette non-users for each corresponding individual-level characteristic.
‡aORs were estimated multilevel logistic random-effects models, to take into account the heterogeneity between the countries. The study country effects were considered as random intercepts, and sex, age, level of education, e-cigarette use status and smoking status as adjusting variables. Estimates in bold are statistically significant at 0.05 level.
§Reference category.
¶The sum does not add to the total because of missing values.

**Table 4** Proportion (%) and adjusted OR (aOR) for at least weekly exposure to e-cigarette secondhand aerosol (SHA) and corresponding 95% CI according to selected country-level characteristics among e-cigarette non-users of European population aged ≥15 years.* TackSHS survey, 2017 to 2018

| Country-level characteristics | N† | At least weekly exposure to SHA from e-cigarettes % | aOR (95% CI)‡ |
|---|---|---|---|
| Geographical area | | | |
| Northern Europe | 2865 | 28.2 | 1§ |
| Western Europe | 1974 | 17.6 | 0.52 (0.22 to 1.27) |
| Southern Europe | 4013 | 10.9 | **0.27 (0.11 to 0.68)** |
| Eastern Europe | 2752 | 11.9 | **0.35 (0.13 to 0.94)** |
| Gross domestic product per capita | | | |
| ≤25.000€ | 5711 | 13.7 | 1§ |
| >25.000€ | 5893 | 16.7 | 1.22 (0.51 to 2.89) |
| Tobacco control scale score | | | |
| ≤50 | 5712 | 12.8 | 1§ |
| >50 | 5892 | 18.0 | 1.31 (0.62 to 2.79) |
| Total population smoking prevalence (%) | | | |
| <20 | 2901 | 20.4 | 1§ |
| 20 to 30 | 2727 | 11.4 | 0.52 (0.22 to 1.25) |
| >30 | 5976 | 16.4 | 0.58 (0.25 to 1.37) |
| P for trend | | | <0.266 |
| Total population e-cigarette use prevalence (%) | | | |
| <1 | 2727 | 8.3 | 1§ |
| 1 to 4 | 6004 | 11.9 | **1.64 (1.05 to 2.56)** |
| >4 | 2873 | 27.8 | **4.35 (2.72 to 6.96)** |
| P for trend | | | **<0.001** |

*Country weightwas applied with each country contributing in proportion to its population aged 15 years or over.[38]
†Sample size (N) is the unweighted number of e-cigarette non-users for each corresponding country-level characteristic.
‡aOR were estimated multilevel logistic random-effects models, to take into account the heterogeneity between the countries. Estimates in bold are statistically significant at 0.05 level.
§Reference category.
¶Geographical area was categorised into Northern Europe (Ireland, Latvia and England), Western Europe (France and Germany), Southern Europe (Italy, Greece, Portugal and Spain) and Eastern Europe (Bulgaria, Poland and Romania) according to United Nations M49 Standard,[35] by the World Bank gross domestic product (GDP) per capita into GDP per capita[36] ≤25.000€ (Bulgaria, Latvia, Romania, Poland, Portugal and Greece) and GDP per capita>25.000€ (England, France, Germany, Ireland, Italy and Spain), by score of[37] Tobacco Control Scale≤50 (Bulgaria, Poland, Portugal, Latvia, Greece and Germany) and Tobacco Control Scale>50 (England, Ireland, France, Romania, Italy and Spain), by country's total smoking prevalence into <20% (Ireland, Italy and England), 20%–30% (Germany, Latvia and Poland) and >30% (Bulgaria, France, Greece, Portugal, Romania and Spain)[33] and by country's total population e-cigarette use prevalence into <1% (Poland, Portugal and Spain), 1%–4% (Bulgaria, Germany, Ireland, Italy, Latvia and Romania) and >4% (France, Greece and England). The latter two were estimated from the TackSHS survey data.

non-users, as it is likely that users and bystanders are peers and they socialise together.

Exposure to SHA has its impact on social norm and using e-cigarette. Constant SHA exposure among the youth may increase their susceptibility to using e-cigarettes and tobacco products, as well as decreased their harm perception of e-cigarettes.[19 57] A higher likelihood of SHA exposure among e-cigarette past users (compared with never users) found in this study may pose a risk of relapse for those who have quit using e-cigarette. An experimental study reported that passive exposure to e-cigarette significantly increased desire to use e-cigarette.[21] Additionally, exposure to SHA may put current smokers at a risk of being dual users, as they might start using e-cigarettes.[58 59] Thus, more preventive campaigns are needed to avoid initiation, relapse and dual use in such vulnerable populations.

In line with a study among youth in the USA,[57] our study found that those who perceived SHA as harmful were less likely to report SHA exposure. Generally, people viewed SHA as less harmful than SHS.[60] A parental interview data in the USA has shown that, while compared with smoke-free policy at homes and cars, there were fewer parents who enforced 'vape-free' homes and cars, suggesting that parents perceived e-cigarette aerosol was safe for their children.[61] Therefore, increasing awareness of the potential harmful effects might decrease SHA exposure.

This study was limited by the inherent nature of the cross-sectional study design and the use of self-reported data by respondents. The accuracy of responses, indeed, relies on participants' perception to sense the passive exposure itself. Moreover, our question did not define the specific sign of SHA exposure (eg, smell, visibility of the cloud, etc) as it may freely capture all possible indicators of SHA exposure. A similar question has also been used by the ITC six European Country survey.[23] Another strength associated with using self-reported exposure is that the respondents assign it to specific setting, which cannot be ascertained when using personal biomarkers of exposure. As the design of our questionnaire does not have a separate question for educational venues, we were unable to estimate specific exposure at such setting. However, we believe this would not undermine our results given the low proportion of student participants (less than 10%) in this study. The questionnaire gathered information on SHA in working and non-working days iseparately, thus preventing potential information bias derived from using longer times of recall but it cannot ascertain daily prevalence. We have computed prevalence of 'at least weekly' exposure that in addition to be reliable, is useful, given the relatively low exposure to SHA.

There was relatively small sample size in each country (approximately 1000 subjects), but the total sample size is large enough to draw an overall inference. Finally, this study had some differences in sampling methods across countries.[33] However, we ensured the representativeness of the sample in proportion to each country's population aged 1 ≥5 years by applying the weight factors into the analyses.

To our knowledge, this is the first study that investigates self-reported exposure to SHA at the population level in European countries using a standardised questionnaire that allows comparison among countries. The duration of SHA exposure described in this study may offer an alternative measure of SHA exposure burden apart from the prevalence. Additionally, countries selected in this study enable us to understand the variation of SHA exposure in countries with diverse e-cigarette regulatory environment.

In conclusion, we found that there was a substantial proportion and duration of exposure to SHA among non-users of e-cigarettes in indoor settings in European countries, with heterogeneity of exposure across countries and among sociodemographic groups. Thus, governments are strongly recommended to include e-cigarettes in smoke-free laws and tailor such legislation to be specifically targeted to vulnerable groups, particularly young people and former users, to protect them from the harms of SHA exposure and the temptation to (re)fall into nicotine addiction. Enforcement to increase compliance with existing e-cigarette use legislation is needed. Finally, future work should include repeated cross-sectional and/or longitudinal studies on SHA exposure to monitor its burden over time.

### What this paper adds

- The growing use of e-cigarettes has raised concerns as the product is potentially harmful both to users and to bystanders. Yet, e-cigarette use has often been observed in indoor places where smoking is prohibited.
- Little is known about population exposure to secondhand aerosol from e-cigarette (SHA) in indoor settings in European countries.
- Our study found that there was a notable proportion and duration of exposure to SHA among non-users in indoor settings in 12 European countries, with variability of exposure across and within countries.

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**Contributors** BA, EF and SG had the original idea for the study; SG, XL and AL contributed to the finalisation of the survey questionnaire; BA and XL carried out the statistical analysis with the supervision of AL; BA wrote the first draft of the article in collaboration with XL, AL, MF, EF and SG; AO, SS, LC, JBS and PAvdB made substantial contributions to conception, design and interpretation of data; all the authors contributed to manuscript preparation and approved its final version prior to submission. SG and EF are the guarantors.

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Supplementary Table 1. Sociodemographic characteristics of e-cigarette non-users of European population aged ≥15 years.* TackSHS survey, 2017-2018 (Total: 11,604)

| | N^ | % | 95% CI |
|---|---|---|---|
| Country | | | |
| Bulgaria | 1035 | 8.9 | 8.4-9.4 |
| England | 940 | 8.4 | 7.6-8.6 |
| France | 974 | 8.6 | 7.9-8.9 |
| Germany | 1000 | 8.3 | 8.1-9.1 |
| Greece | 959 | 7.9 | 7.8-8.8 |
| Ireland | 916 | 9.0 | 7.4-8.4 |
| Italy | 1045 | 8.7 | 8.5-9.6 |
| Latvia | 1009 | 6.2 | 8.2-9.2 |
| Poland | 718 | 8.5 | 5.8-6.6 |
| Portugal | 991 | 8.6 | 8.0-9.1 |
| Romania | 999 | 8.8 | 8.1-9.1 |
| Spain | 1018 | 8.1 | 8.3-9.3 |
| Sex | | | |
| Women | 6122 | 52.4 | 51.4-53-3 |
| Men | 5482 | 47.6 | 46.7-48.5 |
| Age group (years) | | | |
| <25 | 1401 | 12.8 | 12.2-13.5 |
| 25-44 | 3955 | 33.5 | 32.6-34.3 |
| 45-64 | 4218 | 34.6 | 33.8-35.5 |
| ≥65 | 2030 | 19.0 | 18.3-19.7 |
| Level of education° | | | |
| Low | 4381 | 38.6 | 37.7-39.5 |
| Intermediate | 4064 | 35.8 | 35.0-36.7 |
| High | 3156 | 25.5 | 24.7-26.3 |
| E-cigarette use status | | | |
| Never user | 11299 | 97.5 | 97.1-97.8 |
| Past user | 305 | 2.5 | 2.2-2.8 |
| Smoking status | | | |
| Never smoker | 6478 | 59.0 | 58.1-59.9 |
| Former smoker | 1943 | 15.8 | 15.2-16.5 |
| Current smoker | 3183 | 25.2 | 24.4-26.0 |
| Perception of SHA exposure harm° | | | |
| Harmless | 2104 | 23.6 | 22.7-24.4 |
| Harmful | 7662 | 76.4 | 75.6-77.3 |
| Geographic area | | | |
| Northern Europe | 2865 | 14.3 | 13.7-15.0 |
| Western Europe | 1974 | 36.5 | 35.6-37.4 |
| Southern Europe | 4013 | 32.8 | 31.9-33.6 |
| Eastern Europe | 2752 | 16.4 | 15.7-17.1 |
| Gross Domestic Product | | | |

| | | | |
|---|---|---|---|
| per Capita | | | |
| ≤25.000€ | 5711 | 22.2 | 21.4-22.9 |
| >25.000€ | 5893 | 77.8 | 77.0-78.6 |
| Tobacco Control Scale score | | | |
| ≤50 | 5712 | 38.0 | 37.1-38.9 |
| >50 | 5892 | 62.0 | 61.1-62.9 |
| Total population smoking prevalence (%) | | | |
| <20 | 2901 | 29.5 | 28.6-30.3 |
| 20-30 | 2727 | 30.9 | 30.0-31.7 |
| >30 | 5976 | 39.7 | 38.8-40.6 |
| Total population e-cigarette use prevalence (%) | | | |
| <1 | 2727 | 24.1 | 23.4-24.9 |
| 1-4 | 6004 | 44.7 | 43.7-45.6 |
| >4 | 2873 | 31.2 | 30.3-32.0 |

Abbreviation: CI, Confidence Interval

* Country-level weight factors are applied with each country contributing in proportion to its population aged 15 years or over, except for country variable where individual-level weight factors in proportion to country's population aged 15 years or over are applied to all estimates in each country.[38]
^ Sample size (N) is the unweighted number of e-cigarette non-users
° The sum does not add to the total because of missing values.

# PAPER 4

## Environmental and individual exposure to secondhand aerosol of electronic cigarettes in confined spaces: Results from the TackSHS Project

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ORIGINAL ARTICLE

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# Environmental and individual exposure to secondhand aerosol of electronic cigarettes in confined spaces: Results from the TackSHS Project†

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## Abstract

Secondhand electronic cigarette (e-cigarette) aerosol (SHA) might impair indoor air quality and expose bystanders. This study aims to investigate exposure to SHA in controlled conditions of enclosed settings simulating real-world scenario. An experiment was performed in a car and in a room, in which SHA was generated during a 30-minute *ad libitum* use of an e-cigarette. The experiment was replicated on five consecutive days in each setting. We measured $PM_{2.5}$, airborne nicotine concentrations, and biomarkers of exposure to SHA, such as nicotine metabolites, tobacco-specific nitrosamines, propylene glycol, and glycerol in bystanders' saliva samples before, during, and after the exposure period. Self-reported health symptoms related to exposure to SHA were also recorded. The results showed that the highest median $PM_{2.5}$ concentration was recorded during the exposure period, being 21 μg/m$^3$ in the room setting and 16 μg/m$^3$ in the car setting—about twofold increase compared to

* The TackSHS Project Investigators provided in Appendix 1.

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the baseline. Most concentrations of the airborne nicotine and all biomarkers were below the limit of quantification in both settings. Bystanders in both settings experienced some short-term irritation symptoms, expressed as dry throat, nose, eyes, and phlegm. In conclusion, short-term use of an e-cigarette in confined spaces increased indoor $PM_{2.5}$ level and caused some irritation symptoms in bystanders.

**KEYWORDS**
biomarker, electronic cigarette, electronic nicotine delivery systems, environmental pollution, passive exposure

**Practical Implications**

- Our study demonstrates that short-term electronic cigarette (e-cigarette) use in confined spaces, a room and a car, more than doubled the $PM_{2.5}$ concentration and, in a room, the concentration remained higher than the baseline level after the e-cigarette use was stopped.
- When air ventilation was present in an enclosed space, the distance apart between e-cigarette user and bystanders used in this study did not change substantially the short-term exposure to $PM_{2.5}$.
- Although we detected very low levels of airborne nicotine and biomarkers of passive exposure to e-cigarette aerosol after a brief e-cigarette use, bystanders reported some mild irritation symptoms, such as dry throat, eyes, and nose, after the exposure to e-cigarette aerosol.
- These findings are useful to inform policy makers that e-cigarette use should be considered in indoor clean air policy given its ability to impair the indoor air quality and negatively affect bystanders.

## 1 | INTRODUCTION

The use of electronic cigarettes (e-cigarettes) is spreading worldwide, and subsequent exposure to their secondhand aerosol (SHA) is becoming a matter of concern.[1] Recent studies show that exposure to SHA among non-users of e-cigarettes is not negligible, as 16% of adults from the general population in 12 European countries reported to be exposed to SHA within the past 7 days,[2] and about 37% of smokers in six European countries reported ever-exposure to SHA.[3]

Unlike secondhand tobacco smoke (SHS), SHA originates from the aerosol exhaled by an e-cigarette user only, because e-cigarettes do not produce sidestream emissions.[4] Nevertheless, many studies reported that SHA contains hazardous compounds such as nicotine, particulate matter ($PM_1$, $PM_{2.5}$, $PM_{10}$), volatile organic compounds, propylene glycol (PG), glycerol, metals, tobacco-specific nitrosamines (TSNAs), and flavorings.[5-9]

A large body of evidence has shown that some of the compounds in SHA impair indoor air quality. Fine particulate matter ($PM_{2.5}$) concentration markedly increased during e-cigarette use sessions with human volunteers in settings such as a room,[9–11] home,[6] or e-cigarette conventions.[12,13] Additionally, airborne nicotine concentration was found to increase after an e-cigarette use session during an experimental study in a room,[10] and in an observational study in which the concentration in homes of e-cigarette users was compared to that of non-users' homes.[14] Some of TSNAs, such as N-nitrosonornicotine (NNN) and nicotine-derived nitrosamine ketone (NNK), which are carcinogenic, [15–18] have been identified in e-cigarette aerosol, although in low levels.[19]

Although the concentrations of toxic compounds in e-cigarette aerosols are lower than those emitted from conventional cigarettes,[8] exposure to SHA may still pose harm to bystanders. Indeed, many substances in SHA are harmful to health. $PM_{2.5}$, for example, is known to cause cardiovascular, respiratory diseases,[20] diabetes, and cancer.[21] Exposure to nicotine may cause nicotine-related diseases, such as cardiovascular disease and impaired brain function.[22–24] Exposure to PG aerosols in the concentration typically found in e-cigarettes has been found to cause irritation to the eyes and throat in some individuals.[8] In an experimental study, exposure to aerosolized glycerol caused a slight local irritant effect on the respiratory tract of mice.[25] Although e-cigarette use has been shown to cause inflammation in users and was recently linked to the development of respiratory diseases,[10,26–28] only a small number of studies have reported adverse health symptoms from exposure to SHA. Some studies found that exposure to SHA may result in a reduced respiratory function and headache, dry mouth, ocular, nasal, and airway irritation symptoms among e-cigarette non-users[29–31] and exacerbate asthma symptoms in youth with asthma.[32]

Assessing the exposure to SHA in bystanders is important, because they may be involuntarily exposed to hazardous substances from the aerosol.[8] However, previous studies on SHA exposure were based on the measurement of indoor air quality and biomarkers that were conducted by using either machine-generated aerosol, in a real-use setting but poorly controlled, or in an extreme scenario such

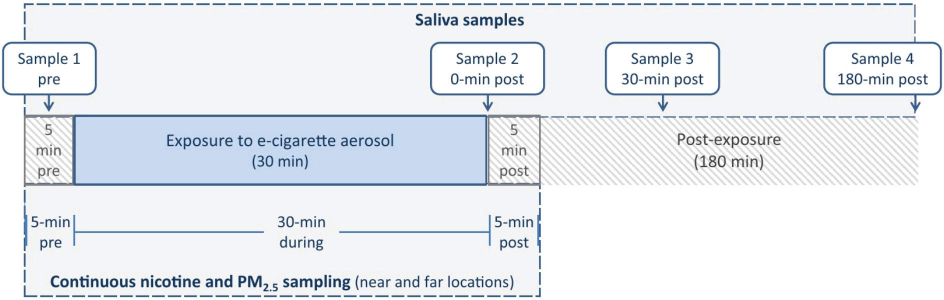


**FIGURE 1** Sequence of environmental and biological exposure measurements conducted in a car and in a room. TackSHS Study, 2019

as e-cigarette events that did not represent common use in real life. They were also largely conducted in single settings.

To address the gap, the present study, developed within the TackSHS project,[33] aimed to comprehensively investigate bystanders' short-term exposure to SHA in controlled conditions that emulate real-life scenarios by carrying out a combination of environmental and biological assessment in confined settings. Furthermore, self-reported health symptoms after SHA exposure were also explored.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

We performed an experimental study in two confined settings, a room and a car, in which two bystanders were exposed to aerosol produced from short-term e-cigarette use. This study was performed with volunteers in the course of one week in each setting, firstly in the room and, after 10 days, in the car. The study was conducted in July and August 2019.

