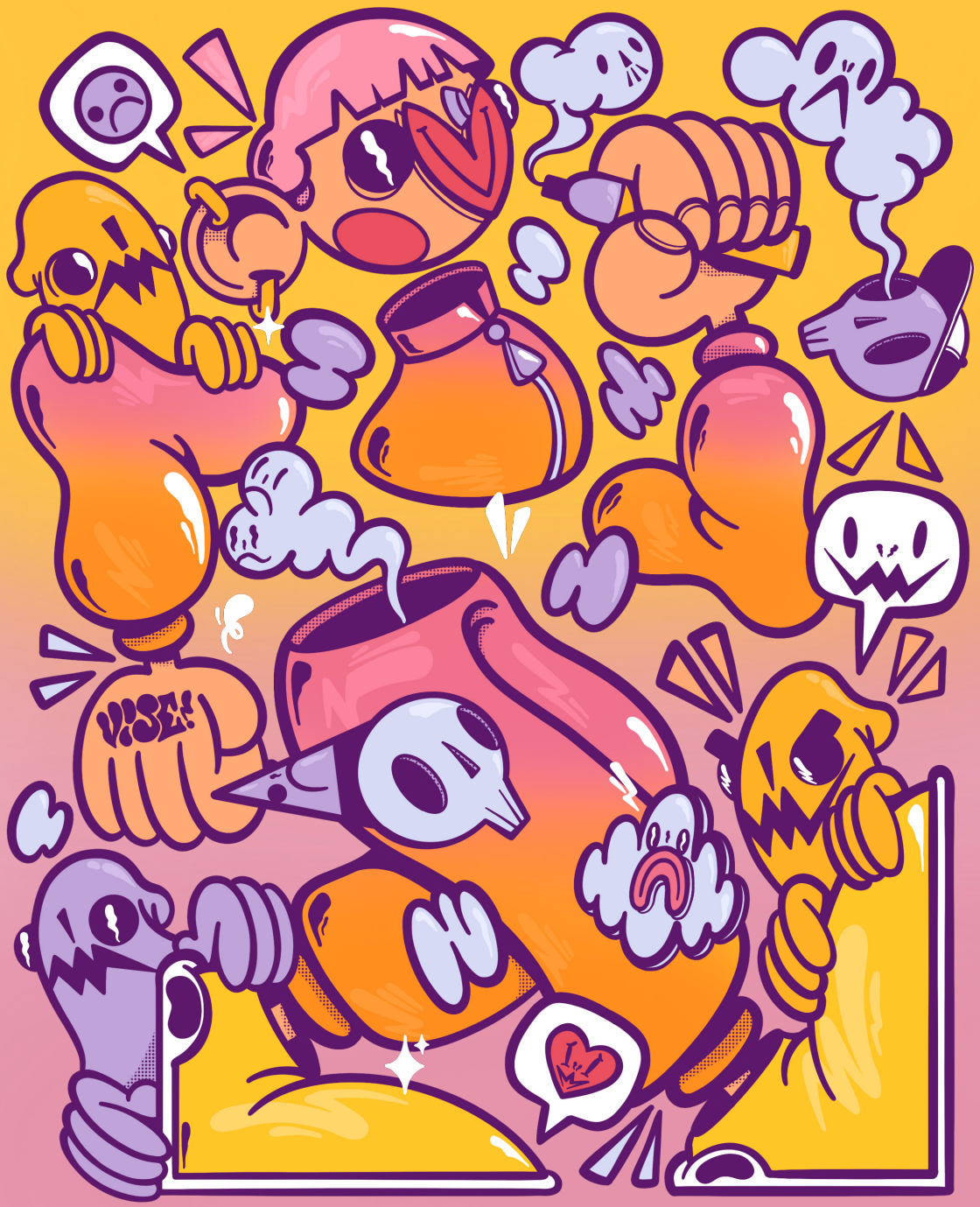
The role of e-cigarettes and heated tobacco products

in tobacco control and health in Italy

Marco Scala



Propositions accompanying the thesis

The role of e-cigarettes and heated tobacco products in tobacco control and health in Italy

1. The majority of e-cigarette and heated tobacco product users are also current cigarette smokers, indicating predominant dual use (this thesis).
2. Despite legal restrictions on sales to minors, the prevalence of novel tobacco and nicotine product use is higher among underage adolescents than among adults in Italy (this thesis).
3. The potential benefits of novel tobacco and nicotine products are outweighed by their risks at a population level (this thesis).
4. The harm reduction narrative is promoted by the tobacco and nicotine industry, but is not supported by independently funded evidence (this thesis).
5. In real-world settings, novel tobacco and nicotine products sustain and induce nicotine addiction rather than promoting cessation.
6. Conflicts of interest in research can systematically bias scientific evidence.
7. Stricter transparency and funding regulations are needed to prevent the tobacco industry from interfering in scientific debates and to promote evidence-based public health policies.
8. The ultimate goal of tobacco control should not be a tobacco endgame, but a nicotine endgame.
9. The framing of nicotine products as “technology” rather than “tobacco” represents a strategic shift in industry marketing.
10. The normalisation of e-cigarette and heated tobacco product use contributes to the renormalisation of smoking behaviours in society.
11. We cannot solve our problems with the same thinking we used when we created them (attributed to Albert Einstein).

Marco Scala

Maastricht, 1st October 2026

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THE ROLE OF E-CIGARETTES AND HEATED TOBACCO PRODUCTS IN TOBACCO CONTROL AND HEALTH IN ITALY

DISSERTATION

to obtain the degree of Doctor at the Maastricht University,

on the authority of the Rector Magnificus, Prof. Dr. Jan Smits, in accordance with the decision of the Board of Deans,

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Chapter 1

Introduction

1.1 Tobacco smoking

1.1.1 Tobacco

Tobacco is a plant belonging to the genus Nicotiana, primarily Nicotiana tabacum, which is cultivated for its leaves that contain nicotine, a psychoactive and addictive alkaloid [1]. Tobacco is consumed in various forms, broadly categorised into smoked and smokeless products. The most prevalent smoked tobacco products are cigarettes. Other smoked tobacco products include cigars, bidis, pipe tobacco, and waterpipes (hookah or shisha). Smokeless forms encompass chewing tobacco, snuff, Swedish snus, and dipping tobacco [1, 2].
Recent archaeological discoveries have provided evidence for the use of tobacco dating back over 12,000 years, with origins among indigenous peoples of the Americas who utilised it in spiritual rituals and traditional medicine [3]. Following the arrival of Europeans in the late 15th century, tobacco was imported into Europe as a trade item for smoking purposes. It was during the 19th century, in the period of the mass production of cigarettes, that tobacco became increasingly popular on a global scale [4].
At present, tobacco continues to be a significant agricultural commodity. Globally, approximately 6 million metric tons of tobacco are produced per annum, with China leading as the top producer, followed by India and Brazil. Italy is the major European producer, with an annual output of over 40,000 tonnes of tobacco [5].

1.1.2 Health effects of tobacco smoking

The causal relationship between cigarette smoking and disease was first established in the early 1950s, when Ernst Wynder and Evarts Graham, and independently Richard Doll and Bradford Hill, provided the first robust epidemiological evidence linking tobacco use to lung cancer [6, 7]. Over the following decades, this association has been confirmed by thousands of epidemiological studies, which have also demonstrated that smoking is a determinant of a wide range of other chronic and fatal conditions [8, 9]. These harmful effects are due to the inhalation of the thousands of chemical compounds contained in tobacco or generated through its combustion, many of which are toxic, mutagenic or carcinogenic [10].
Today, we know that cigarette smoking is responsible for the majority of lung cancer cases worldwide, accounting for approximately 85% of diagnoses, which is a disease with a very poor prognosis (5-year survival of less than 10%) [8]. Furthermore, the carcinogenic effect of smoking extends to other organs besides the lungs. According to the International Agency for Research on Cancer (IARC), smoking contributes to the onset of at least 15 different types of cancer, primarily affecting the respiratory and digestive systems. Heavy smokers face a cancer risk that is 2-10 times higher at these sites [8, 11]. Recent evidence has further expanded the list of cancer sites causally associated with smoking [12-14].