### 2.2 | Participants

We enrolled two healthy non-users of e-cigarettes or any other tobacco/nicotine product (the "non-users") and one healthy experienced e-cigarette user (the "user"). Participants were recruited through a database of previous studies and personal contacts of the research team. All participants agreed to participate and received a monetary compensation for their participation.

The inclusion criteria for the non-users were: to be an adult (18 years old and above), never user of e-cigarettes or have stopped using them for more than 6 months, never user of any tobacco or nicotine product or have quit for more than six months, and not being regularly exposed to SHS or SHA in any setting. For the user, the inclusion criteria were to be an adult (18 years old and above), daily e-cigarette user (at least during the past 2 months prior to the study), and not being a user of any tobacco/other nicotine product (at least 2 months prior to the study). The exclusion criteria for all participants were: pregnancy or breastfeeding, ongoing or recent illness (less than four weeks prior to the study), acute or chronic condition or disease (eg, diabetes, asthma, chronic obstructive pulmonary disease, hypertension), and consumption of any type of medication (less than two weeks before the study).

Characteristics of the volunteers recruited were as follows: non-users were one female and one male; aged 40 and 49, respectively; both Caucasians; the user was a 59-year-old Caucasian female, who had used e-cigarette daily for 3.5 years by the time of the study.

The user was asked to use her own e-cigarette and e-liquid during the study, to reproduce her typical e-cigarette use. The e-cigarette was Eleaf iStick TC40W, this is a "Mod" e-cigarette consisting of a vaporizer with nickel coil wire, a rechargeable battery (capacity 2600 mAh), and a cartridge containing the e-liquid (open tank). The coil was not changed throughout the experiments. The temperature of the e-cigarette used was set by the user (220°C, 1 ohm, 40 watts) and maintained constant across experiments. The e-liquid (60 mL) contained nicotine (3 mg/mL), PG and glycerol (50:50 ratio) and was cinnamon cookie flavored (Atmos Lab brand). The same e-cigarette and e-liquid were used during all replicates of the study.

### 2.3 | Experiment conditions

The study aimed to simulate a real-world exposure to SHA by the use of one e-cigarette in a room and in a car. The experiment was replicated five times, on five consecutive days (Monday-Friday) in each setting. After each daily replicate, all participants were not allowed to use e-cigarette or be exposed to SHA or SHS for three hours after the experiment. To ensure no biological marker of exposure remained in the body of non-users, we made a 10-day washout window between experiments in both settings.

We first conducted the experiment in a 14.08 $m^2$ × 2.50 m (35.2 $m^3$) office room in the Catalan Institute of Oncology, Barcelona. During the experiment, the user and the two non-users sat around a small table (60 × 120 cm); non-users sat approximately one meter from the user. A researcher was also present to monitor the experiment. The overall experiment lasted 40 minutes which was stratified into three parts (Figure 1). The first part included 5-minute baseline measurements, where the user was not allowed to use the e-cigarette. The second part consisted of 30 minutes of exposure to SHA generated by *ad libitum* use of the e-cigarette by the user; the number of puffs per minute was recorded during this period. The third part of the experiment included five minutes of post-exposure measurements when the user stopped using the e-cigarette, but all participants remained in the room. The windows and the door were kept closed during the experiments, simulating a real-life situation during working hours. The room was ventilated by opening the windows for the most part of the day, before and after the experiments, and was kept unoccupied during the whole week when the experiments were not being conducted.

We used a medium-size car (VW Touran, interior size approx. 10 $m^3$) as the second setting, in which cigarettes or e-cigarettes were never used. During the experiment, there were the user (sat on the front passenger seat), the two non-users (sat on the rear seats), the driver, and one researcher on the rear seat. The overall experiment lasted 40 minutes which consisted of the same three parts as in the room (Figure 1). Once the car runs on the circuit, the experiment started. The car ran continuously on 1.3 km circuit at speed up to 70 km/h during the 40-minute experiment, with the two front windows half-opened (30 cm) and the rear windows closed, simulating a real-life situation in a car's short journey. The car was ventilated 15 minutes after each experiment by running the car without passengers and let all the windows fully open. The car remained in the parking unoccupied during the whole week when the experiments were not being conducted.

In both settings, any system of heating or air conditioning during the experiment was avoided. The relative humidity during all experiments was lower than 85%. During the 5-day experiment, the range of the temperature in the room experiment was 22.0°C–26.3°C, with a mean temperature of 26.6°C and an outdoor mean temperature of 27.9°C. The temperature inside the car ranged from 25.7°C to 32.5°C, with a mean of 25.7°C and an outdoor mean temperature of 29.5°C. The outdoor temperature and relative humidity were checked against an official weather report Web site (www.meteo.cat).

## 2.4 | Measurements

### 2.4.1 | Environmental measurements

We monitored gas-phase nicotine using nicotine samplers of 37 mm in diameter containing a filter treated with sodium bisulfate as performed in previous studies.[34–36] We used active sampling with nicotine samplers attached to air pumps (SKC SideKick© 224-52MTX) set at a constant flow rate of 3 L/min. The air pumps were calibrated before and after monitoring using a gas flow calibrator Bios Defender 510 M (Mesa Labs company). We sampled airborne nicotine for each of the three parts of the experiment separately. In total, 60 air samples were analyzed for the determination of nicotine concentration (μg/$m^3$) at the laboratory of the Public Health Agency of Barcelona by gas chromatography-mass spectrometry. For every 20 nicotine samples, one blank filter that had not been exposed was analyzed for control purposes. We quantified the time-weighted average nicotine concentration by dividing the amount of nicotine extracted from the filter by the volume of air sampled (estimated flow rate multiplied by the minutes the filter had been exposed). This procedure has a limit of quantification (LOQ) of 5 ng per filter, which is equivalent to 0.06 μg/$m^3$ of nicotine per 30 minutes of exposure. For values that were under the LOQ, we assigned half of this LOQ's value when they were not more than 20% of data in the category of analysis; otherwise, we presented them as "<LOQ."

Besides airborne nicotine, we measured real-time airborne mass of $PM_{2.5}$ concentration at 1-second interval with two aerosol monitors (TSI SidePak™ AM510). We also used a third monitor to simultaneously measure outdoor $PM_{2.5}$ concentration as background information. Given the absence of standard calibration factors for e-cigarette aerosol, we applied individual SHS gravimetric calibration factors to each of the three devices, as done in other studies.[12,30,37] These k-factors were obtained in individual experiments with a reference instrument (Met One Instruments BAM 1020) that automatically measures and records ambient particulate mass concentration levels using the principle of beta ray attenuation.[33,38] The individual k-factors obtained for each monitor were 0.353, 0.367, and 0.393. $PM_{2.5}$ data were downloaded to a local computer afterward from the monitors' internal memory for further analyses.

Airborne nicotine and $PM_{2.5}$ were measured simultaneously for each of the three parts of the experiment separately in both settings (Figure 1). For indoor measurement, two nicotine air pumps and two $PM_{2.5}$ monitors were used in each setting. We ensured that all devices were placed in a location where the air was adequately circulating. In the room, one nicotine sampler and one $PM_{2.5}$ monitor were placed on a table, about one meter from the user, where all participants sat around (near-field), and the other nicotine sampler and $PM_{2.5}$ monitor on another table, at about three meters away from the user (far-field). In the car, one nicotine sampler and one $PM_{2.5}$ monitor were fixed at the back of the headrest of the driver's seat, about one meter from the user (near-field). For the far-field measurements in the car, we placed the second nicotine sampler and $PM_{2.5}$ monitor about two meters away from the user, on the headrest of the rear seat, so as to simulate a child's exposure from an adult using an e-cigarette in the car.

### 2.4.2 | Biological measurements

Saliva samples were collected from the two non-users four times in each daily replicate in both settings (Figure 1): once pre-exposure (just before starting the exposure) and three times after the exposure period finished (0-, 30-, and 180-minute post-exposure), leading to a total of 80 saliva samples. Samples were prepared into two aliquots for storage at −20°C in a freezer in the laboratory at

ICO-IDIBELL. All samples were sent in dry ice to the laboratory at the Hospital del Mar Medical Research Institute for analyses by liquid chromatography-tandem mass spectrometry to determine the concentration of nicotine (LOQ: 0.50 ng/mL), cotinine (LOQ: 0.05 ng/mL), 3′-OH-cotinine (LOQ: 0.040 ng/mL), nornicotine (LOQ: 0.10 ng/mL), tobacco-specific nitrosamines (NNN, NNK, and 4-(met hylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) with LOQ of 1.0, 2.0, and 0.50 pg/mL, respectively), PG (1,2-PG and 1,3-PG with LOQ for both: 3.0 nmol/mL), and glycerol (LOQ: 10.0 nmol/mL). We assigned half of the LOQ values for biomarker concentrations that were lower than their LOQ if they were not more than 20% of data in the category of analysis; otherwise, we presented them as "<LOQ."[18,39]

#### 2.4.3 | Observational measurements

*Puff frequency*

The volunteer used the e-cigarette *ad libitum*. The number of puffs produced each minute by the user was recorded by a researcher in a register sheet during the 30-minute exposure period.

*Self-reported health symptoms*

Participants were asked to answer a brief questionnaire[30] to identify potential health symptoms associated with their exposure to SHA during its completion. The questionnaire was self-administered during the pre-exposure period and also at 0-, 30-, and 180-minute post-exposure, concurrently with the collection of saliva samples. The questionnaire included symptoms of irritation relating to ocular system (itchiness, burning, watery eyes, and dryness), nasal system (nasal drip, itchiness, dryness, sneezing, and stuffiness), and throat-respiratory system (dryness, soreness, cough, phlegm, and breathlessness) as well as general complaints (headache, nausea, and fatigue). For each symptom in the questionnaire, participants indicated the intensity level of the symptoms they perceived as none (score 0), little (score 1), moderate (score 2), strong (score 3), and very strong (score 4).

*General information*

An *ad hoc* questionnaire was filled in by the participants at the enrollment time to gather information about sociodemographics, smoking status, e-cigarette use patterns, and their usual exposure to SHS and SHA. Also, prior to each experimental session, the participants were asked to fill in a specific form to report if there had been exposed to SHS or SHA in different settings, the day before to that experimental session.

### 2.5 | Statistical analysis

We estimated the median concentration of airborne nicotine and $PM_{2.5}$ ($\mu g/m^3$) before, during, and after exposure periods in each setting across the five replicates (day 1–5) of the experiment. Median test was performed to obtain *p*-values for the difference of estimates of the near- and far-field exposure and in different periods (ie, pre- vs during exposure; during vs post-exposure; pre- vs post-exposure) of $PM_{2.5}$. *p*-values for the difference between $PM_{2.5}$ concentration in indoor (near- and far-field exposure, in both settings) and outdoor were also calculated. In case more than 20% of airborne nicotine values were under the LOQ in a category of analysis, we assigned it as "<LOQ." The number of puffs across time of the exposure period were plotted against $PM_{2.5}$ concentration.

We estimated the median concentration of each biomarker pre-exposure, 0-, 30-, and 180-minute post-exposure in each setting across the five replicates of the experiment. Similar to airborne nicotine, we only calculated the median concentration of a category when more than 20% of its values were higher than the LOQ.

The total number of symptoms reported by non-users was calculated and grouped according to the experiment period (pre-exposure, 0-, 30-, and 180-minute post-exposure) in each replicate and setting. The top three most frequent symptoms reported by the non-users were identified and explored for their intensity level.

In all analyses, the significance level was set at $p$-value < 0.05. The analyses were performed with STATA 14.0.

### 2.6 | Ethical issues

The Ethics & Research Committee of the Bellvitge University Hospital approved the overall project (TackSHS Project, PR341/15)[33] as well as this specific study (PR217/19), which was also registered at www.clinicaltrials.gov (NCT04140617). All participants and researchers taking part in the data collection were properly informed about the potential harms of exposure to SHA, and all of them provided written consent.

## 3 | RESULTS

### 3.1 | Environmental markers

The overall median concentrations of $PM_{2.5}$ over the five replicates in both settings are summarized in Table 1. In the room setting, $PM_{2.5}$ concentration during and after the exposure period was significantly higher than baseline concentrations, while in the car, this occurred only during the exposure period.

The highest median $PM_{2.5}$ concentrations in the room and the car were identified during the exposure period—about twofold the baseline median concentrations in both settings. During exposure, the highest concentration in the room was at near-field exposure (median: 21 $\mu g/m^3$; IQR: 11–88 $\mu g/m^3$), while in the car, the concentration was the same for near- and far-field (median: 16 $\mu g/m^3$; IQR near-field: 10–31 $\mu g/m^3$, IQR far-field: 10–28 $\mu g/m^3$). Additionally, the concentrations of indoor $PM_{2.5}$ in pre-exposure period in both settings and at both distances (near- and far-field) were significantly lower than the outdoor $PM_{2.5}$ levels. During exposure period, the levels of all indoor $PM_{2.5}$ were significantly higher than those of outdoors.

**TABLE 1** Median concentration and its corresponding interquartile range (IQR) of $PM_{2.5}$ (both expressed in µg/m$^3$) measured at near-field (1 meter) and far-field (2–3 meters) distance from an e-cigarette user, and in outdoors before, during, and after exposure from e-cigarette use in room and car settings across five replications. TackSHS Study, 2019

| | Pre-exposure (IQR) | During exposure (IQR) | Post-exposure (IQR) | *p*-value[a] | *p*-value[b] | *p*-value[c] |
|---|---|---|---|---|---|---|
| Room | | | | | | |
| Near-field | 8 (6–11) | 21 (11–88) | 19 (11–50) | <0.001 | 0.398 | <0.001 |
| Far-field | 7 (6–9) | 18 (9–81) | 19 (12–40) | <0.001 | 0.280 | <0.001 |
| Outdoors | 17 (14–25) | 11 (9–12) | 10 (9–11) | <0.001 | <0.001 | <0.001 |
| *p*-value[d] | <0.001 | <0.001 | 0.729 | | | |
| *p*-value[e] | <0.001 | <0.001 | <0.001 | | | |
| *p*-value[f] | <0.001 | <0.001 | <0.001 | | | |
| Car | | | | | | |
| Near-field | 7 (6–10) | 16 (10–31) | 8 (6–10) | <0.001 | <0.001 | <0.001 |
| Far-field | 7 (6–11) | 16 (10–28) | 8 (6–11) | <0.001 | <0.001 | 0.553 |
| Outdoors | 17 (14–25) | 11 (9–12) | 10 (9–11) | <0.001 | <0.001 | <0.001 |
| *p*-value[d] | 0.001 | 0.474 | 0.483 | | | |
| *p*-value[e] | <0.001 | <0.001 | <0.001 | | | |
| *p*-value[f] | <0.001 | <0.001 | <0.001 | | | |

[a]*p*-value for pre- vs during exposure.
[b]*p*-value for during vs post-exposure.
[c]*p*-value for pre- vs post-exposure.
[d]*p*-value for near-field vs far-field.
[e]*p*-value for near-field vs outdoor.
[f]*p*-value for far-field vs outdoor.

After the user stopped using the e-cigarette in the room, $PM_{2.5}$ concentration (median: 19 µg/m$^3$; IQR: 11–50 µg/m$^3$ and 12–40 µg/m$^3$ at near- and far-field exposure, respectively) did not fall significantly from the concentration during the exposure period ($p = 0.398$ for the comparison at near-field exposure and $p = 0.280$ for the comparison at far-field exposure) and remained significantly higher than the corresponding pre-exposure levels. A significantly higher median $PM_{2.5}$ concentration was also found at near-field (21 µg/m$^3$; IQR: 11–88 µg/m$^3$) compared to the far-field (18 µg/m$^3$; IQR: 9–81 µg/m$^3$) exposure when the e-cigarette was used, but not after its use was stopped. After e-cigarette use was stopped, indoor $PM_{2.5}$ levels at both distances returned being lower than the outdoor $PM_{2.5}$ in the room, but not in the car.

The median concentrations of $PM_{2.5}$ after the exposure session in the car at both distances dropped significantly to half the concentration measured during the exposure period. After the puffing ceased, $PM_{2.5}$ concentration at near-field exposure remained at a higher level (8 µg/m$^3$; IQR: 6–10 µg/m$^3$, $p < 0.001$) compared to the pre-exposure level. The median concentration of $PM_{2.5}$ at near- and far-field exposure was similar in both periods, during ($p = 0.474$) and after exposure ($p = 0.483$).

For airborne nicotine, the majority of the median concentrations were below the LOQ, and, thus, we were unable to estimate the differences of the nicotine concentration in pre-, during, and post-exposure periods, and between near- vs far-field measurements.

The distribution of real-time $PM_{2.5}$ concentration during a whole experimental session at near- and far-field exposure is shown in Figure 2 derived through particles monitoring before (first 5 minutes), during (30 minutes), and after exposure period (last 5 minutes) in the 5th and 4th day of the 5-day replication for room (Panel A) and car (Panel B), respectively. The graphs show that the trend of $PM_{2.5}$ concentration follows the variation in the number of puffs produced by the user (indicated with bars).

The total number of puffs per 30-minute exposure period across the five-day replication ranged from 28 to 42 in the room and from 51 to 84 in the car. As illustrated in Figure 2, $PM_{2.5}$ concentration at near- and far-field exposure increased immediately as the first puff was made in the room (Panel A) and in the car (Panel B) and quickly decreased after the puffing stopped. In the room, the peak values for near- and far-field reached about four and three times, respectively, higher than pre-exposure concentration. $PM_{2.5}$ concentration lasted 1–5 minutes to reach its peak concentration when the e-cigarette was used. A similar trend occurs in the car where the highest number of puffs per minute (4 puffs) was followed by the highest peak value of $PM_{2.5}$ concentration at near- and far-field exposure. Also, the peak concentration during the exposure period was sevenfold higher than the baseline concentration at both distances. The time lag for $PM_{2.5}$ concentration to reach its peak after a given puff in the car setting was about 0–1 minutes, shorter than in the room.