Beyond its role in cancer, smoking is also the most significant risk factor for chronic obstructive pulmonary disease (COPD), a progressive condition characterized by persistent airflow limitation, frequent exacerbations, and long-term disability. COPD places a significant burden on society in terms of hospitalisations, treatment costs, and reduced quality of life [9]. Cardiovascular disease is another major consequence of smoking. Ischemic heart disease and stroke are both significantly more prevalent among smokers than among non-smokers, and tobacco use is considered a leading modifiable determinant of cardiovascular mortality [9, 13]. Other systemic effects include complications in pregnancy, metabolic disorders, and increased vulnerability to infections [15, 16]. The principal health consequence of tobacco smoking is premature death. Classic prospective studies, such as the 50-year follow-up of British doctors, have shown that smokers live, on average, about 10 years less than non-smokers, and have substantially lower probabilities of surviving to advanced ages [17]. According to the World Health Organization (WHO), smoking causes more than 7 million deaths each year, including around 1.6 million deaths among non-smokers exposed to second-hand smoke (SHS) [18]. In addition, tobacco use accounts for around 200 million disability-adjusted life years (DALYs) worldwide, making smoking the single greatest preventable cause of death in the world [19]. In Italy, it is estimated that smoking is responsible for 70,000-90,000 deaths per year, accounting for at least 12.5% of total mortality [20, 21].

1.1.3 Second-hand smoke

Exposure to SHS, also known as environmental tobacco smoke, has been classified by IARC as a Group 1 carcinogen, meaning that there is sufficient evidence of carcinogenicity in humans [11]. Exposure to SHS is associated with a range of adverse health effects, particularly cardiovascular and respiratory diseases. Non-smokers exposed to SHS have a substantially increased risk of ischemic heart disease, stroke, chronic respiratory conditions, and lung cancer [11, 22]. In addition to the millions of deaths caused directly by active smoking, SHS is responsible for more than 1.2 million deaths among non-smokers worldwide every year [23]. Exposure occurs across settings of daily life, including homes and workplaces, but also in hospitality venues, parks, and beaches where smoking restrictions are frequently not strictly enforced or are completely absent [24-27].

1.1.4 Smoking cessation

The benefits of smoking cessation are well established. Stopping smoking reduces the risk of cancer, cardiovascular disease, and respiratory illness, and improves overall life expectancy. Evidence from the long-term follow-up of the British doctors' cohort demonstrated that smokers who quit before the age of 40 avoid almost all of the excess mortality associated with continued smoking. Those

who stopped before 50 years of age eliminated most of the risk, and even quitting before 60 halved the excess mortality compared with persistent smokers [17]. Smoking cessation remains the single most effective intervention to improve health among smokers, conferring substantial benefits regardless of age or smoking history [28]. From a public health perspective, widespread smoking cessation translates these individual-level benefits into substantial reductions in population-level morbidity, mortality, and healthcare burden [29, 30].

1.1.5 The epidemiology of smoking

According to the most recent Global Burden of Disease (GBD) estimates (2023), there are about 1.10 billion individuals aged 15 years and older who are current smokers globally [31]. The age-standardised prevalence among this population has been decreasing: compared to 1990, the prevalence among males fell by about 30%, and among females by about 43%. Despite this decline in prevalence, the absolute number of smokers has grown by approximately 120 million since 1990, largely because of global population growth. Focusing on the WHO European Region, tobacco use remains substantial. In 2024, the WHO reported that the adult prevalence (age 15+) in the European Region is about 25.3%, with 30.8% among men and 17.4% among women [32, 33].
In Italy, recent national surveys show that in 2024 about 26.6% of the population aged 15 years and over are current smokers (31.1% among men, 22.3% among women) [34]. After years of decline, smoking prevalence has stopped decreasing in Italy. Among adolescents, Italian data are also concerning. According to a 2023-2024 national survey of students aged 14-17 years, about 20% reported using conventional cigarettes in the past 30 days [35].

1.2 Tobacco control

1.2.1 History of global tobacco control

Tobacco control is a public health field devoted to regulating tobacco use to reduce tobacco-related morbidity and mortality. The aim of tobacco control is therefore to identify and promote interventions that can reduce smoking prevalence. [36, 37].
During the first half of the 20th century, cigarette smoking became a global phenomenon, fuelled by mass production, military distribution during wars and the tobacco industry’s aggressive marketing strategies. Throughout the 1950s, scientific evidence on the health consequences of tobacco use accumulated, culminating in the 1964 U.S. Surgeon General’s Report which formally established smoking as a cause of lung cancer and other diseases [38]. Similar reports were issued in the United Kingdom and other countries, prompting the

introduction of the first governmental restrictions, such as health warnings on cigarette packets and limits on advertising.

During the same period, tobacco companies publicly questioned the emerging scientific evidence on smoking-related harms. Internal documents later made public demonstrated that companies had deliberately suppressed or manipulated scientific findings, funded front groups to create uncertainty, and launched public campaigns to reassure consumers [39]. A 1969 internal memo from Brown & Williamson (i.e., a U.S. subsidiary of the British multinational company British American Tobacco) stated, “Doubt is our product,” reflecting a strategy to perpetuate controversy and delay policy measures. Tobacco companies also promoted filtered and “light” cigarettes as healthier options despite evidence to the contrary [40, 41].

Legal challenges against the tobacco industry gained momentum in the 1990s. In the United States, this culminated in the Master Settlement Agreement (MSA) of 1998 between major tobacco manufacturers and 46 states. The MSA mandated payments exceeding USD 200 billion, prohibited certain marketing strategies and required the disclosure of more than 14 million internal documents, thereby exposing decades of deception [42]. Similar litigation processes occurred in Canada, Australia and several European countries, raising public and political awareness of misconduct by the tobacco industry.

A major milestone in international public health was the adoption of the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) in 2003 which came into force in 2005 [43]. As the first global health treaty, the WHO FCTC provides a comprehensive legal framework for tobacco control. This includes measures on pricing and taxation (Article 6), smoke-free environments (Article 8), packaging and labelling (Article 11), advertising bans (Article 13) and support for quitting (Article 14). Notably, Article 5.3 requires signatory countries to avoid any influence from the tobacco industry on debates about the implementation of tobacco control policies [43].

To facilitate implementation, the WHO introduced the MPOWER package in 2008, which summarises six key interventions: Monitor tobacco use; Protect from tobacco smoke; Offer help to quit; Warn about dangers; Enforce bans on advertising; Raise taxes on tobacco [37]. Since then, adoption of at least one of these measures at the highest level has expanded to cover more than 5.6 billion people worldwide [18]. Policies such as smoke-free legislations, pictorial health warnings, increased taxation, and advertising bans have significantly reduced smoking prevalence and consumption in many countries.

Further progress has been achieved through innovative measures. Large pictorial health warnings have become mandatory in over 120 countries. In 2012, Australia became the first country to implement plain packaging, removing logos and branding from cigarette packs. This was later adopted by several other countries [44]. Recognised as the most effective measure to reduce smoking, particularly

among young people, tobacco taxation has been widely implemented, though often insufficiently in low- and middle-income countries [45].
As a result of these coordinated global efforts, age-standardised smoking prevalence has declined steadily for decades in most high-income countries, alongside a substantial decline in the social acceptability of tobacco use [20, 46]. The protagonists of this success were: i) the scientific community, which effectively divulged the harmful effects of smoking and SHS on human health, ii) the growing tobacco control movement, which recommended the implementation of effective tobacco control strategies, and iii) the firm viewpoint of the WHO.