## 3.2 | Biomarkers

The non-users' median concentration of saliva nicotine, cotinine, 3-OH-cotinine, nornicotine, NNN, NNK, NNAL, 1,2-PG, 1,3-PG, and glycerol before, during, and after the exposure period in the room and

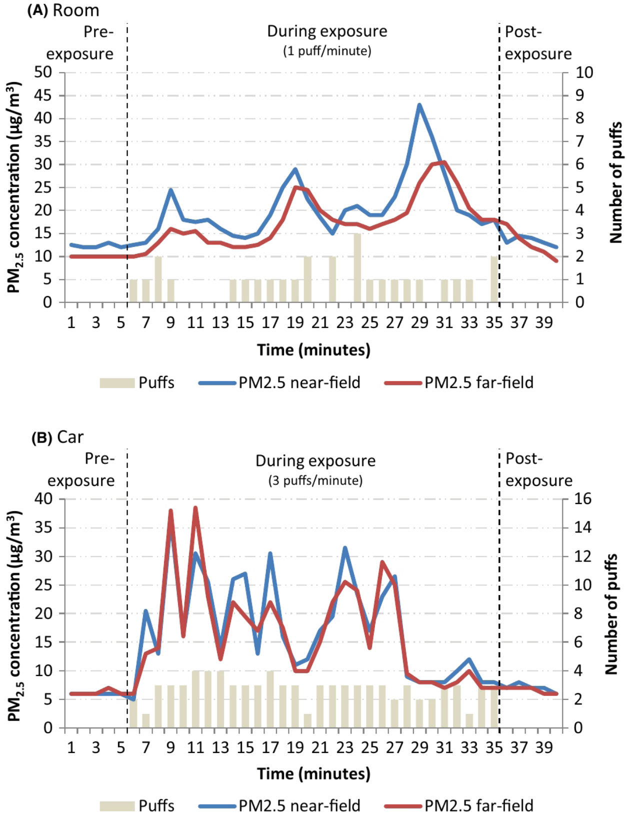


FIGURE 2 The time course of $PM_{2.5}$ concentration at near- (1 meter) and far- (2–3 meters) field exposure in day 5 of room (Panel A) and day 4 of car experiment session (Panel B) related to the number of puffs performed by an e-cigarette user. The exposure period lasted 30 minutes (between minutes 5 and 35 in the graphs). The three parts of the experiment are indicated by vertical dashed lines. TackSHS Study, 2019

car settings were mostly below the LOQ. Eight out of 10 values of the cotinine concentration at 0-minute post-exposure in the room were higher than its LOQ (0.050 ng/mL), ranging from 0.051 to 0.093 ng/mL, with a median of 0.071 ng/mL (IQR: 0.054–0.087 ng/mL).

### 3.3 | Short-term health symptoms

Figure 3 shows the total number of short-term symptoms reported by each non-user before (pre-exposure), right after (0-min post-exposure), 30 minutes (30-minute post-exposure), and 3 hours (180-minute post-exposure) after the exposure period ended across the five replicates in each setting. The highest combined number of all symptoms reported by both non-users occurred on the first day in each setting, reporting 14 and 9 symptoms in the room, and 13 and 8 symptoms in the car for non-user 1 and 2, respectively. In the room (Figure 3, Panel A), the highest number of symptoms was mainly reported right after the exposure period (0-minute post-exposure) except for day 4, where the non-user 1 had more symptoms later (30-minute post-exposure). Some symptoms were still reported at 30 and 180 minutes after exposure. The three most reported symptoms in the room by both non-users were dry throat, dry nose, and phlegm in the throat, with mild intensity (average score 1 in the 0–4 range). In the car (Figure 3, Panel B), most symptoms were also reported just after the exposure ended (0-min post-exposure), and few symptoms remained until 180 minutes after exposure period. Dry throat, dry nose, and dry eyes were the three most frequently reported symptoms by the non-users. Both non-users experienced a mild intensity (average score 1) for the three symptoms from immediately (0-minute post-exposure) until 180 minutes after exposure.

## 4 | DISCUSSION

This study evaluated exposure to SHA by measuring the concentration of airborne markers, biomarkers, and self-reported short-term

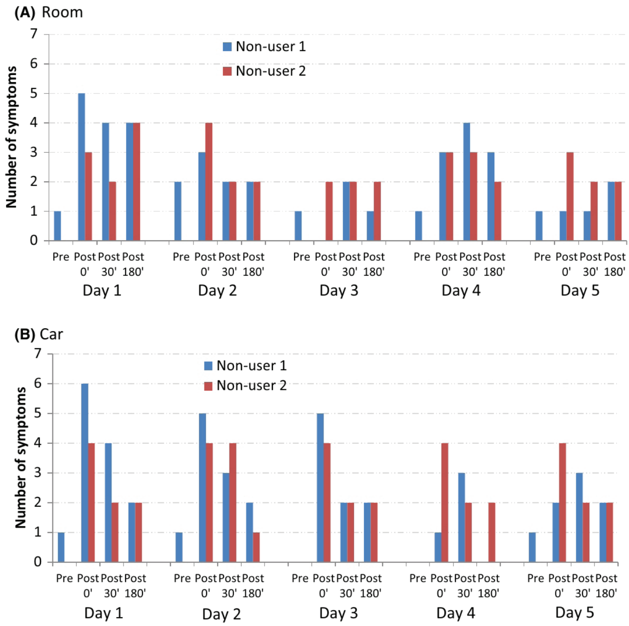


FIGURE 3 Number of short-term health symptoms reported by the two non-users exposed to secondhand aerosol from e-cigarettes at different times of the experiment across 5-day replications in room (Panel A) and car settings (Panel B). No symptoms were reported by the non-users at the time where the bars are not present in the graph. TackSHS Study, 2019

health symptoms in bystanders while an e-cigarette was used in a room and in a car, simulating real-world conditions.

The highest median $PM_{2.5}$ concentration during e-cigarette use across the 5 days replication found in the present study (21 µg/m$^3$) was lower than those found in similar studies conducted in a room (mean concentrations: 246.9–289.5 µg/m$^3$) and in cars (mean concentrations: 75–490 µg/m$^3$).[11,40] However, in those studies, the exposure period lasted shorter than the present study, (6.5 minutes[11] and 20 minutes[40]), did not utilize *ad libitum* use of e-cigarette,[11,40] used different e-cigarette types (cigalike, tank, and adjustable model),[11] and higher nicotine level (12 mg/mL[40] and 18 mg/mL[11] ) than in our study (3 mg/mL). Previous studies suggested that variations in the concentration compounds of e-cigarette aerosol, including $PM_{2.5}$, might be accounted to user puffing pattern (duration and frequency) as well as to e-cigarette brand, type, voltage, and flavor additive.[11,41] Also, the studies from Schober et al., 2019 and Volesky et al., 2018[11,40] measured the $PM_{2.5}$ load by reporting the mean concentration of $PM_{2.5}$, instead of median concentration as used in the present study, which might lead to a higher, but biased, estimation of $PM_{2.5}$ concentrations due to their non-normal data distribution. We used the median as point of estimates for the $PM_{2.5}$ concentration due to extremely skewed distribution of our data. For example, the mean $PM_{2.5}$ concentrations during exposure for the near-field exposure were 104 and 35 µg/m$^3$ in room and car, while the reported median values were 21 and 16 µg/m$^3$, respectively.

Although the highest median $PM_{2.5}$ concentration in our study did not exceed the outdoor guidance level of World Health Organization air quality standard (25 µg/m$^3$ as daily average)[42] and the United States Environmental Protection Agency Air quality index (35 µg/m$^3$ as daily average),[43] the concentration we found is not negligible and illustrates that fine particulate concentrations approximately double when bystanders spend time in typical indoor environments where one e-cigarette user is present. A multi-country pooling of 22 European cohorts found that there was a significant increase in the hazard ratio for natural-cause mortality for each 5 µg/m$^3$ increase in $PM_{2.5}$ exposure, even when the concentration was below the limit value of 25 µg/m$^3$.[44] Extensive evidence indicates that e-cigarette particles and droplets are less toxic compared to cigarette smoke. Evidence also indicates that one single e-cigarette user generates substantially lower $PM_{2.5}$ concentration compared to that of cigarettes, but the concentration markedly increases with the increase in the number of e-cigarette users.[8] However, other studies focusing on the physical properties of the aerosol and its deposition in the respiratory system have found that the numbers of e-cigarette droplets doubled those of cigarettes' particles[45,46]; thus, this should be taken into consideration when assessing the potential toxicity of e-cigarette aerosol and its compounds.

E-cigarette use increases indoor $PM_{2.5}$ concentration, as shown by a significantly higher concentration during e-cigarette use (vs. pre-exposure) at both near- and far-field exposure. This trend was in line with previous experimental studies which showed an increase in

$PM_{2.5}$ concentration during puffing period to a mean concentration level that ranged from 20 to 290 µg/m$^3$.[9–11] In an extreme situation, a study conducted during an e-cigarette convention found that the concentration of $PM_{2.5}$ was able to reach as high as 819 µg/m$^3$,[12] levels that are higher than in hookah cafes and bars that allow smoking inside.[47] The increased level of indoor $PM_{2.5}$ during exposure period at both settings was also confirmed by the higher concentrations of indoor $PM_{2.5}$ than that of the outdoors, while they were lower than the outdoor measurements in the pre-exposure period.

The increasing pattern of $PM_{2.5}$ concentration was also suggested by Figure 2, where the more puffs generated by the user, the higher the $PM_{2.5}$ concentration in the room and the car. This is consistent with the findings from a study where $PM_{2.5}$ peaks were concurrent with e-cigarette puffs made at homes of e-cigarette users[6] and another study conducted in a room.[11]

We found that $PM_{2.5}$ concentration, at both distances in the room, did not return to the baseline level five minutes after the e-cigarette use ceased, while at a far-field exposure in the car, the concentrations significantly decreased from that registered during the puffing period, dropping to the baseline level. $PM_{2.5}$ levels remained higher in the room, as also suggested by the comparison with the outdoor levels in the post-exposure period. The observed differences between room and car might be explained because the concentrations did not start dropping from the same level—$PM_{2.5}$ concentrations during the exposure period were higher in the room than in the car—and because the car, unlike the room, had half-open windows while moving allowing ventilation, which has been shown to impact $PM_{2.5}$ measurements.[48] Previous studies found a variation in the duration of $PM_{2.5}$ decay, from four minutes to one day after e-cigarette use stopped, depending of the peaked concentrations observed.[11,12,41] The diversity in the rate of decay may be affected by the dilution, evaporation of the e-cigarette emission, and the ambient partial pressure of the emission.[41] Thus, it is hypothesized that the setting's volume and air flow may play a role in the $PM_{2.5}$ evaporation rate. One aspect that merits a mention is the fact that e-cigarette aerosol starts evaporating within seconds, and thus there is a potential gap between the $PM_{2.5}$ concentration released by the puffing and that counted by the devices; this may result in a potential underestimation of the immediate $PM_{2.5}$ concentration exhaled by the user. Nevertheless, the $PM_{2.5}$ concentrations measured by the devices were likely to be closer to those inhaled by bystanders in real conditions as the devices were placed in typical distance of bystanders from e-cigarette user.

The variability observed between $PM_{2.5}$ concentrations at near- and far-field exposures during e-cigarette use periods in the room indicates that the distance between e-cigarette user and bystander does matter in short periods of exposure when there is not any system to dissipate the particles such as a fan or other ventilation methods. Nevertheless, the distance became an unimportant factor if air ventilation is present, as we found in the car. Previous evidence shows that the further the distance $PM_{2.5}$ was measured from the e-cigarette user, the lower the $PM_{2.5}$ concentration measured.[11,49] At a further distance, the particles in the aerosol are less detected because of the nature of the particles which are volatile and that are less able to travel far from the user without ventilation systems.[49] It is worth to note that this finding does not have implications with regard to the safe distance for SHA exposure.

Unlike the present study, previous experiments showed an increased concentration of airborne nicotine during e-cigarette use period. However, these studies had longer periods of e-cigarette use, from 2 to 12 hours, involved more than one user at a time, and did not employ *ad libitum* use.[9,10,40] The unquantifiable concentration of airborne nicotine in this study may be because the method only captured the nicotine in the gas phase, not particle phase, thus, underestimating the chemicals present.[50] The largest increase in airborne nicotine from e-cigarette use is in the particle phase compared to the gas phase.[9] Additionally, the e-cigarette user in our study used a relatively low concentration of nicotine in the e-liquid (3 mg/mL) compared to the typical concentration (18 mg/mL) used by users found in 33 countries.[51] We did not modify the concentration as we wanted to preserve participant typical patterns of use. Previous studies reported that the higher the nicotine concentrations in the e-liquid the higher the indoor air nicotine concentration.[10,50] Moreover, other factors may determine nicotine yield from e-cigarette use, such as e-cigarette type and brand, PG/vegetable glycerine ratio, and electrical power.[52] Although the e-cigarette used in this study was a Mod type, the user did not change the setting to follow her typical pattern of use.

Although the present study found that most biomarkers were below the LOQ, a previous study found a systemic absorption of nicotine by detecting a significant rise of saliva cotinine in non-users after two hours of exposure to SHA with three e-cigarette users at the same time in the same room.[53] In another study, saliva cotinine also increased up to 12-fold after 6-hour exposure, but the concentration was also very low (range: 0.030–0.017 ng/mL), peaking at four hours after the e-cigarette use period stopped.[31] Thus, a shorter exposure period and lower e-cigarette user density might be accountable for the samples under the LOQ in the current study. We were also unable to measure the trend of TSNAs concentrations in bystanders' saliva since they were below the LOQ, which was consistent with a previous study using urinary samples.[31] However, NNN and NNK were previously detected in e-cigarettes' emission,[19] and NNAL has been found in the urine of people living with e-cigarette users at a concentration significantly higher than those living with non-users and non-smokers.[7] This may reflect the effects of long or sustained exposure instead of short exposure to e-cigarette use. The unquantifiable salivary PG and glycerol concentration in our study might be due to the unclear relation between both biomarkers in the saliva and the e-cigarettes' exposure, as previous studies used plasma samples to identify the biomarkers.[8]

The four most reported short-term symptoms by non-users were dry throat, dry nose, dry eyes, and phlegm in the throat. Ocular, nasal, and throat-respiratory irritation complaints were also increasingly reported after exposure to SHA in a room in a previous experiment with 40 volunteers, with the last ones persisting even until 30-minute post-exposure.[30] The study also found that the reported nasal and throat-respiratory symptoms were significantly associated with volatile organic compound concentrations present in the SHA. However, $PM_{2.5}$, PG, and glycerol may also partly play a role in generating the irritation symptoms, as these constituents are known to provoke eyes and airway irritation symptoms.[8,21]

Although elevation of biomarkers was unable to be detected in the current study, the participants reported short-term health symptoms during and even after the exposure period, suggesting that exposure to SHA is associated with some adverse health effects in bystanders. This raises concern for vulnerable groups like children, elderly, and people with respiratory diseases in a long term and intense exposure, especially for children, since our far-field exposure in the car resembles a child's exposure in the back seat, but parents tend to perceive e-cigarette use in enclosed spaces as safe for their children.[54] Moreover, infants are at the highest risk among other age groups because they receive the highest doses per kg body weight of e-cigarette aerosol.[4] The discrepancy between the level of biomarkers and the frequency of short-term health symptoms found in this study may indicate that future studies should evaluate the relevant biomarkers that correspond to such symptoms. Given the small number of non-users in this study, the symptoms they reported, however, may also reflect individual sensitivity to SHA. Thus, our results should be interpreted with caution.

There are some limitations in this study that should be noted. Firstly, our sample included only two non-users, which made our findings on biomarkers and reported symptoms not generalizable. Nevertheless, regardless of the complexity of the study design (two experiments one week apart, lasted 3.6 hours, replicated 5 times in consecutive days), we aimed to provide a comprehensive assessment of SHA exposure in the same individuals, avoiding potential intervariability. Furthermore, we only tested one type of e-cigarette and e-liquid combination used by one e-cigarette user. Thus, the results of this study did not take into account different puffing topography by different users and might underestimate the exposure to SHA from other types or models of e-cigarette in the current market, which are continuously developing and becoming more popular, especially among youth, like pod and disposable e-cigarettes.[55,56] Nevertheless, e-cigarettes with the tank system, like the one we used in the present study, are more likely to be used by experienced users.[57] Secondly, our study might not accurately estimate the actual $PM_{2.5}$ concentrations given the absence of a specific calibration factor for e-cigarette aerosol. Nevertheless, we consider it is an acceptable approach because SHA contains particles and the interpretation of the results is unlikely to change significantly, as a calibration factor would only affect the magnitude of the changes observed. Thirdly, we did not include a full control session with the same characteristics as the sessions in which the e-cigarette was used; instead, we provided a 5-minute baseline condition every day (pre-exposure period with no e-cigarette use and all participants present) for comparison, as done in previous studies.[11,49] It is unlikely to observe an increase in $PM_{2.5}$ concentration because of the mobilization of small particles from the surfaces, since the participants were asked to be sat throughout the experiments. Nevertheless, if the activities without e-cigarette use in both settings generated $PM_{2.5}$, it has been taken into account by comparing the concentration in pre- vs during vs post-exposure across the five replications in the room, thus avoiding potential source of bias from the non-exposure condition.

Fourthly, we did not take into account the air exchange rate or other measures of ventilation conditions in the analysis that might affect the concentration of airborne markers. However, we measured them in two confined settings at near- and far-field exposure to control the potential effect of the distance from the user. As we wanted to reflect short-term exposure in real-life scenarios, we did not allow ventilation in the office room during the exposure, while in the case of the car, air exchange was allowed by a half-open window, as likely done in real-life conditions. Additionally, we took into account potential variability across days by conducting five-day replicates in each setting. Lastly, this study measured short-term exposure to SHA; chronic exposure might have a different outcome. However, longer-term exposure might result in worse indoor air quality and adverse health effects.

Despite the above limitations, we assessed SHA exposure by using environmental and biological measurements concurrently with short-term health symptoms evaluation from the same subjects; thus, it captures comprehensive dimensions of the passive exposure to e-cigarette aerosol. By maintaining similar conditions across the five replicates, we ensured the repeatability of the experiment and, hence, controlled the potential systematic errors which sometimes are present in observational studies. Additionally, the arrangement of the settings (half-open windows for the car and closed windows for the room) and the involvement of an actual exclusive user puffing *ad libitum* were simulating real-world e-cigarette use conditions.

## 5 | CONCLUSION

Our study showed that a short-term e-cigarette use increases $PM_{2.5}$ concentration in a room and a car, while the concentrations of airborne nicotine and biomarkers of passive exposure to e-cigarette aerosol were very low. The distance apart between e-cigarette user and bystanders that we used did not alter short-term exposure to $PM_{2.5}$ significantly when air ventilation was present in a confined space. Bystanders reported a mild level of eye and airway irritation symptoms after short-term exposure to SHA.

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### CONFLICT OF INTEREST

No conflict of interest declared.

## AUTHOR CONTRIBUTIONS

Beladenta Amalia contributed to investigation, formal analysis, and writing—original draft; Marcela Fu involved in methodology, resources, investigation, and writing—review and editing, visualization, and supervision; Olena Tigova contributed to methodology, resources, investigation, writing—review and editing, supervision, and project administration; Montse Ballbè involved in methodology, resources, investigation, and writing—review and editing, and supervision; Yolanda Castellano contributed to data curation, formal analysis, and writing—review and editing; Sean Semple, Luke Clancy, Constantine Vardavas, and María J. López involved in conceptualization and writing—review and editing; Nuria Cortés, Raul Pérez-Ortuño, and José A. Pascual contributed to formal analysis, resources, and writing—review and editing; Esteve Fernández involved in conceptualization, methodology, supervision, funding acquisition, project administration, and writing—review and editing.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

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## APPENDIX 1

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# PAPER 5

## Exposure to secondhand aerosol from electronic cigarettes at home: a real-life study in four European countries

Beladenta Amalia, Marcela Fu, Olena Tigova, Montse Ballbé, Blanca P. Castillo, Raul Pérez-Ortuño, José A. Pascual, Constantine Vardavas, Vergina K. Vyzikidou, Fernando Gil, Pablo Olmedo, Joan B. Soriano, Maria Jose López, Nuria Cortés, Roberto Boffi, Chiara Veronese, Silvano Gallus, Alessandra Lugo, Rachel O'Donnell, Ruaraidh Dobson, Sean Semple, Esteve Fernández, the TackSHS Project Investigators.

(In preparation)

**Exposure to secondhand aerosol from electronic cigarettes at home: a real-life study in four European countries**

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# ABSTRACT

Electronic cigarette (e-cigarette) use is known to emit toxic chemicals and deteriorate outdoor and indoor air quality. Home is a place where e-cigarette users may frequently use their devices amid increasing prohibition of e-cigarette use in public places. This study aims to assess the real-life scenario of bystanders' exposure to secondhand e-cigarette aerosol (SHA) at home. A one-week observational study was conducted in four countries (Greece, Italy, Spain, and the United Kingdom) in 2019 within: 1) homes of e-cigarette users living together with a non-user nor non-smoker; and 2) control homeswith no cigarette or e-cigarette use. Indoor airborne nicotine and $PM_{2.5}$ concentrations were measured as environmental markers of SHA, as well as concentrations of nicotine and its metabolites, tobacco-specific nitrosamines, propanediols, glycerol, and metals in participants' saliva and urine samples as biomarkers of exposure to SHA. E-cigarette use determinants, such as e-liquid's nicotine concentration, e-cigarette types, place of e-cigarette use at home, and frequency of room ventilation were also collected. A total of 29 e-cigarette users' homes and 21 control homes were included in this study. The results showed that the levels of seven-day airborne nicotine were quantifiable in 21 (72.4%) out of 29 e-cigarette users' homes; overall they were low (median: 0.01 $\mu g/m^3$; mean: 0.02 $\mu g/m^3$) but significantly higher than those found in control homes. Concentrations of seven-day $PM_{2.5}$ in e-cigarette and control homes were similar. Airborne nicotine and $PM_{2.5}$ concentrations did not differ according to different e-cigarette use conditions. Non-users residing with e-cigarette users had low but significantly higher levels of nicotine, cotinine, 3'-OH-cotinine, and 1,2-propanediol in saliva, and cobalt in urine than non-users living in control homes. In conclusion, e-cigarette use at home created bystanders' exposure to SHA regardless of the conditions of use. We recommend the inclusion of e-cigarettes in smoke-free home rules to protect e-cigarette non-users from any exposure to SHA.


**Keywords:** electronic cigarettes, electronic nicotine delivery systems, secondhand aerosol, passive exposure, biomarkers, indoor pollution.

## HIGHLIGHTS

- This is the first multi-country study examined passive exposure to e-cigarette aerosol at home
- Airborne nicotine was quantifiable in 21 (72.4%) out of 29 e-cigarette users' homes
- Airborne nicotine was not quantifiable in smoke- and e-cigarette-free homes
- E-cigarette non-users living with an e-cigarette user absorbed e-cigarette emissions at home

# 1. INTRODUCTION

The widespread use of electronic cigarettes (e-cigarettes) in Europe and other parts of the world, especially among young people [1,2], has led to the growing occurrence of secondhand exposure to e-cigarette aerosol (SHA) . In the United States (US), exposure to SHA in indoor or outdoor public places was reported by nearly one in three middle- and high-school students in 2018 [3]. In Europe, 16.0% of bystanders (e-cigarette non-users) reported exposure to SHA, at least weekly, in 2017-2018, in any indoor setting [4]. The prevalence was higher among smokers, with 19.7% exposed to SHA in smoke-free indoor places, according to a survey in six European countries in 2016 [5].

Previous studies have identified chemical compounds in SHA such as coarse ($PM_{10}$), fine ($PM_{2.5}$) and ultrafine ($PM_{0.1}$) particulate matter, nicotine, volatile organic compounds, propanediols, glycerol, metals, formaldehyde, acetaldehyde, tobacco-specific nitrosamines (TSNAs), and flavourings [6,7]. Such substances in indoor environments were found to increase in concentration as a result of e-cigarette use, and could be absorbed by bystanders through inhalation and dermal exposure [8]. Airborne nicotine has been detected in higher concentrations after e-cigarette use by human volunteers in experimental studies in offices or rooms [9–11] and in some observational studies inside homes of e-cigarette users [12], in e-cigarette convention events [13,14], vape shops [15,16], and even their neighbouring businesses [16]. Nicotine and its metabolites, such as cotinine and trans-3'-hydroxycotinine (3'-OH-cotinine), were identified in biologic samples (i.e., serum, saliva or urine) of e-cigarette non-users who were exposed to SHA [9,12,17] indicating nicotine was systematically absorbed by non-user bystanders. Concentration of $PM_{2.5}$ also substantially increased while e-cigarettes were used in locations such as rooms [7,9,11,18], homes [6,19], cars [19], e-cigarette events [20], and e-cigarette shops [15,16]. Another major concern pertaining to SHA was the presence of metal elements (e.g., aluminium, silver, arsenic, iron), propanediols and glycerol in e-cigarette aerosols, which were absent or found only in a small amount in conventional cigarette smoke [10,21].

As pollutants in SHA may impair indoor air quality and biomarkers of exposure to these pollutants have been found in e-cigarette non-users, the possibility of adverse health effects in exposed bystanders has been a matter of discussion. Exposure to SHA from short-term use of e-cigarettes may cause reduced respiratory function, headache, and irritation symptoms of eyes, nose, and airways among e-cigarette non-users [22–24]. It may also provoke respiratory inflammation in chronic obstructive pulmonary disease patients [25], and exacerbate asthma symptoms in youth with asthma [26]. A qualitative study exploring e-cigarette use at homes found that asthmatic young people, who lived together with e-cigarette users, reported the e-cigarette aerosol worsened their respiratory symptoms [27].

Although e-cigarette use and exposure to SHA among non-users at homes was less frequently reported than in public places (e.g., workplaces, restaurants) [4,28], exposure to SHA in homes was found to be extensive, with the median duration of SHA exposure being 43 minutes/day as shown in a multi-country study in Europe [4]. Qualitative studies revealed that the home was a location where e-cigarette use by both young people and adults commonly occurred [29–31].

The above evidence underscores the importance of assessing involuntary exposure to pollutants from SHA at homes. However, there is still limited knowledge on the objective level of such exposure in real life, since the available evidence has derived from laboratory or controlled study designs. This paper aims to comprehensively characterise environmental and individual exposure to SHA in real life conditions at homes among people who cohabit with e-cigarette users.

# 2. MATERIAL AND METHODS

## 2.1. Study Design

An observational study was performed to examine the environmental and individual exposure to SHA in two types of households: e-cigarette users' homes and control homes. The study was conducted in Greece (Athens), Italy (Milan), Spain (Barcelona), and the United Kingdom (UK, Edinburgh) from June to September 2019 within the course of one week for each home. This study was developed under the TackSHS project which comprehensively assessed the impact of secondhand smoke (SHS) and SHA on the European population [32].

## 2.2. Ethical Issues

An ethics and research committee from each country approved this study (Greece: 086; Italy: INT 5/19; Spain: PR002/19; UK: NICR 18/19 037). The project was registered at www.clinicaltrials.gov (NCT04140630). All participants were properly informed about the potential risks of taking part in this study, and all of them provided written consent in advance of participating.

## 2.3. Participants

In each participating country, we recruited participants from both types of households. For each e-cigarette user's home (e-cigarette homes), we included one exclusive e-cigarette user and one non-user of any tobacco or nicotine products who resided in the same household. From each control home, we enrolled one non-user of any tobacco and nicotine products who did not live with any tobacco or nicotine products user.

Non-users in both home types were eligible to participate if they were: a) aged 18 or over, b) a never user of e-cigarettes or a former e-cigarette user for more than one month, and c) a never user of any tobacco or nicotine products or a former user for more than one month. E-cigarette users were eligible to participate if they were: a) aged 18 or over, b) a daily e-cigarette user at home (at least during one month prior to the study), and c) a never user of any other tobacco or nicotine products (at least one month prior to the study). The exclusion criteria for all participants were being regularly exposed to SHS or SHA in places other than home, or having another e-cigarette or tobacco user in the same household. We aimed to recruit 20 e-cigarette homes and 5 control homes in each country, summing to 80 e-cigarette homes (160 participants) and 20 control homes (20 participants) from the four countries; but logistical reasons prevented achievement of the target sample size. Nevertheless, based on a previous pilot study [12], our final sample size still allowed us to detect differences in the environmental and biological markers according to different home types [12].

Participants were recruited through advertisements in social networks, databases of previous e-cigarette studies and personal contacts of the research teams. All participants who agreed to participate received a gift card of a local cultural store to acknowledge participation.

## 2.4. Measurements

### 2.4.1. Environmental Measurements

Airborne nicotine: Gas-phase nicotine was measured with passive sampling, using nicotine samplers of 37 mm in diameter containing a filter treated with sodium bisulphate as performed in previous studies [33]. The nicotine concentrations (μg/m$^3$) were determined using gas chromatography-mass spectrometry at the laboratory of the Public Health Agency of Barcelona. The time-weighted average nicotine concentrations were quantified by dividing the amount of nicotine extracted from the filter by the volume of air sampled (estimated flow rate of 24 ml/min multiplied by the minutes the filter had been exposed). The procedure has a limit of quantification (LOQ) of 5 ng per filter, which is equivalent to 0.02 μg/m$^3$ of nicotine per seven days of exposure. For values that were under the LOQ, half of this LOQ's value was assigned [34].

$PM_{2.5}$: The real-time $PM_{2.5}$ concentration at 10-sec interval was measured with an aerosol monitoring device (AirVisual Pro, IQAir). The device did not give feedback to the participants about the air quality measured in the house. $PM_{2.5}$ data were downloaded to a local computer from the monitors' internal memory for further analyses.

### 2.4.2. Biological measurements

The personal exposure to SHA was assessed through the quantification of e-cigarette aerosols-related biomarkers in saliva and urine samples of e-cigarette users and non-users from both home types. The saliva and urine samples were stored at -20° C in a freezer and sent in dry ice to the laboratory at IMIM-Hospital del Mar Medical Research Institute and University of Granada, respectively, for analyses. This study determined the concentration of nicotine, cotinine, 3'-OH-cotinine, nornicotine, TSNAs (N'-nitrosonornicotine; NNN, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNK, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNAL), propanediols (1,2-propanediol; 1,2-PD and 1,3-propanediol; 1,3-PD), and glycerol in saliva and urine samples using liquid chromatography-tandem mass spectrometry. Analysis of 27 metal elements in urine samples was performed on an Agilent 8900 triple-quadrupole inductively coupled plasma-mass spectrometry (Agilent Technologies, Santa Clara, CA, USA). Suitable certified reference material [Seronorm (Sero, Billingstad, Norway) Trace Elements Urine L1 and L2 (references 210605, 210705)] was reanalysed together with a blank and an intermediate calibration standard every 12 samples. The list of metals we analysed is provided in Supplementary 1. The LOQ for each biomarker is presented in Table 3 and Supplementary 1. We assigned half of the LOQ values for biomarker concentrations that were lower than their LOQ as has been done in previous studies [35,36].

### 2.4.3. Observational data

Questionnaire: Information on sociodemographic profile (i.e., sex, age, and highest education level) and the self-rated overall health status (categorised as good, fair, and poor) of the participants were collected from the interview at the first visit using an *ad hoc* questionnaire. From the questionnaire completed by users, data on duration of being an e-cigarette user, type of e-cigarette commonly used (categorised as 1$^{st}$, 2$^{nd}$, 3$^{rd}$, or 4$^{th}$ generation), self-reported nicotine concentration in the e-liquid commonly used, place of e-cigarette use at home (categorised as everywhere, only indoor places, and only outdoor places), and use of ventilation during e-cigarette use (categorised as never, sometimes, and always) were obtained.

Diary: Information on the cooking time at home was registered in the given diary by e-cigarette users and non-users every day. Daily reminders were sent via SMS to ensure all the participants fill in the diary.

## 2.5. Fieldwork

The fieldwork was conducted in the e-cigarette and control homes over seven consecutive days. A researcher visited the homes on the first and last day of the period. In the first visit, participants provided written informed consent to participate in this study, and monitoring devices for airborne nicotine and $PM_{2.5}$ sampling were installed in the home's main room. Airborne nicotine was collected using a passive nicotine sampler that was installed and hung for one week in the main room of the house where air circulated properly, at least two metres from any air flow, and one metre away from an open window or a ventilation system. The location for the $PM_{2.5}$ monitoring device was placed more than 30 centimetres away from the wall and the floor. The $PM_{2.5}$ monitoring device was switched on and left in the participants' house for a week. In the visit, the researchers also interviewed the participants and collected participant's saliva sample, from both user and non-user, using a candy to stimulate salivation, if needed, for the amount of at least 2 ml of saliva into a test tube.

In the subsequent seven days, participants completed the daily diary. The $PM_{2.5}$ concentrations were continuously measured for the seven days by the monitoring device installed. In the last day, the researcher switched off and collected the $PM_{2.5}$ monitoring device, the passive nicotine sampler, and the diary. At this timepoint, urine samples were collected from the participants in Italy and Spain.

## 2.6. Statistical Analysis

We calculated descriptive statistics of the sociodemographic and health profile of users and non-users from e-cigarette and control homes. For the environmental markers, we estimated the $25^{th}$, $50^{th}$ (median), $75^{th}$, and $95^{th}$ percentiles and mean concentrations with their standard deviation of airborne nicotine and $PM_{2.5}$ (both in $\mu g/m^3$) according to home types. We also stratified the median concentrations of airborne nicotine and $PM_{2.5}$ in e-cigarette homes by factors related to e-cigarette use, such as e-liquid's nicotine level, e-cigarette devices types, place of use and ventilation during e-cigarette use at home. For the $PM_{2.5}$ concentrations, we excluded the data recorded during cooking time at homes of participants as the concentrations increased dramatically. We performed the Mann-Whitney test to assess differences in estimates of e-cigarette and control homes, and the Kruskal-Wallis test for differences in estimates of different conditions related to e-cigarette use.

We also estimated the median and mean concentrations of each biomarker in saliva and urine according to group of participants (i.e., users, non-users, and controls). *P-values* for difference in estimates between groups of participants (i.e., users vs. non-users vs. controls) were computed using the Mann-Whitney test.

All analyses were performed with STATA 14.0, and set the significance level at *p-value* <0.05.

# 3. RESULTS

## 3.1. Demographic and e-cigarette use profile

Table 1 shows the sociodemographic and health profile distribution of the participants from the four countries. In total, 79 participants, consisting of 29 users and 29 non-users from e-cigarette homes, and 21 non-users from control homes (controls) were enrolled. Most of the users (67.9%) were male, while non-users (75.0%) and controls (66.7%) were mostly female. The majority of the participants (50.6%) were aged 30-49 years; the median age for users, non-users, and controls was 43.1, 41.7, and 41.3 years, respectively. Almost all of the participants (74 participants; 96.1%) considered themselves in good or fair health.

Users reported that they had used the e-cigarette for a median duration of 36 months (interquartile range, IQR: 19-54 months) by the time of the study, most of which (n=18; 64.3%) used the 3$^{rd}$ generation of e-cigarette (e.g., Eleaf, Vaporesso), and one user used the 4$^{th}$ generation (Juul). The median nicotine concentration in their e-liquids reported by users was 3 mg/ml, ranging from 0 to 20 mg/ml.

Table 1. Sociodemographic and health characteristics of electronic cigarette users, non-users and controls in four European countries. TackSHS Study, 2019

| | Total N (%) | E-cigarette users User N (%) | E-cigarette users Non-user N (%) | Controls Control N (%) |
|---|---|---|---|---|
| Total | 79 (100.0) | 29 (100.0) | 29 (100.0) | 21 (100.0) |
| Country | | | | |
| Greece | 25 (31.6) | 10 (34.5) | 10 (34.5) | 5 (23.8) |
| Italy | 14 (17.7) | 4 (13.8) | 4 (13.8) | 6 (28.6) |
| Spain | 21 (26.6) | 8 (27.6) | 8 (27.6) | 5 (23.8) |
| United Kingdom | 19 (24.0) | 7 (24.1) | 7 (24.1) | 5 (23.8) |
| Sex [a] | | | | |
| Male | 33 (42.9) | 19 (67.9) | 7 (25.0) | 7 (33.3) |
| Female | 44 (57.1) | 9 (32.1) | 21 (75.0) | 14 (66.7) |
| Age (year) [a] | | | | |
| 15-29 | 10 (13.0) | 3 (10.7) | 2 (9.5) | 5 (17.9) |
| 30-49 | 39 (50.6) | 14 (50.0) | 12 (57.1) | 13 (46.4) |
| $\geq$50 | 28 (36.4) | 11 (39.3) | 7 (33.3) | 10 (35.7) |
| Highest education level [a] | | | | |
| Primary school | 2 (2.6) | 1 (3.6) | 1 (3.6) | 0 (0.0) |
| Secondary school | 20 (26.0) | 13 (46.4) | 7 (25.0) | 0 (0.0) |
| University or similar | 55 (71.4) | 14 (50.0) | 20 (71.4) | 21 (100.0) |
| Overall health status [a,b] | | | | |
| Good | 61 (79.2) | 22 (78.6) | 22 (78.6) | 17 (80.9) |
| Fair | 13 (16.9) | 4 (14.3) | 5 (17.9) | 4 (19.0) |
| Poor | 3 (3.9) | 2 (7.1) | 1 (3.6) | 0 (0.0) |

[a] Total 77 subjects (due to missing data)

[b] Self-reported health status

## 3.2. Environmental markers

The concentration of airborne nicotine throughout seven days of observation was quantifiable in 21 out of 29 e-cigarette homes, and in none of the control homes. The seven-day airborne nicotine concentration in e-cigarette homes (median: 0.01; IQR: 0.01-0.02; mean: 0.02; SD: 0.02 $\mu g/m^3$) was significantly higher than that of in control homes (median: 0.01; IQR: 0.01-0.01; mean: 0.01; SD: 0.00 $\mu g/m^3$), with the 95$^{th}$ percentile concentration in e-cigarette homes reaching eight-fold (0.08 vs. 0.01 $\mu g/m^3$) of concentration in control homes (Figure 1). Figure 2 shows that the median (8.00; IQR: 5.00-10.00 $\mu g/m^3$) and mean (8.56; SD: 4.49 $\mu g/m^3$) of $PM_{2.5}$ concentration in e-cigarette homes during the observation week was higher than that of in control homes (median: 5.50; IQR: 3.50-9.00; mean: 6.19; SD: 3.52 $\mu g/m^3$), but not significantly different ($p=0.082$).