1.2.2 Tobacco control in Italy

Within the European Union (EU), tobacco control has been progressively shaped by transnational legislation. The most relevant initiatives include the Tobacco Products Directive (2014/40/EU), which regulates the sale and marketing of tobacco products with the aim of improving the functioning of the internal market, and the Tobacco Taxation Directive (2011/64/EU), which sets out the structure and rates of excise duty applied to manufactured tobacco products [47-49]. These measures provide the regulatory framework within which national policies operate. There are significant differences between EU Member States in the adoption of the main tobacco control strategies at a government level.
In Italy, tobacco control policy is largely associated with Law 3/2003, commonly known as the Sirchia Law. This legislation introduced a comprehensive ban on smoking in indoor public places and workplaces. This represented a significant advancement in safeguarding the population from SHS, establishing Italy as a pioneer in this area within Europe [50]. However, after this initial progress, policy development has stagnated. According to the Tobacco Control Scale (TCS), Italy has progressively lost ground compared to other Western European countries, particularly with regard to taxation, funding for cessation services and public health campaigns, and the implementation of plain packaging [51].
A key barrier to further progress is the persistent influence of the tobacco industry. Despite being a Party to the WHO FCTC, Italy's implementation of Article 5.3, which requires the protection of public policies from industry interference, remains weak. According to the Global Tobacco Industry Interference Index, Italy is one of the countries in Europe with the highest levels of industry interference, with a score of 76/100 in 2025 indicating extensive lobbying and corporate social responsibility initiatives by the industry [52].
Consequently, although Italy initially made progress with smoke-free legislation, there is still room for improvement, particularly with regard to fiscal policies (a pack of cigarettes in Italy costs €6, compared to €10 or more in France and the UK), cessation support, public health communication and safeguarding policymaking from industry influence.

1.2.3 Towards a “Tobacco Endgame”

The Tobacco Endgame strategy represents a shift from mitigating smoking-related harms to actively eliminating the commercial sale and use of tobacco products. Rather than accepting smoking as an enduring societal norm, this approach aims to reduce prevalence to minimal levels (often <5%) [53, 54]. The idea gained global recognition after 2010, and several countries have since adopted explicit endgame goals. New Zealand approved legislation to reduce nicotine content and retail outlets, and proposed to ban tobacco sales to those born after 2009 [55]. Finland targets a tobacco-free society by 2030 [56], and other countries have set similar targets [57]. Although, in practice, the barriers against the adoption of a tobacco endgame strategy were impressive [58-62], for the first time, it was licit to imagine a world without tobacco.
In parallel, initial enthusiasm grew towards the “harm reduction” strategy of promoting electronic cigarettes (e-cigarettes) as tools for achieving a smoke-free society. Government agencies such as Public Health England considered the possibility of fully replacing conventional cigarettes with e-cigarettes as part of the Tobacco Endgame strategy [63]. However, subsequent evidence has complicated this expectation.

1.3 Electronic cigarettes

1.3.1 The advent of electronic cigarettes

At the beginning of the 21st century, the electronic nicotine delivery system (ENDS) known as e-cigarette was first introduced to the Chinese market in 2005 by the Beijing-based company Ruyan [64-68]. E-cigarettes are battery-powered devices designed to heat a liquid - typically composed of propylene glycol, glycerine, and often nicotine and flavouring agents - into an aerosol that users inhale. The process does not involve tobacco combustion, but rather the vaporization of the e-liquid, producing an inhalable aerosol [66, 69]. Because of their design, mode of inhalation, and sensory characteristics - including throat hit, taste, and nicotine delivery - e-cigarettes can replicate many of the sensations associated with conventional cigarette smoking [67].
A wide variety of e-cigarette products are currently available on the market, differing in their design, nicotine concentration, flavour formulations, and levels of harmful constituents emitted. E-cigarettes are commonly categorized by “generation,” based on their technological development. Table 1 summarizes the main developmental stages of e-cigarettes, describing the defining features of each generation of ENDS [70-72].

Table 1: Description of different types of e-cigarettes.