The seven-day airborne nicotine and $PM_{2.5}$ levels in e-cigarette homes did not vary by any determinant factors examined (Table 2).

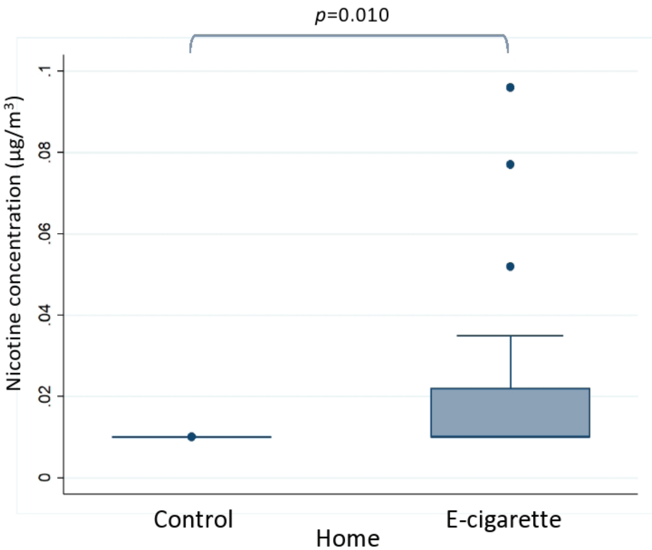


Figure 1. Seven-day airborne nicotine concentrations (µg/m³) in homes of electronic cigarette users (n=29) and control (n=21). *P*-value was calculated with Mann-Whitney test. TackSHS Study, 2019

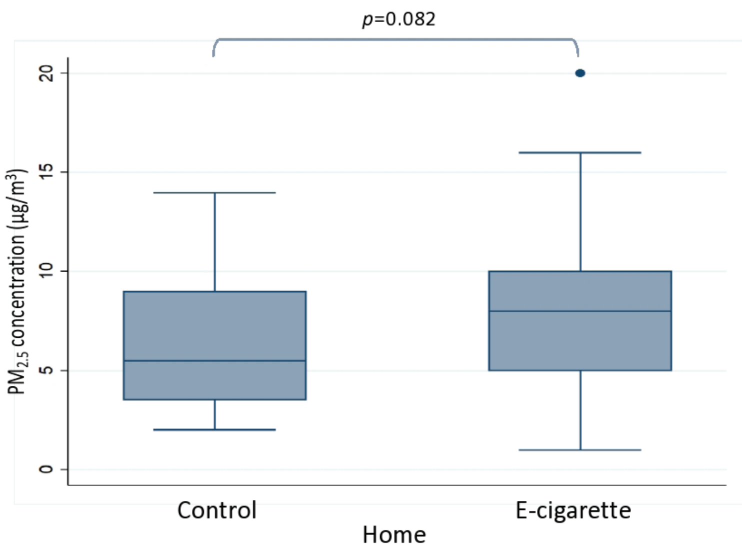


Figure 2. Seven-day $PM_{2.5}$ concentrations (µg/m³) in homes of electronic cigarette users (n=29) and control (n=21). *P*-value was calculated with Mann-Whitney test. TackSHS Study, 2019

Table 2. Seven-day concentrations (µg/m³) of airborne nicotine and $PM_{2.5}$ in 29 homes[a] of electronic cigarette (e-cigarette) users by different determinant factors. TackSHS Study, 2019

| | Nicotine | | | $PM_{2.5}$ | | |
|---|---|---|---|---|---|---|
| | N | Median (IQR) | p-values[b] | N | Median (IQR) | p-values[b] |
| Reported by manufacturer nicotine concentration (mg/mL)[c] in e-cigarette liquid | | | | | | |
| 0 | 1 | 0.01 | 0.757 | 1 | 5.00 | 0.609 |
| >0 - <6 | 10 | 0.01 (0.01-0.03) | | 9 | 7.00 (5.00-14.00) | |
| >=6 | 8 | 0.01 (0.01-0.04) | | 8 | 7.50 (5.50-9.50) | |
| Type of e-cigarettes | | | | | | |
| 1st generation | 3 | 0.02 (0.01-0.05) | 0.314 | 3 | 10.00 (7.00-16.00) | 0.337 |
| 2nd generation | 6 | 0.01 (0.01-0.03) | | 4 | 4.50 (3.00-9.50) | |
| 3rd generation | 18 | 0.01 (0.01-0.01) | | 18 | 7.50 (5.00-10.00) | |
| 4th generation | 1 | 0.02 | | 1 | 10.00 | |
| Place of e-cigarette use at home | | | | | | |
| Everywhere | 15 | 0.01 (0.01-0.03) | 0.827 | 13 | 7.00 (5.00-13.00) | 0.296 |
| Only indoor places | 13 | 0.01 (0.01-0.02) | | 13 | 8.00 (6.00-10.00) | |
| Only outdoor places | 1 | 0.01 | | 1 | 2.00 | |
| Use of ventilation during e-cigarette use | | | | | | |
| Never | 7 | 0.01 (0.01-0.02) | 0.981 | 6 | 9.50 (9.00-14.00) | 0.073 |
| Sometimes | 10 | 0.01 (0.01-0.02) | | 9 | 6.00 (5.00-7.00) | |
| Always | 12 | 0.01 (0.01-0.02) | | 12 | 9.00 (5.50-13.00) | |

IQR: Interquartile range

[a] Due to missing data, not all determinant factors are add up to 29

[b] Kruskal-Wallis test

[c] Self-reported nicotine concentration

## 3.3. Biomarkers

Table 3 shows that the concentrations of nicotine and its metabolites, except nornicotine, of non-users were significantly higher than those found in controls only in saliva samples. The median concentrations of salivary cotinine and 3'-OH-cotinine in non-users were more than two times higher than in controls, with 0.12 ng/ml (IQR: 0.50-0.40 ng/ml) and 0.05 ng/ml (0.02-0.07 ng/ml), respectively for cotinine and 0.05 ng/ml (IQR: 0.02-0.13 ng/ml) and 0.02 ng/ml (IQR: 0.02-0.02 ng/ml), respectively for 3'-OH-cotinine. Similarly, non-users had fewer number of samples that were < LOQ compared to controls for salivary nicotine, cotinine, and 3'-OH-cotinine. The median concentration salivary 1,2-PD in non-users (7.97 nmol/ml; IQR: 6.00-13.47 nmol/ml) was almost twice ($p < 0.001$) as high as that was in controls (4.00 nmol/ml; IQR: 1.50-6.00 nmol/ml). The concentrations of urinary 1,2- and 1,3-propanediol of non-users were similar to controls. Out of 27 metal elements analysed in this study (Supplementary 1), cobalt (Co) was the only metal showing a median concentration in non-users (1.32 µg/L; IQR: 0.32-2.26 µg/L) higher than that of in controls (0.26 µg/L; IQR: 0.13-0.47 µg/L; $p=0.031$).

Compared to e-cigarette users, the concentrations of salivary and urinary nicotine as well as all its metabolites of non-users and controls were significantly lower. 1,2-propanediol was the only biomarker of humectants that was found at consistently higher level in both samples of users than that of non-users and controls. Additionally, no significant difference was found in concentrations of TSNAs markers in both saliva and urine, and metals in urine of users, non-users, and controls, except for NNN, where a higher concentration was identified in the saliva of users (Table 3).

Table 3. Concentrations of biomarkers in saliva and urine samples of electronic cigarette users, non-users, and controls in homes of European countries. TackSHS Study, 2019

| Biomarkers | | Saliva[a] | | | | | | Urine[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | User (N=29) | Non-user (N=29) | Control (N=21) | p-values[c] non-user vs. control | p-values[c] user vs. non-user | p-values[c] user vs. control | User (N=12) | Non-user (N=12) | Control (N=11) | p-values[c] non-user vs. control | p-values[c] user vs. non-user | p-values[c] user vs. control |
| Nicotine (LOQ: 0.50 ng/ml) | Number of samples < LOQ | 1 | 18 | 19 | | | | 1 | 5 | 3 | | | |
| | Median (IQR) | 323.81 (7.15-1155.40) | 0.25 (0.25-0.77) | 0.25 (0.25-0.25) | 0.023 | <0.001 | <0.001 | 185.68 (5.87-500.74) | 0.61 (0.25-1.45) | 0.63 (0.25-0.78) | 0.777 | <0.001 | <0.001 |
| | Mean (SD) | 820.00 (1247.74) | 97.46 (381.08) | 0.30 (0.20) | | | | 545.45 (1007.69) | 2.18 (4.98) | 0.63 (0.33) | | | |
| Cotinine (LOQ: 0.10 ng/ml) | Number of samples < LOQ | 1 | 7 | 10 | | | | 0 | 0 | 0 | | | |
| | Median (IQR) | 134.54 (28.75-276.39) | 0.12 (0.05-0.40) | 0.05 (0.02-0.07) | 0.003 | <0.001 | <0.001 | 427.47 (15.30-1485.10) | 0.44 (0.26-2.78) | 0.32 (0.13-0.70) | 0.242 | 0.003 | <0.001 |
| | Mean (SD) | 195.49 (238.51) | 14.52 (48.82) | 0.09 (0.12) | | | | 764.70 (887.61) | 17.26 (51.37) | 0.47 (0.43) | | | |
| 3'-OH-cotinine (LOQ: 0.04 | Number of samples < LOQ | 2 | 12 | 18 | | | | 0 | 0 | 0 | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ng/ml) | Median (IQR) | 42.51 (7.01-70.60) | 0.05 (0.02-0.13) | 0.02 (0.02-0.02) | 0.002 | <0.001 | <0.001 | 1066.48 (118.58-5841.89) | 1.65 (0.87 (20.76) | 0.98 (0.71-3.26) | 0.325 | 0.001 | <0.001 |
| | Mean (SD) | 62.21 (82.83) | 5.91 (17.91) | 0.03 (0.03) | | | | 2869.79 (3753.83) | 55.73 (144.32) | 4.30 (9.07) | | | |
| | Number of samples < LOQ | 6 | 27 | 21 | | | | 2 | 7 | 8 | | | |
| Nornicotine (LOQ: 0.10 ng/ml) | Median (IQR) | 1.16 (0.11-1.98) | 0.05 (0.05-0.05) | 0.05 (0.05-0.05) | 0.224 | <0.001 | <0.001 | 12.60 (0.98-49.36) | 0.05 (0.05-0.22) | 0.05 (0.05-0.11) | 0.347 | 0.003 | 0.001 |
| | Mean (SD) | 2.65 (5.86) | 0.24 (0.84) | 0.05 (0.00) | | | | 37.85 (63.49) | 0.51 (1.38) | 0.07 (0.05) | | | |
| | Number of samples < LOQ | 21 | 27 | 21 | | | | 11 | 11 | 10 | | | |
| NNN (LOQ: 1.00 pg/ml) | Median (IQR) | 0.50 (0.50-1.20) | 0.50 (0.50-0.50) | 0.50 (0.50-0.50) | 0.224 | 0.032 | 0.010 | 0.50 (0.50-0.50) | 0.50 (0.50-0.50) | 0.5 (0.5-0.5) | 0.900 | 0.952 | 0.900 |
| | Mean (SD) | 10.57 (44.70) | 0.69 (0.72) | 0.50 (0.00) | | | | 0.55 (0.19) | 0.55 (0.12) | 0.56 (0.21) | | | |
| | Number of samples < LOQ | 27 | 28 | 21 | | | | 12 | 12 | 11 | | | |
| NNK (LOQ: 2.00 pg/ml) | Median (IQR) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 0.395 | 0.557 | 0.224 | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | NA | NA | NA |
| | Mean (SD) | 1.27 (1.12) | 1.07 (0.39) | 1.00 (0.00) | | | | 1.00 (0.00) | 1.00 (0.00) | 1 (0) | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number of samples < LOQ | 26 | 28 | 21 | | | | 9 | 10 | 10 | | | |
| NNAL (LOQ: 0.50 pg/ml) | Median (IQR) | 0.25 (0.25-0.25) | 0.25 (0.25-0.25) | 0.25 (0.25-0.25) | 0.395 | 0.165 | 0.079 | 0.25 (0.25-0.42) | 0.25 (0.25-0.25) | 0.25 (0.25-0.25) | 0.528 | 0.569 | 0.306 |
| | Mean (SD) | 0.56 (1.11) | 0.29 (0.24) | 0.25 (0.00) | | | | 0.78 (1.19) | 0.42 (0.39) | 0.29 (0.13) | | | |
| | Number of samples < LOQ | 2 | 7 | 6 | | | | 0 | 0 | 0 | | | |
| 1,2-PD (LOQ: 3.00 nmol/ml) | Median (IQR) | 52.56 (38.46-458.59) | 7.97 (6.00-13.47) | 4.00 (1.50-6.00) | <0.001 | <0.001 | <0.001 | 183.96 (53.30-1364.27) | 11.27 (5.56-94.98) | 10.73 (7.19-51.26) | 0.951 | 0.003 | 0.002 |
| | Mean (SD) | 1052.46 (2243.71) | 85.23 (333.72) | 6.40 (10.41) | | | | 1309.34 (2603.02) | 53.15 (72.07) | 44.50 (73.51) | | | |
| | Number of samples < LOQ | 17 | 24 | 15 | | | | 5 | 6 | 9 | | | |
| 1,3-PD (LOQ: 3.00 nmol/ml) | Median (IQR) | 1.50 (1.50-7.23) | 1.50 (1.50-1.50) | 1.50 (1.50-3.10) | 0.424 | 0.050 | 0.200 | 3.69 (1.50-13.85) | 2.25 (1.50-6.76) | 3.99 (3.00-5.62) | 0.314 | 0.504 | 0.755 |
| | Mean (SD) | 8.40 (13.46) | 7.77 (23.84) | 3.00 (3.08) | | | | 29.54 (80.35) | 5.74 (6.98) | 11.39 (23.77) | | | |
| | Number of samples < LOQ | 1 | 3 | 3 | | | | 0 | 2 | 0 | | | |
| Glycerol (LOQ: 10.00 nmol/ml) | Median (IQR) | 100 (87.01-597.91) | 100 (43.29-100.00) | 58.47 (23.53-100.00) | 0.512 | 0.034 | 0.020 | 34.04 (18.15-63.11) | 36.11 (12.07-63.24) | 58.38 (29.94-68.22) | 0.295 | 0.644 | 0.325 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mean (SD) | 793.22 (1721.70) | 136.42 (166.71) | 175.36 (298.79 ) | | 58.16 (63.95) | 39.37 (27.61) | 54.16 (26.97) |

Abbreviations: LOQ: limit of quantification; NNN: N'-nitrosonornicotine; NNK: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; 1,2-PD: 1,2-propanediol; 1,3-PD: 1,3-propanediol; IQR: interquartile range; SD: standard deviation; NA: not applied.

[a] Saliva samples were collected from participants in Greece, Italy, Spain, and United Kingdom

[b] Urine samples were collected from participants in Italy and Spain

[c] Mann-Whitney test

## 4. DISCUSSION

This study evaluated the real-world condition of bystanders' exposure to SHA at home environment by measuring the concentration of indoor airborne markers and biomarkers of e-cigarette non-users. Our findings show that there were low concentrations of airborne nicotine and $PM_{2.5}$ in homes of e-cigarette users, but the former was significantly higher than in control homes. Our study also found higher levels of some SHA biomarkers, such as nicotine, cotinine, 1,2-PD, and cobalt, in biological samples taken from bystanders living with e-cigarette users compared to controls.

The present study demonstrates that e-cigarette use at home impairs indoor air quality by increasing the concentrations of airborne nicotine. The marker in e-cigarette users' homes was quantified at significantly higher levels than that in control homes; and even reached eight times higher at the top margin ($95^{th}$ percentile). As nicotine is a specific marker for the consumption of any nicotine-containing product, and participants were not using any other form of nicotine-containing products, we may ascertain that the source of this pollutant was the exhaled e-cigarette aerosol.

Using the same observation period (seven days), sampling and analysis method, Ballbè et al. also reported a significantly higher concentration of airborne nicotine in homes of e-cigarette users compared to control homes in Catalonia (Spain) [12]. However, the study found a higher median concentration of airborne nicotine in e-cigarette homes than in the present study (0.11 vs. 0.01 $\mu g/m^3$). The discrepancy might be due to the variation in determinant factors of airborne nicotine level [37] that were not captured in the study, such as duration and frequency of e-cigarette use at homes, users' puffing topography, type of housing (e.g., house vs. apartment) and ventilation system, nicotine concentration in the e-liquid, and e-cigarette's design and operating parameters (e.g., battery power output, voltage).

An increased level of indoor airborne nicotine due to SHA in different settings has been also documented by previous non-interventional studies. The studies measured airborne nicotine levels ranged from 1.1 to 124.7 $\mu g/m^3$ in e-cigarette conventions [13,14], and from 0.9 to 3.3 $\mu g/m^3$ inside vape shops [15,16]. As expected, the present study, capturing typical daily use of e-cigarettes at home, shows a lower level of airborne nicotine than those in e-cigarette conventions and vape shops [15,16], which rather reflected intensive use of e-cigarettes.

Due to the limited number of homes included in this study, we were not able to detect the difference between concentrations of $PM_{2.5}$ in e-cigarette and control homes, despite the significantly higher levels ($p<0.001$) in e-cigarette homes in our pooled estimates. Similar to the present study (8 µg/m$^3$; IQR: 5-10 µg/m$^3$), a previous observational study detected a median concentration of $PM_{2.5}$ in an e-cigarette user's home of 9.88 ug/m$^3$ (IQR: 8.84–11.96 µg/m$^3$) and not significantly different from control homes [6]. Although found in relatively low concentration, the peaks of $PM_{2.5}$ level were observed concurrent with e-cigarette puffs [6,18], indicating that e-cigarette users exhaled $PM_{2.5}$ in the aerosol Another observational study revealed that use of e-cigarettes in an indoor home environment can release a strikingly high level of $PM_{2.5}$ at 843 µg/m$^3$ (min-max: 19-8250 µg/m$^3$), higher than that of measured in an indoor home environment without e-cigarette use [19]. However, the study did not employ *ad libitum* use of e-cigarette, and only used one home, which may partly explain the higher level of $PM_{2.5}$ than that was found in the present study.

Despite the relatively low level of indoor pollutants found in this study, our findings are of importance given the higher levels of nicotine in e-cigarette homes compared to the control homes in natural conditions, which indicates that e-cigarette use at home generates SHA and might involuntary expose other residents in the same home to the pollutants. Furthermore, previous research demonstrated that $PM_{2.5}$ and nicotine emitted from e-cigarette use indoors may travel to adjacent rooms and to the outdoor environment, resulting in an air quality deterioration of smoke- and aerosol-free areas [16].

Interestingly, we observed no variation of airborne nicotine and $PM_{2.5}$ levels across different determinant factors which, under controlled conditions in previous research, has been found to influence the concentration of both markers in e-cigarette emission [11,38]. More observational studies are needed to identify the determinant factors of SHA at home setting under real conditions.

The higher concentrations of salivary nicotine and some of its metabolites, such as cotinine and 3'-OH-cotinine, found in bystanders in our study suggests that the airborne nicotine in SHA can be systematically absorbed by bystanders, confirming a preliminary study [12]. Unlike our study, the previous study found a higher level of urinary cotinine in non-users living with e-cigarette users, while our study did not find any significant increase in concentration of any nicotine metabolites in urine which may have been affected by our small sample size for urinary assessment. Differences might be attributed to the inter individual variability in the nicotine and cotinine metabolism, which are affected by factors including race, gender, age, genetic variances, diet, and medications [39]. Children are especially at risk of nicotine exposure by e-cigarette use of their caregivers at home, as has been shown in a past study [40].

We also identified e-liquid's humectant component, 1,2-PD, in saliva samples of non-users who lived with e-cigarette users at level significantly higher than that was found in control subjects. It is well known that 1,2-PD and glycerol are the most abundant constituents in e-liquid ($\geq$ 80% of e-liquid mass) [41], and have been identified in elevated levels in e-cigarette users' plasma [42]. The heating of 1,2-PD and glycerol by e-cigarette use has been found to form toxic thermal degradation by-products, such as acrolein, formaldehyde, acetaldehyde, and propylene oxide [43]. As solvents are the main constituents of e-liquids, the harmful by-products are expected to be present in SHA regardless of limits imposed to individual nicotine, additives, and/or flavourings.

With regards to metals, previous studies also found cobalt in serum and urine of e-cigarette users, even at similar level that was found in combustible cigarette smokers [21]. Cobalt was detected in e-liquids, suggesting that the cobalt in e-cigarette users was inhaled from e-cigarette aerosol [21]. Our study indicates that bystanders may also be exposed to the metal element present in SHA from e-cigarette use at home. To our knowledge, the present study is the first that determined metal elements in e-cigarette non-users' biological samples. Although cobalt is a biologically essential element part of vitamin $B_{12}$, excessive exposure has been shown to pose various adverse health effects, from allergic skin and respiratory reactions to neurological (hearing and visual impairment), cardiovascular, and endocrine diseases [44].

Although some TSNAs (i.e., NNN, NNK) were previously detected in e-cigarettes' aerosol [45], our study did not find differences in TSNAs concentrations in saliva or urine between non-users in e-cigarette homes and non-users in control homes. Previous observational studies did not detect TSNAs in urine sample of bystanders attending e-cigarette events [24], nor found NNAL at significant level in urine of non-users living with e-cigarette users [46]. NNK was detected in children who lived with e-cigarette users, but at level not different from children lived with non-users [40]. Future studies need to explore the extent of TSNAs systemic absorption among bystanders exposed to SHA.

Our findings highlight the importance of monitoring e-cigarette use at home. Previous research has indicated that young people living with e-cigarette users were 11 times more likely to be exposed to SHA compared to those not living with users of any tobacco products [47], and youth from disadvantaged groups were more likely to be affected by any risks of home e-cigarette use compared to their more advantaged peers [27]. Pregnant women were also found to be frequently exposed to SHA at homes from their partner's e-cigarette use [48].

E-cigarette use inside homes was common when people perceived that SHA was less harmful than SHS [27]. Indeed, there is limited public knowledge about the potential harms of e-cigarettes and SHA [49], and low perceptions of harm from e-cigarettes among youth [47,50]. Furthermore, the pervasive use of e-cigarette at home might be partly due to the lack of voluntary e-cigarette use restriction at homes. In some states of the US, 70% of parents visiting paediatric clinics used e-cigarette at home, but less than a quarter of them forbidding their use in their homes [51]. Less than 60% of e-cigarette users in the UK voluntary applied e-cigarette-free rules in their homes [52]. According to a survey in 48 countries of the WHO European Region in 2018, private areas, including homes, were the least protected place from SHA by national legislation on e-cigarette use [53].

Although a ban on e-cigarette use at home is not commonly found, some studies suggest that such restriction might be effective in tackling exposure to SHA. In the US, people who lived within households with voluntary e-cigarette use restrictions had lower odds and frequency of e-cigarette use, while those who worked in workplaces with full prohibition of e-cigarette use had significantly reduced likelihood of SHA exposure [54]. In the context of the COVID-19 pandemic, many e-cigarette users in the US reported using e-cigarettes inside their homes more than before the pandemic, which may increase SHA exposure to others who were confined together with the users [55]. Thus, the implementation of aerosol-free homes, similar to smoke-free homes, might protect non-users as smoke-free homes have been proven effective in minimising SHS at homes [56].

Our study was limited by a small sample size that might hamper the identification of differences between groups in comparison. The convenience sampling of participants does also limit generalisation of our results. Nevertheless, we included participants from different countries with different sociodemographic context. We cannot disregard that the installed airborne monitors inside the e-cigarette users' homes might have created a social-desirability bias where users might have changed their e-cigarette use behaviour during the observation period (e.g., not using e-cigarette in room in which the monitors were placed). We also acknowledge the lack of information on e-cigarette use duration at home in this study.

However, our intention was to identify SHA exposure at e-cigarette users' homes by means of comparison with non-users' homes, regardless the variations in e-cigarette use including length of e-cigarette use at home. With only the gas phase that was quantified for the airborne nicotine in this study, our results on airborne nicotine concentrations might have been underestimated. A previous study noted that the largest increase of airborne nicotine from e-cigarette use is in the particle phase compared to the gas phase [7]. Furthermore, we did not take into account the air exchange rate in the analysis that might affect the concentration of indoor airborne markers. Nevertheless, this study included variability across homes by sampling homes from different countries and incorporating the information on frequency of room ventilation during e-cigarette use at home in our analysis.

Notwithstanding the mentioned limitations, the present study is the first multi-country study that examined simultaneously environmental and personal exposure to SHA at homes using a non-interventional study design with a relatively long observation period, enabling to see the comprehensive picture of the real-life scenario. Our study was also relevant with the situation when the study performed as most of the e-cigarette users recruited (64%) were using the tank system of e-cigarette 3rd generation which was the popular e-cigarette model in the market [57]. Additionally, there were similar characteristics of participants across different groups (i.e., users, non-users, controls) in this study, which made them comparable. We also minimised the distortion in $PM_{2.5}$ measurement by taking into account the cooking activity that might be another source of indoor $PM_{2.5}$ pollutant.

## 5. CONCLUSION

E-cigarette use at home was associated with increased concentrations of indoor airborne nicotine and exposed bystanders to compounds present in the SHA, such as nicotine, 1,2-PD, and metal elements. Indoor airborne nicotine from e-cigarette use at home may be difficult to eliminate through measures such as increasing room ventilation and/or reducing nicotine content in e-liquid. Promotion of aerosol-free homes through evidence-based strategies is needed to protect bystanders at home from exposure to SHA and its health risks.

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**Table S1. Limit of quantifications (LOQ) and concentrations (μg/L) of urinary metal elements of electronic cigarette users, non-users, and controls in homes of two European countries. TackSHS Study, 2019**

| Metals | LOQ | | User (N=12) | Non-user (N=12) | Control (N=11) | p-values* non-user vs. control | p-values* user vs. non-user | p-values* user vs. control |
|---|---|---|---|---|---|---|---|---|
| Beryllium (Be) | 0.00 | Median (IQR) | 0.00 (0.00-0.00) | 0.00 (0.00-0.00) | 0.00 (0.00-0.00) | 0.898 | 0.230 | 0.430 |
| | | Mean (SD) | 0.00 (0.00) | 0.01 (0.01) | 0.01 (0.03) | | | |
| Natrium (Na) | 257.86 | Median (IQR) | 1863455 (1342072-2921840) | 2187965 (1450262-3650862) | 1596386 ( 1413443-3168551) | 0.622 | 0.603 | 0.902 |
| | | Mean (SD) | 2208962 (1021240) | 2580961 (1659690) | 2159211 (1144710) | | | |
| Magnesium (Mg) | 11.07 | Median (IQR) | 67669.95 (30522.1-102100.3) | 66171.13 (30865.53-91540.86) | 68489.39 (41622.64-82393.99) | 0.902 | 0.817 | 0.951 |
| | | Mean (SD) | 74587.49 (50795.51) | 66347.47 (45363.17) | 69350.48 (38399.2) | | | |
| Aluminum (Al) | 21.58 | Median (IQR) | 10.79 (10.79-10.79) | 10.79 (10.79-10.79) | 10.79 (10.79-10.79) | NA | NA | NA |
| | | Mean (SD) | 10.79 (0) | 10.79 (0) | 10.79 (0) | | | |
| Potassium (K) | 36.66 | Median (IQR) | 1076733 (709515.5-2265527) | 1927193 (565738.7-2766079) | 1103417 (581331.8-3828413) | 0.758 | 0.773 | 0.758 |
| | | Mean (SD) | 1595672 (1236385) | 1773013 (1247173) | 2176763 (2007826) | | | |
| Calcium (Ca) | 123.85 | Median (IQR) | 153624.1 (61655.8-210642.4) | 134892.8 (64670.1-208353.8) | 137499.5 (65146.17-205457) | 0.805 | 0.729 | 0.951 |
| | | Mean (SD) | 165649.3 (138416.3) | 146271.4 (99577.99) | 173209.2 (159136.6) | | | |
| Vanadium (V) | 3.65 | Median (IQR) | 1.82 (1.82-1.82) | 1.82 (1.82-1.82) | 1.82 (1.82-1.82) | NA | NA | NA |
| | | Mean (SD) | 1.82 (0) | 1.82 (0) | 1.82 (2.33) | | | |
| Chromium (Cr) | 0.55 | Median (IQR) | 0.28 (0.28-0.28) | 0.28 (0.28-0.28) | 0.28 (0.28-0.28) | NA | NA | NA |
| | | Mean (SD) | 0.28 (0) | 0.28 (0) | 0.28 (0) | | | |
| Manganese (Mn) | 0.25 | Median (IQR) | 0.12 (0.12-0.12) | 0.12 (0.12-0.12) | 0.12 (0.12-0.12) | 0.296 | NA | 0.296 |
| | | Mean (SD) | 0.12 (0) | 0.12 (0) | 1.01 (2.95) | | | |
| Iron (Fe) | 3.88 | Median (IQR) | 1.94 (1.94-3.46) | 1.94 (1.94-1.94) | 1.94 (1.94-8.36) | 0.080 | 0.307 | 0.385 |
| | | Mean (SD) | 3.20 (2.61) | 2.35 (1.41) | 4.89 (4.42) | | | |
| Cobalt (Co) | 0.04 | Median (IQR) | 0.16 (0.09-0.40) | 1.32 (0.32-2.26) | 0.26 (0.13-0.47) | 0.031 | 0.064 | 0.479 |
| | | Mean (SD) | 0.58 (1.13) | 1.35 (1.13) | 0.28 (0.18) | | | |
| Nickel (Ni) | 0.22 | Median (IQR) | 0.37 (0.11-1.20) | 0.66 (0.11-1.79) | 0.33 (0.11-0.58) | 0.521 | 0.711 | 0.653 |
| | | Mean (SD) | 1.56 (3.14) | 1.13 (1.33) | 0.46 (0.47) | | | |
| Copper (Cu) | 0.94 | Median (IQR) | 4.91 (3.09-9.62) | 5.00 (3.33-9.08) | 11.02 (4.40-15.85) | 0.148 | 0.954 | 0.139 |
| | | Mean (SD) | 6.60 (5.86) | 6.67 (5.81) | 11.57 (9.41) | | | |
| Zinc (Zn) | 17.13 | Median (IQR) | 361.22 (191.85-515.16) | 242.66 (141.20-363.28) | 293.29 (140.01-434.35) | 0.498 | 0.273 | 0.712 |
| | | Mean (SD) | 411.82 (292.96) | 264.21 (170.13) | 466.37 (544.02) | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Arsenic (As) | 0.47 | Median (IQR) | 42.26 (24.09-88.59) | 41.60 (20.75-112.18) | 37.28 (17.47 (163.25) | 0.951 | 0.954 | 0.902 |
| | | Mean (SD) | 58.86 (46.51) | 121.42 (184.84) | 83.02 (89.45) | | | |
| Selenium (Se) | 1.22 | Median (IQR) | 39.37 (17.84-55.64) | 35.40 (24.82-47.46) | 31.25 (17.48-70.39) | 0.758 | 0.773 | 0.712 |
| | | Mean (SD) | 40.13 (23.25) | 36.55 (19.98) | 43.95 (29.41) | | | |
| Molybdenum (Mo) | 0.08 | Median (IQR) | 41.47 (8.23-79.37) | 34.03 (13.83-56.74) | 49.56 (28.10-134.01) | 0.218 | 0.862 | 0.325 |
| | | Mean (SD) | 49.30 (42.47) | 54.62 (72.70) | 92.66 (89.06) | | | |
| Silver (Ag) | 0.16 | Median (IQR) | 0.08 (0.08-0.08) | 0.08 (0.08-0.08) | 0.08 (0.08-0.08) | NA | NA | NA |
| | | Mean (SD) | 0.08 (0) | 0.08 (0) | 0.08 (0) | | | |
| Cadmium (Cd) | 0.38 | Median (IQR) | 0.19 (0.19-0.19) | 0.19 (0.19-0.41) | 0.19 (0.19-0.52) | 0.664 | 0.544 | 0.381 |
| | | Mean (SD) | 0.43 (0.69) | 0.27 (0.12) | 0.39 (0.34) | | | |
| Tin (Sn) | 4.72 | Median (IQR) | 2.36 (2.36-2.36) | 2.36 (2.36-2.36) | 2.36 (2.36-2.36) | NA | 0.317 | 0.338 |
| | | Mean (SD) | 2.79 (1.49) | 2.36 (0) | 2.36 (0) | | | |
| Antimony (Sb) | 0.38 | Median (IQR) | 0.19-0.19) | 0.19 (0.19-0.19) | 0.19 (0.19-0.19) | NA | NA | NA |
| | | Mean (SD) | 0.19(0.00) | 0.19 (0) | 0.19 (0) | | | |
| Barium (Ba) | 0.44 | Median (IQR) | 1.30 (0.22-4.89) | 0.87 (0.22-2.90) | 0.78 (0.22-2.09) | 0.875 | 0.406 | 0.574 |
| | | Mean (SD) | 2.46 (2.52) | 1.45 (1.43) | 1.98 (3.16) | | | |
| Mercury (Hg) | 0.66 | Median (IQR) | 1.19 (0.33-1.19) | 1.02 (0.54-2.25) | 2.22 (1.12-3.78) | 0.079 | 0.791 | 0.113 |
| | | Mean (SD) | 1.37 (1.22) | 1.49 (1.19) | 2.72 (2.08) | | | |
| Thallium (Tl) | 0.03 | Median (IQR) | 0.24 (0.02-0.35) | 0.20 (0.04-0.29) | 0.23 (0.12-0.39) | 0.536 | 0.749 | 0.757 |
| | | Mean (SD) | 0.22 (1.18) | 0.27 (0.34) | 0.29 (0.28) | | | |
| Lead (Pb) | 0.45 | Median (IQR) | 0.41 (0.22-0.74) | 0.22 (0.22-0.87) | 0.22 (0.22-0.86) | 0.576 | 0.699 | 0.947 |
| | | Mean (SD) | 0.51 (0.33) | 0.60 (0.70) | 0.86 (1.21) | | | |
| Thorium (Th) | 0.01 | Median (IQR) | 0.00 (0.00-0.00) | 0.00 (0.00-0.00) | 0.00 (0.00-0.00) | NA | 0.317 | 0.338 |
| | | Mean (SD) | 0.01 (0.00) | 0.00 (0) | 0.00 (0.00) | | | |
| Uranium (U) | 0.00 | Median (IQR) | 0.02 (0.01-0.05) | 0.01 (0.00-0.04) | 0.02 (0.00-0.05) | 0.782 | 0.326 | 0.424 |
| | | Mean (SD) | 0.06 (0.13) | 0.03 (0.05) | 0.04 (0.05) | | | |

Abbreviations: IQR: interquartile range; SD: standard deviation; NA: not applied.
* Calculated using Mann-Whitney test

# DISCUSSION

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Although e-cigarette consumption has been widespread (29–34), the evidence on its impact on bystanders has only recently emerged. This PhD thesis has comprehensively elucidated the issue on the exposure to SHA among bystanders in Europe by means of different studies with different methodologies that covered different aspects: 1) policy approaches taken by European countries in regulating the use of e-cigarettes in different settings by a survey to in-country informants, 2) population's exposure to SHA by a cross-sectional survey in the European population, 3) personal exposure to SHA by an experimental and an observational study, and 4) environmental exposure to SHA by an experimental and an observational study.

# Regulations of e-cigarette use in European countries

We have investigated e-cigarette use regulation in public and private settings, as it is considered a measure closely related to SHA exposure. Our study has shown that within the WHO European Region, e-cigarette use restriction was still less commonly adopted than the smoke-free policies, given the limited number of countries across the region that had enacted any national legislation on e-cigarette use by 2018; that was around 60% of the studied countries compared to 87% of countries with the smoke-free legislation at national level (137). E-cigarette use legislation was also less adopted compared to other regulatory domains related to e-cigarettes, such as pricing, product standard, marketing, and retail, among countries globally, suggesting that countries still focused solely on those domains (127).

Our results, however, have provided evidence on the urge to mainstream the e-cigarette use restriction, at least in indoor spaces. We have learned from our studies that e-cigarette use in enclosed settings may expose bystanders to the chemical and physical constituents of SHA, which may result in some adverse health effects. Bystanders were extensively exposed to SHA in indoor settings and potentially in outdoor settings, too, as shown in our multi-country study across Europe. Additionally, countries with more prevalent e-cigarette use in the population also had a higher occurrence of SHA exposure among bystanders in indoor settings and higher visibility in outdoor areas, including those frequented by children. Thus, strategies to limit e-cigarette use consumption are needed to reduce the population's exposure to SHA.

Although legislation on e-cigarette use, especially in private areas, has not been widely adopted by countries, as shown in this thesis, existing evidence suggests that e-cigarette use restrictions in public and private areas might be effective in tackling SHA exposure. In the US, for example, the state-wide ban for e-cigarette use indoors (i.e., workplaces, restaurants, or bars) was associated with reduced e-cigarette use in adults and youth (118,119). Additionally, voluntary partial or full e-cigarette use restrictions at home were found to lower the likelihood of e-cigarette use among the residents, and full prohibition of e-cigarette use at workplaces was associated with significantly reduced SHA exposure among workers (120).

This thesis also demonstrated that the adoption and enforcement of the law on e-cigarette use are equally important. This is because our studies revealed that e-cigarette use was still observed in some school entrances where e-cigarette use was already prohibited, and some countries' representatives expressed challenges for enacting and enforcing the e-cigarette use legislation. Most difficulties came from e-cigarette industry front-groups and lobbies, and the government's poor political will. Activities of tobacco and e-cigarette industry interference in e-cigarette-related policies have been well documented from many parts of the world. In Europe, the tobacco industry and pro-e-cigarette groups have been actively promoting e-cigarettes as a better alternative to combustible cigarettes, and, thus, they lobbied European Commission and some European countries to tax and regulate the products less restrictively than combustible cigarettes (138). Finland has seen obstacles in enforcing its characterising flavours ban in e-liquids since e-cigarette businesses were non-compliant with the regulation and filed a court case to overturn the rules (139). In India, strong resistance to e-cigarette ban has been received from the e-cigarette industry as the country faced legal challenge shortly after the issuance of the country's law on the e-cigarette ban (140).

Another challenge in regulating e-cigarette use that worth noting from this thesis is the discrepancy in the regulation between countries. The diverse e-cigarette use regulation among countries might be due to the divergent regulatory stances towards e-cigarettes, as shown in comparative studies among high-income countries (127,141). Some contextual factors that we identified affecting variation in e-cigarette use legislation among countries were country's EU membership status, income level, and population smoking prevalence. EU MS had a higher proportion of countries with national legislation for e-cigarette use in any place, and they encountered less difficulty in adopting the legislation than non-EU countries. Although the existing EU-wide policy on e-cigarettes, which is stipulated in Article 20 of EU TPD 2014/40/EU, does not include e-cigarette use regulatory domain (125), the EU TPD might have served as a motivator for EU MS to advance their e-cigarette-related regulations, including introducing e-cigarette use legislation. However, this thesis showed that non-EU countries had higher public support than EU MS for implementing the e-cigarette use regulations. Countries with lower income status also had more difficulty passing the e-cigarette use legislation, but for those that had adopted the law, they had more places with some forms of e-cigarette use restriction than countries with higher income status. Although our study was not designed to explain the reason behind this distinct public support and expansion of the regulated places, some determinant factors in the population that are beyond EU membership and country's income status, such as e-cigarette use status and risk perception towards e-cigarette use, may play a role in affecting those differences, as shown in previous studies (42,123). This thesis also noted that higher country's smoking prevalence was associated with more places regulated by e-cigarette use legislation in that corresponding country, which might be related to countries' ability to bring e-cigarette use under the definition of "smoking" in their policy documents (142).

The above evidence has unravelled the complicated yet important work policymakers have to manage and consider while regulating e-cigarette use. Despite the challenges, this thesis shows that countries may be encouraged by a considerably high public support for the implementation of e-cigarette use regulation, as has been also observed in other studies (42,122,123), which may serve as an opportunity for strong enforcement of the regulation.

# Population's exposure to SHA in Europe

This thesis has shown that the extent of SHA exposure in the European population is not negligible; 16.0% of e-cigarette non-users aged ≥ 15 years were exposed in any indoor setting in 12 European countries in 2017-2018, with a median duration of exposure of 43 minutes per day. It disproportionally affected men and vulnerable groups in the population, like young people and former e-cigarette users. This thesis, however, did not find that those in lower socioeconomic status, which was determined by the level of education in this thesis, were at a higher risk of being exposed to SHA. Instead, our findings demonstrate that highly educated bystanders were more likely to be exposed to SHA, suggesting determinant factors of SHA exposure are similar to e-cigarette use (143–145). E-cigarette users, who are likely peers and socialise with SHA bystanders, were also mostly from higher educational groups than non-users, indicating they were early adopters for new technologies according to the theory of innovation diffusion (146).

SHA exposure among e-cigarette non-users in Europe was more common in certain places where people usually socialise together, like bars and workplaces or education facilities, although at least half of the European countries we studied had restricted the use of e-cigarettes in those places. Even in places frequented by minors, such as children's playgrounds and school gates, e-cigarette use activity was visible in some European countries, although it was less apparent than in outdoor hospitality venues. Similarly, SHS in outdoor settings of designated areas for children was less commonly found than in those for the general public (147). The common negative perceptions of e-cigarette risks for minors might play a role in discouraging e-cigarette users from using their products in places where children are likely around (148,149).

Homes, where e-cigarette non-users are likely to spend more time together with the users, were the place where the longest median duration of SHA exposure occurred (43 minutes per day) compared to other indoor settings we studied, including public places. In Barcelona, the use of e-cigarettes in 2015 was higher in private venues, particularly homes, than indoor public places, such as workplaces and restaurants (37). Indeed, private areas, including homes, were the least regulated place by countries within WHO European Region, with only 39.6% of them having national legislation on e-cigarette use at homes, according to our study. Home-use of e-cigarettes were perceived safer than tobacco smoking and, thus, often occurred inside the home while tobacco smoking was prohibited (117). Among residents who banned e-cigarette use within the home environment, protecting young people was cited as the main reason (117). Although 6 out of 10 US adults reported prohibiting e-cigarette use inside their home, the voluntary restrictions were less commonly enforced than the smoke-free policy at that setting (149,150). Additionally, two-fifth of adults in the US were still unsure about how to rule e-cigarette use inside their homes (151).

Exposure to SHA was also identified in some smoke-free areas, such as inside restaurants, educational venues, and public transport. In children's playgrounds and school entrances, where some European countries have banned smoking, e-cigarette use was also observed. Indeed, e-cigarette use in places where smoking was prohibited has been commonly found in indoor places in Europe, suggesting that e-cigarettes were used to evade the smoke-free regulations by users who were mostly dual-users (35,40,152). This is despite the fact that WHO FCTC has advised Parties to ban e-cigarette use in smoke-free places (124). Including e-cigarettes in smoke-free rules can simplify the communication and implementation of the rules. Furthermore, a great proportion (84%) of US adults believed that e-cigarette use should not be allowed in places that prohibit smoking (149).

The variation in SHA exposure across European countries found in our study was true not only at the individual level but also at the country level. The variation created a wide gap in the prevalence of SHA exposure in any indoor place between the highest (Greece: 29.6%) with the lowest one (Spain: 4.3%). We found that Greece and Spain also had the highest and lowest visibility of e-cigarette use in outdoor settings, respectively. The important driver behind the variations in SHA exposure and e-cigarette use outdoors that we found in our studies was the country's e-cigarette use prevalence. Countries with more prevalent e-cigarette use in the general population had higher prevalence of SHA exposure in indoor settings and more widespread e-cigarette use in outdoor settings. Unlike SHS, SHA exposure indoors and e-cigarette use outdoors in European countries did not differ by country's tobacco control performance. This might be because the country's existing tobacco control strategies have not covered e-cigarette use restrictions that they did not affect SHA exposure indoors nor e-cigarette use outdoors. The findings highlight the importance of introducing e-cigarette use regulation as part of the country's tobacco control framework.

# Environmental exposure to SHA in indoor settings

This thesis determined the environmental exposure to SHA by assessing $PM_{2.5}$ and airborne nicotine concentrations in indoor settings. $PM_{2.5}$ levels were found to be elevated due to the use of an e-cigarette in controlled confined settings (i.e., a room and a car), but not in real-life conditions (i.e., homes of e-cigarette users). However, $PM_{2.5}$ concentrations followed the variation of puff numbers made by the e-cigarette user in the experiment room and car, meaning the indoor $PM_{2.5}$ pollutant we detected was originated from e-cigarette use. The discrepancy between our two studies might be partly explained by the small sample size in our observational study (29 e-cigarette homes and 21 control homes) that we were not able to detect the differences of $PM_{2.5}$ level between e-cigarette homes and control homes, or due to the different physical conditions between the spaces (houses and other confined spaces) where we collected the samples.

Conversely, the increased level of airborne nicotine was only observed in real-life conditions, where the seven-day concentration of airborne nicotine in e-cigarette users' homes was higher than that was found in non-users' homes. We were not able to see the increased level of airborne nicotine in the controlled confined settings, presumably due to the short duration of e-cigarette use in such settings; only 30 minutes of *ad libitum* use, while users in our observational study were allowed to use their e-cigarettes as long and as many times as they wanted in their homes during the seven-day period of fieldwork. The discrepancy, therefore, highlights the importance of having a long-term assessment of environmental exposure to SHA in order to avoid underestimating the level of airborne markers from e-cigarette use. Nevertheless, our findings in both studies have confirmed that SHA impairs indoor air quality by increasing both $PM_{2.5}$ and airborne nicotine concentrations.

We employed different airborne nicotine sampling methods in our studies, applying the best fit for the collection duration of each study (153). In our experimental study, we used active sampling method because the method was more appropriate to collect the airborne nicotine for a short-term assessment (40 minutes per day in our study), while in our observational study, we used passive sampling methods because the method was better fit for a longer period of nicotine collection (a continuous seven-day measurement in our study). Both sampling methods have been proven equally effective in measuring SHS exposure in many environments (153). Therefore, we may assume that the discrepancy in the airborne nicotine concentrations in our studies was not due to the different sampling techniques employed.

Although the scope of this thesis was limited to indoor spaces where the e-cigarette use was taking place, we cannot rule out the possibility of the SHA pollutants contaminating the nearby indoor and outdoor environments. A previous study has revealed that airborne nicotine and $PM_{2.5}$ originated from e-cigarette use in e-cigarette shops can travel to the adjacent smoke-and aerosol-free indoor spaces in multiunit buildings (89). According to the study, $PM_{2.5}$ also transferred from inside the e-cigarette shops to outdoor areas when the shops' doors were open. The study suggests that involuntary exposure to SHA may also occur in neighbouring residents or by-passers of the e-cigarette user's home.

The measurement of some determinant factors of environmental exposure to SHA in our two studies may help us better understand what might or might not cause the variation in SHA marker levels. Firstly, the number of puffs made by the e-cigarette user can influence the concentrations of exhaled $PM_{2.5}$ in indoor settings; the more puffs generated, the higher the $PM_{2.5}$ concentration detected. Secondly, in condition without any ventilation system used in an enclosed setting, the distance from the e-cigarette user did affect the indoor $PM_{2.5}$ level. However, from our observational study, we found that $PM_{2.5}$ and airborne nicotine levels inside e-cigarette users' homes did not vary by the frequency of ventilation use during e-cigarette use. Lastly, the nicotine concentration in e-liquid, type of e-cigarette, and place of e-cigarette use at home seemed to be playing no role in mitigating the indoor SHA pollutants because there was no significant difference in $PM_{2.5}$ and airborne nicotine levels in e-cigarette users' homes according to those conditions.

# Personal exposure to SHA in indoor settings

Through the personal SHA exposure assessment conducted in our two complementing studies, the experiment and observational studies, we found that the concentrations of the studied biomarkers of SHA exposure in samples taken from bystanders who were e-cigarette non-users were generally low. Nevertheless, when we compared them with the control subjects who lived in non-users' homes, the levels of some biomarkers (i.e., nicotine, cotinine, 3'-OH-cotinine, 1,2-PG) in saliva sample and cobalt in the urine sample of e-cigarette non-users living with the users were found to be higher. In contrast, the elevated levels of the studied biomarkers in the saliva sample during and after e-cigarette use were not observed in our experimental study, although we used the same analytical method (liquid chromatography-tandem mass spectrometry). The inconsistent results in the two studies might be partly explained by the different duration of e-cigarette use performed in the two studies. In the experiment study, e-cigarette user was conditioned to puff only within the 30-minute session per day for five consecutive days, while in the observational study, users might have used their e-cigarettes in home for a longer time by the time of the study conducted. The biomarkers were likely accumulated in the body of e-cigarette non-users who resided together with the users due to the long-term exposure to SHA at home, making them easier to be detected and quantified in the biological samples (154). As was the case in our environmental SHA assessment, our findings in the studies of personal SHA assessment further suggest the importance of performing a long-term observation to see the impact of e-cigarette use on bystanders in real-life conditions.

Whether the increased biomarkers in bystanders can be translated into adverse health outcomes is still questionable but concerning. Our experimental study mimicking real conditions found that SHA exposure from short-term (30 minutes) e-cigarette use in enclosed settings, such as room and car, triggered several irritation symptoms in eyes and airway of bystanders, which also have been observed in volunteers of an experimental study in a laboratory (97). Although the symptoms were perceived as mild, they remained up to three hours after the e-cigarette use ended. Furthermore, although we did not control other potential sources of cobalt exposure in our study (e.g., occupational and dietary intake) because of the low levels found, exposure to excessive cobalt has been found to cause respiratory reactions, neurological impairment, and cardiovascular diseases (155). This is worth noting as in the long run, and under repeated SHA exposure, like the typical pattern at home, the health effects on bystanders might be worse. This thesis, however, confirmed that the toxic chemicals present in SHA might be systematically absorbed by e-cigarette non-users and created some acute health effects in bystanders.

# SHA is incomparable with SHS

The narrative of exposure to e-cigarettes is often presented in comparison with tobacco smoke exposure. Many studies have compared the chemical compounds of e-cigarette aerosol, including in SHA, with tobacco smoke in an attempt to understand the relative harm of e-cigarette use compared to tobacco smoking (156). Thus, discussing the findings of this thesis in the context of existing knowledge of SHS is also warranted, although the comparison is outside of the scope of this thesis. Our results suggests that SHA exposure has different characteristics from SHS for some reasons.

Firstly, SHA contains fewer hazardous compounds present in SHS, such as $PM_{2.5}$, nicotine, and TSNAs, but consists of constituents that are absent or present in small amount in SHS or tobacco mainstream smoke, such as metals, PG, and glycerol. Our experimental and observational studies showed that TSNAs, which were abundantly found in biosamples of tobacco smokers (106), were not quantifiable in the saliva and urine of bystanders exposed to SHA. Similarly, our studies indicate that the levels of indoor $PM_{2.5}$ and airborne nicotine were low (median concentrations of $PM_{2.5}$ were 21 µg/m$^3$ in the room and 8 µg/m$^3$ in homes, and median concentrations of airborne nicotine were not quantified in the room and 0.01 µg/m$^3$ in homes), compared to previously found in SHS (median concentration of homes' $PM_{2.5}$ was 31 µg/m$^3$ and airborne nicotine was 0.18 µg/m$^3$) (157,158). However, smaller particles (ultrafine particulate matter; $PM_{0.1}$ or $PM_1$), which may penetrate deeper into the lungs, in e-cigarette aerosol has been measured at a greater level than in tobacco smoke (47,48).

Furthermore, our study identified cobalt in the urine of e-cigarette non-users that were exposed to SHA at a significantly higher level than those non-exposed, while in previous studies, cobalt was detected in the urine sample of e-cigarette users at a similar level to tobacco smokers (159). Cobalt was not even found in tobacco smoke, while it was present in e-cigarette aerosol (46). Many other metal elements, such as copper, selenium, silver, strontium, and vanadium, have been found in biological samples (i.e., urine, serum) of e-cigarette users at higher levels than in tobacco smokers (159). We did not detect the higher levels of other metals in urine samples of e-cigarette non-users living with e-cigarette users compared to those living in control homes probably due to the small urine sample size included in our observational study. The levels of 9 out of 11 metal elements measured in e-cigarette aerosol, including chromium, copper, and nickel, were also reported to be higher than or similar to the levels in combustible cigarette smoke (45,160). When SHA was compared to SHS in a study using human volunteers in a room that simulated real-life conditions, nickel and silver in SHA were found in higher emission rates than their presence in SHS (161). The concentrations of metal elements in e-cigarette aerosol were strongly associated with their levels found in biomarkers of e-cigarette users, which provided support that aerosol metals were inhaled and absorbed by e-cigarette users (43).

Regarding the PG and glycerol, our study found them in biosamples of non-users living in e-cigarette users' homes at higher levels than in those of non-users in control homes, while these compounds, to our knowledge, have never been reported in biosamples of tobacco smokers as well as their bystanders. This is because PG and glycerol are the most dominant constituents in e-liquid (≥ 80% of e-liquid mass), while they are often absent or present as additives of combustible cigarettes' ingredients in a tiny amount (< 5% weight) (162,163). PG and glycerol have been found in increased concentrations in indoor air during e-cigarette use (80,84,86) and can transform into toxic degradation by-products, such as acrolein, formaldehyde, acetaldehyde, upon heating process (164).

The highly diverse e-liquid flavours and e-cigarette models, which also allow e-cigarette users to modify the functioning of the products, compared to the more homogenous characteristics of combustible tobacco products, might contribute to the distinct emission of SHA from SHS. This is unsurprising because product standard regulations for e-cigarettes are still less common than those for tobacco products or are usually less stringent than those applied to tobacco products, if at all (127). However, in some countries, e-cigarettes are put within the framework of tobacco products regulation, such as in the EU TPD, so that it is expected to minimise the variability of e-cigarettes and e-liquids (125).

Secondly, SHA exposure identified in our study was found to be less prevalent in Southern, and Eastern Europe (e.g., Italy, Spain, Romania, Bulgaria) compared to other European regions, while countries in these regions were known to have higher SHS exposure prevalence. According to the Eurobarometer 2021 Report, seeing people smoking inside restaurants and bars was dominantly reported by people in Bulgaria, Italy, and Spain than other countries (33). Previous studies also highlighted the prominent SHS in outdoor settings of eastern and southern countries of Europe, such as Romania, Bulgaria, Greece, and Italy (147,165). The contradiction between SHA and SHS might be partly due to the still limited or weak enforcement of smoke-free rules, and less prevalent e-cigarette use in those countries compared to countries in other European regions, as suggested by our population study.

Thirdly, unlike SHS, SHA exposure in Europe was more frequent in people with higher SES, according to our population study. Adults in 27 EU MS with lower SES were more likely to report being exposed to SHS in indoor areas, such as bars, restaurants, and workplaces (166). The reason behind this unique phenomenon warrants further study. Yet, evidence shows that e-cigarette users, who socialise with their non-user peers, were also from affluent groups who tend to early adopt innovative technologies, including e-cigarettes (146). E-cigarettes were still considerably less affordable than combustible cigarettes in some countries (167). This might also reflect the result of e-cigarette and tobacco industry strategy in targeting more advantaged communities, like educated and young people, for taking up their novel products (67,68).

Fourthly, SHA is perceived differently by society; most people think it is harmless, while SHS has been perceived as an established threat to bystanders. This is supported by the higher likelihood of SHA exposure among non-users who perceived SHA as harmless, as shown in our population study. Public perceptions of harms associated with SHA were generally lower than SHS (168,169). This might be influenced by limited public knowledge about SHA, with a great proportion of adults in the US reported not knowing whether SHA contained only water vapour (169) and failed to identify potential harms of SHA for children (148). Therefore, only 1 in 5 adults would ask others not to use e-cigarettes in public places (e.g., restaurants, bars, parks) compared with 1 in 2 adults who would ask others not to smoke in those places (170). Additionally, fewer adults enforced aerosol-free policy in cars and homes than smoke-free policy, and many of them were still reluctant in prohibiting e-cigarette use inside their house (150,151,171).

Some explanations for this less harmful perception towards SHA might stem from the perceived harm on the product itself. Generally, people thought e-cigarettes were less harmful than combustible cigarettes (172,173), which could be attributed to e-cigarette advertising by e-cigarette manufacturers presenting the benefits of e-cigarettes for harm-reduction strategy (174). They also tried to build a different image of e-cigarettes from combustible cigarette with different shape of e-cigarette products and the pleasant smell of their aerosol (174). Furthermore, the discriminative regulatory treatment that applied to e-cigarette use (e.g., many smoke-free rules do not apply to e-cigarettes, e-cigarette use was regulated less stringent than smoking) might cause society perceived e-cigarette use, and hence, SHA exposure as harmless.

Given the complexity and many distinct characteristics of SHA compared with SHS in many aspects as described above, this thesis asserts that it is inappropriate to compare SHA with SHS at any level. Instead, the justified comparison of SHA should be with “pure air” as all humans have the right to breathe clean air. Thus, SHA cannot be considered as safer or more harmful than SHS.

# Limitations and strengths

This thesis has some limitations that are worth noting. First, most of the studies of this thesis had a cross-sectional design, while e-cigarette products and their use pattern were rapidly evolving, which might affect SHA exposure at individual and population levels. Thus, causal relationship cannot be inferred from those studies. Even our experimental study in the room and the car used only one type of e-cigarette while there were a wide range of e-cigarette models, systems, and e-liquid flavours and ingredients available in the market. With those varied product features, in real life, e-cigarette users can mix the e-liquids and set their devices according to their need, which makes a standardised SHA assessment even more challenging, not exclusively in our study, but also in other studies that attempt to assess SHA exposure. The variations in e-cigarette and e-liquid products might be exaggerated by inadequate product regulations in many European countries. Even if they had transposed Article 20 in EU TPD 2014/40/EU concerning e-cigarette product regulations, there was still room for product modifications. For example, nicotine concentrations in e-liquids were still widely ranged below 20 mg/ml (175), the maximum concentration allowed by the provision (125). Given this limitation, our findings should be interpreted with caution; they captured only the situation when the studies were conducted and relevant to the product used. Our experiment study, however, has tried to mitigate the limitation by utilising the most widely used e-cigarette type at that time; that was the tank type (3$^{rd}$ generation), and by not fully controlling the parameters of e-cigarette use (e.g., number and duration of puffs, flavour of e-liquid, and ventilations of the room) to mimic the real-life conditions.

Second, we did not investigate all chemical constituents that may be present in SHA, which may underestimate the SHA exposure. Instead, our environmental and personal exposure assessments only covered the important airborne and biological markers commonly present in SHA based on the existing evidence. Given our knowledge in this area was still in infancy, there had not been such standard markers to be assessed in SHA exposure. At that stage, we were rather exploring the possible markers of SHA exposure, and adopting what we had known in SHS exposure. The need to further identify more useful markers to assess SHA exposure is justified given the unique characteristics of SHA for the reasons that have been explained in the previous section (see "SHA is incomparable with SHS").

Third, we used specific analytical methods for the samples collected in our studies, amid plenty of options available for the analytical methods, which might have affected the outcome of our analysis on SHA exposure's markers. To measure the concentrations of SHA constituents, we used gas chromatography-mass spectrometry (GC-MS) for airborne nicotine and liquid chromatography-tandem mass spectrometry (LC-MS-MS), and inductively coupled plasma mass spectrometry (ICP-MS) for the biomarkers in saliva and urine. Apart from the three techniques, there were at least 19 other analytical techniques, such as gas chromatography with tandem mass spectroscopy, high performance liquid chromatography, and ultraperformance liquid chromatography-mass spectrometry, for the determination of compounds in e-cigarette aerosol that have been utilised in past studies (11). However, GC-MS and LC-MS-MS were the most common techniques and proven to be effective in quantifying airborne and biological markers of exposure to e-cigarette aerosol (11,176).

Lastly, our studies were performed in European countries, with their legal, socio-economic, and demographic characteristics. Therefore, the findings in this thesis should be understood in light of the region-specific context, and external generalisation to other regions should be made with caution. Nonetheless, the European region was an important environment to assess SHA exposure given the growing e-cigarette market and a unique jurisdiction system with a common regulation of several aspects of e-cigarettes (the EU TPD) in the region.

Despite the limitations, this thesis has some strengths that can be highlighted. Firstly, the novelty of the studies included in this thesis. We conducted a series of studies that first assessed SHA exposure comprehensively in Europe. Built on previous knowledge, our studies complement each other by using different study designs, allowing us to assess different aspects of SHA exposure. Our experimental study was performed under controlled conditions and resembled real-life use of e-cigarettes in two confined spaces (a room and a car). Secondly, this thesis comprises multi-country studies, using standardised protocols which enabled us to understand the variation of SHA exposure in different contextual factors. Our population study was the first that assessed SHA exposure in a representative sample of the European population, including smokers and non-smokers. Despite the small sample size, our observational study in e-cigarette users' homes was conducted in four different European countries; that was beyond what had been done before. As our studies were conducted in the context of the European population, our results can be useful for research and policymaking in the region.

# Implications

## For public health and policymakers

This thesis may inform public health policy and practice in the area of tobacco control. With the widespread e-cigarette use and aggressive marketing of e-cigarettes targeting youth and non-smokers (67,68), the health and safety of e-cigarette non-users or bystanders should be in the mind of policymakers while they make any e-cigarette-related policy. They even should be at the center of discussion and be prioritised given that these groups constitute the majority of the population. While estimating the net population health benefit associated with e-cigarettes, public health experts and policymakers shall consider the impact of e-cigarette use on e-cigarette non-users against the rationale of harm-reduction strategy for smokers, which is still highly debatable.

Policymakers might want to extend the existing smoke-free laws to cover e-cigarettes or introduce an aerosol-free policy if no smoke-free rule is present, especially in public enclosed settings and places frequented by children. The forthcoming revision of EU TPD, which is legally binding on its MS, may improve the provision on safety and quality requirements for e-cigarettes to support MS in protecting their citizens from SHA exposure. Regardless of the EU TPD, European countries shall put e-cigarette use restrictions in their policymaking agenda.

In addition to the top-down strategy, public health discourse may start tapping on the issue of SHA exposure as part of the bottom-up approach. Voluntary aerosol-free homes should be normalised and encouraged in public health campaigns. As this thesis shows that places frequented by children (i.e., school gates and children's playgrounds) had relatively low visibility of e-cigarette use, suggesting common risk perception of e-cigarette use for minors, a children-safety theme might be introduced in the public awareness campaign to reinforce the policy adoption and to shape a social norm towards e-cigarette use.

To ensure the effectiveness of policies related to e-cigarette use, an awareness campaign of the policies should be implemented among the general public. The policies should remain informed and responsive to the development of evidence given the rapidly evolving research in the e-cigarette landscape. Furthermore, policymakers and enforcing authorities should be prepared for the challenges they may face while regulating and implementing e-cigarette use regulations. They must be well equipped with adequate capabilities to tackle all possible challenges, especially those posed by e-cigarette or tobacco industry interference, as expressed in our RASHA-E study. Countries may adopt their existing strategies for tobacco control in dealing with the industry interference. Furthermore, technical assistance for capacity building might be needed for some countries with low resources.

This thesis acknowledges that research in the area of SHA exposure is still in its early stage, but prompt action for a precautionary approach is warranted. It may take decades to see the real impact of SHA exposure in the population, but society cannot afford another late action, as has been shown in the SHS case (177).

## For research

This thesis has contributed to the recent highly contested scientific discussion on e-cigarettes by building on previous evidence about SHA exposure assessment. Future research might want to monitor SHA exposure in the population and evaluate SHA-related policies, particularly on how they might affect vulnerable populations and tobacco control strategies. Investigating SHA exposure in other environments and countries or regions for comparison is also warranted.

The studies included in this thesis have given light on the complexity of SHA exposure assessment. Some aspects should be considered when planning SHA studies, such as selecting the most appropriate study design, participant recruitment methods, markers of SHA exposure, and sample collection methods. To better understand e-cigarette use legislation in particular countries, qualitative studies might be more instrumental, and longitudinal studies would be beneficial to evaluate the effects of SHA exposure on bystanders at the individual, environmental, and population levels. This thesis admits the difficulty in recruiting exclusive e-cigarette users, particularly the long-term users, since they accounted for a smaller proportion (8% of non-smokers) compared to dual users (36% of smokers) in the European population (33). Thus, future studies might need to take this challenge into consideration. Researchers might also want to explore other markers of SHA exposure to allow the identification of more possible constituents present in the SHA that potentially affect the health of bystanders.

Ultimately, SHA exposure assessment is a promising and growing research area in public health. This thesis, thus, calls for more quality evidence aiming at improving the knowledge in SHA exposure. This goal, furthermore, leads to a demand for investing more resources, like time and money, in this research area.

# CONCLUSIONS

# CONCLUSIONS

The conclusions below are presented in response to each of the hypotheses mentioned earlier in this PhD thesis.

1. The adoption status of e-cigarette use legislation at the national level differed by country's EU membership status, with EU MS having a significantly higher proportion of countries adopting e-cigarette use legislation at the national level compared to their non-EU counterparts within the WHO European Region.

2. The country's smoking prevalence and income level were associated with the number of places regulated by country's e-cigarette use legislation. However, country's tobacco control performance and EU membership status were not linked to the number of places regulated by country's e-cigarette use legislation.

3. There were smaller proportions of school entrances and children's playgrounds with e-cigarette use presence than outdoor hospitality venues with e-cigarette use in 11 European countries.

4. The prevalence of SHA exposure in European countries was higher among e-cigarette non-users with higher level of education, but not differed by country's socioeconomic status. Also, country's e-cigarette use prevalence was positively associated with the prevalence of SHA exposure.

5. The $PM_{2.5}$ concentrations increased about two-fold during short-term e-cigarette use in a controlled room and car compared to those before e-cigarette use in the settings. However, airborne nicotine concentrations in a controlled room and car remained very low during and after the short-term e-cigarette use.

6. The concentrations of biomarkers of SHA exposure (i.e., nicotine, cotinine, 3'-OH-cotinine, nornicotine, TSNAs, PG, and glycerol) measured in bystanders remained very low after short-term e-cigarette use in a controlled room and car.

7. The concentration of $PM_{2.5}$ in e-cigarette users' homes was not significantly different from non-users' homes, whilst the concentration of airborne nicotine in e-cigarette users' homes was significantly higher than that was found in non-users' homes.

8. Some biomarkers of SHA exposure, such as nicotine, cotinine, 3’-OH-cotinine, 1,2-PG in saliva, and cobalt in the urine sample of e-cigarette non-users living with the users, were found to be at levels higher than those living in homes with non-users.

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# ANNEXES

# ANNEXES

## Annex 1: RASHA-E Questionnaires

The files are available online and accessible via this link: http://bit.ly/annex1sha

## Annex 2: TackSHS Work Package 2 (WP2) Data Collection Forms

The files are available online and accessible via this link: http://bit.ly/annex2sha

## Annex 3: TackSHS Work Package 3 (WP3) Questionnaire

The file is available online and accessible via this link: http://bit.ly/annex3sha

## Annex 4: TackSHS Work Package 8 (WP8) Experimental Study Questionnaires and Data Collection Forms

The files are available online and accessible via this link: http://bit.ly/annex4sha

## Annex 5: TackSHS Work Package 8 (WP8) Observational Study Questionnaire, Diary Cards, and Data Collection Forms

The files are available online and accessible via this link: http://bit.ly/annex5sha

# Annex 6: Ethics Approval for Thesis Project and Included Studies

The files are available online and accessible via this link: http://bit.ly/annex6sha

# Annex 7: Curriculum Vitae and Publications of the PhD candidate

## 7.1 Curriculum Vitae

Beladenta Amalia was born in Tangerang, Indonesia in 1991. She obtained her medical doctor title in 2014 from Universitas Indonesia. She continued her education in Master of Public Health in Imperial College London and graduated in 2017 with a thesis entitled "The Impact of Indonesia's Tobacco Control Policy on Trends of Cigarette Smoking Among Indonesian Adults, 2007 – 2014". She started pursuing her PhD in Universitat de Barcelona in 2018 with INPhINIT fellowship by the "La Caixa" Foundation.

From 2015 to 2016, she worked as a general practitioner in a public primary healthcare centre and a public hospital in a rural area in Indonesia. In 2016-2017, she co-founded and managed a private healthcare centre in an urban area in Indonesia that provided a comprehensive community health service. During her PhD, she spent her research stays in the Laboratory of Lifestyle Epidemiology, Istituto Di Ricerche Farmacologiche "Mario Negri", Milan, Italy in 2019 under the supervision of Dr. Silvano Gallus, and in International Union Against Tuberculosis and Lung Disease (The Union), South-East Asia Regional Office, New Delhi, India in 2019-2020 under the supervision of Dr. Rana Jugdeep Singh. She also did a remote internship to provide technical and administrative assistance in the STOP project that exposes tobacco industry interference at Global Center for Good Governance in Tobacco Control (GGTC) in 2019 under the supervision of Debby Sy.

She is often involved in tobacco control advocacy activities and wrote articles in Indonesian media outlets on tobacco control issues, such as *The Conversation Indonesia*, *Jakarta Globe*, and *The Jakarta Post*.

## 7.2 List of publications

### *7.2.1 Publications in scientific journals*

**Amalia B,** Fu M, Tigova O, Ballbè M, Castellano Y, Semple S, Clancy L, Vardavas C, López MJ, Cortés N, Pérez-Ortuño R, Pascual JA, Fernández E, the TackSHS Project Investigators. Environmental and individual exposure to secondhand aerosol of electronic cigarettes in confined spaces: Results from the TackSHS Project. *Indoor Air*. 2021; ina.12841. doi: 10.1111/ina.12841

Feliu A, Filippidis FT, Joossens L, **Amalia B**, Tigova O, Martínez C, Fernández E. The association between tobacco control policy implementation and country-level socioeconomic factors in 31 European countries. *Sci Rep*. 2021;11(1):8912 . doi: 10.1038/s41598-021-88194-8

**Amalia B**, Liu X, Lugo A, Fu M, Odone A, van den Brandt P, Semple S, Clancy L, Soriano JB, Fernández E, Gallus S, the TackSHS Prpject Investigators. Exposure to secondhand aerosol of electronic cigarettes in indoor settings in 12 European countries: data from the TackSHS survey. *Tob Control*. 2021;30(1):49-56. doi:10.1136/tobaccocontrol-2019-055376

**Amalia B**, Fu M, Feliu A, Tigova O, Fayokun R, Mauer-Stender K, Fernández E. Regulation of electronic cigarette use in public and private areas in 48 countries within the WHO European Region: a survey to in-country informants. *J Epidemiol*. Published online 2020:JE20200332. doi:10.2188/jea.JE20200332

**Amalia B**, Rodríguez A, Henderson E, Fu M, Continente X, Tigova O, Semple S, Clancy L, Gallus S, Fernández E, López MJ, the TackSHS Project Investigators. How widespread is electronic cigarette use in outdoor settings? A field check from the TackSHS project in 11 European countries. *Environ Res*. 2021;193:110571. doi:10.1016/j.envres.2020.110571

**Amalia B**, Kapoor S, Sharma R, Fu M, Fernández E, Singh RJ. Online sales compliance with the electronic cigarettes ban in India: a content analysis. *Int J Public Health*. 2020;65(8):1497-1505. doi:10.1007/s00038-020-01480-6

**Amalia B**, Kapoor S, Sharma R, Singh RJ. E-cigarette retailer storefront availability following a nationwide prohibition of e-cigarettes in India: A multicentric compliance assessment. *Tob Prev Cessat*. 2020;6(July). doi:10.18332/tpc/123822

Tigova O, **Amalia B**, Castellano Y, Fu M, Nogueira SO, Kyriakos CN, Mons U, Trofor AC, Zatoński WA, Przewoźniak K, Demjén T, Tountas Y, Quah ACK, Fong GT, Fernández E, Vardavas C, the EUREST-PLUS consortium. Secondhand exposure to e-cigarette aerosols among smokers: A cross-sectional study in six European countries of the EUREST-PLUS ITC Europe Surveys. *Tob Induc Dis.* 2019;16(2). doi:10.18332/tid/99117

### *7.2.2 Publications in media outlets*

"Passive vaping: an impending threat to bystanders" – April 2021, published in The Conversation Indonesia.

"Young Smokers in Indonesia at Greater Risk of Contracting Serious Cases of Covid-19" – April 2020, published in The Jakarta Globe.

"Still at war with the tobacco epidemic, Indonesia must control e-cigarettes too" – October 2019, published in The Conversation Indonesia.

"Konsumsi rokok remaja tinggi, menagih janji pengendalian tembakau Jokowi" (*Language: Bahasa Indonesia*) – May 2018, published in The Conversation Indonesia.

"Vaping: Threat or Opportunity?" – December 2017, published in The Jakarta Post daily.

"Tobacco Epidemic a Threat to Indonesia's Bid to Achieve SDGs" – May 2017, published in The Jakarta Post.

## 7.3 Presentations in scientific events

Poster presenter in the IDIBELL's PhD Day 2020. Title: "Are bystanders passively exposed to e-cigarette aerosol in enclosed settings?". Barcelona, Virtual (12-13 November 2020).

Poster presenter in the 51st Union World Conference on Lung Health. Title: "Compliance assessment of electronic cigarettes online sales following a nation-wide ban of electronic cigarettes in India". Barcelona, Virtual (20-24 October 2020).

Poster presenter in the 8th European Conference on Tobacco or Health (ECToH). Title: "Passive exposure to aerosol of electronic cigarettes in indoor settings in 12 European countries". Berlin, Germany (19-22 February 2020).

Oral presenter in the 50th Union World Conference on Lung Health. Title: "Regulatory Approaches to Protect Bystanders from Passive Exposure to

Aerosol of E-cigarettes in European Countries". Hyderabad, India (30 October-2 November 2019).

Poster presenter in Society for Research on Nicotine and Tobacco (SRNT) Europe the 19th Annual Conference – SRNTE. Title: "Are bystanders protected by regulation of e-cigarette use in countries within WHO European Region?". Oslo, Norway (12-14 September 2019).

Oral presenter in The 4th ENSP-SRP International Conference on Tobacco Control 2019. Title: "Regulation for e-cigarette use in public and private areas within European countries". Bucharest, Romania (27-29 March 2019).

Oral presenter in the 12th Asia-Pacific Conference on Tobacco or Health – KOMNASPT. Title: "The Impact of Indonesia's Tobacco Control Policy on Socioeconomic Inequalities in Cigarette Smoking Among Indonesian Adults, 2007-2014". Bali, Indonesia (13-15 September 2018).

Poster presenter in ENSP-CNPT International Conference on Tobacco Control – ENSP and CNPT. Title: "The Impact of Indonesia's Tobacco Control Policy on Cigarette Smoking Among Indonesian Adults: A Longitudinal Study". Madrid, Spain (14-16 June 2018).

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