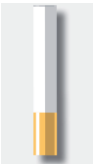
Example	Generation / Product	Description of the device
	1st generation: cig-a-like; disposable e-cigarettes; closed system	A type of e-cigarette designed to be used one time, only. Not rechargeable or refillable. Discarded when it runs out of charge or e-liquid. Designed to mimic the look and feel of combustible cigarettes.
	2nd generation: vape-pen; e-cigarettes with prefilled or refillable cartridge	Rechargeable e-cigarette product designed to be used multiple times. E-liquid comes in prefilled or refillable cartridges. Substances usually include nicotine. The cartridge is attached to a battery pen—which contains the battery.
	3rd generation: Box-mod; vape tanks; open systems; refillable e-cigarettes	Rechargeable e-cigarette product designed to be used multiple times. The size is much larger than a conventional cigarette with a higher-capacity battery. Modifiable devices (“mods”), allowing users to customize the substances in the device. The e-liquid is refillable.
	4th generation: Pod mods; vape pod with nicotine salts (as JUUL)	E-cigarette product with a prefilled or refillable ‘‘pod’’ or pod cartridge with a modifiable (mod) system (“Pod-Mods”). Pod Mods come in many shapes, sizes, and colours. Instead of e-liquids it typically includes nicotine salts (i.e., readily available nicotine, which makes it highly addictive) that should be pre-heated before inhalation.
	5th generation: Disposable pod devices	Disposable e-cigarette devices. Pre-filled with e-liquid and equipped with a charged battery. Allow 400 to 1200 puffs. Affordable, colourful and flavoured.

Image source: Centers for Disease Control and Prevention (CDC), E-cigarette, or vaping, products visual dictionary. 2019. Available at: https://stacks.cdc.gov/view/cdc/103783

The most recent generation of e-cigarettes, disposable JUUL-type pods, are typically brightly coloured and affordable, features that enhance their visual appeal and make them particularly attractive to youths [72]. They are often pre-filled with a variety of sweet or fruity flavours. Independent research has highlighted the public health challenges they pose, particularly with regard to

initiation and sustained use among adolescents and young adults [72, 73]. In addition to public health concerns, disposable e-cigarettes raise significant environmental issues. These products generate significant waste due to their single-use plastic casings and integrated lithium-ion batteries, which contain metals such as lithium, cobalt and nickel and require specialised disposal [73, 74]. The growing awareness of their environmental impact and strong appeal to young people has led several countries to consider, or to implement, regulatory restrictions or outright bans on the sale of disposable e-cigarettes [75-77].
Besides the device itself, the e-liquids used in e-cigarettes are highly heterogeneous, containing a variety of ingredients including flavouring agents. It has been estimated that there were up to 20,000 unique e-liquid flavours in the market [78].

1.3.2 Composition and safety

The composition and safety profile of e-cigarettes remain the subject of extensive scrutiny. Public Health England, a government agency within the UK's Department of Health and Social Care, and e-cigarette advocates promote replacing conventional cigarettes with e-cigarettes among all smokers, suggesting a potential reduction in harm [79, 80]. This stance is heavily based on the assumption that “e-cigarettes are 95% less harmful than combustible cigarettes”. However, this “95%” claim originates from a study with little supporting evidence, which was backed by the industry to promote the “harm reduction” strategy using scientific evidence sold as independent [81].
On the other hand, the WHO has warned against the use of e-cigarettes, even as a smoking cessation tool. They state that e-cigarettes are “undoubtedly harmful” and evidence shows that they produce toxic substances and increase the risk of cardiovascular and respiratory disorders [82]. The aerosol from e-liquids typically contains nicotine plus propylene glycol, glycerine, flavourings, and other chemicals, which carry known or potential health risks [18, 83]. Consequently, there is growing evidence that e-cigarette use has harmful short- to intermediate-term health effects. In particular, e-cigarettes have been shown to increase the risk of cardiovascular diseases, affecting heart rate and blood pressure [84]. Daily e-cigarette use has also been associated with increased risk of myocardial infarction [85]. E-cigarette use might also be associated with asthma and COPD [86, 87]. A recent systematic review concluded that e-cigarette use does not substantially reduce the risk of diseases caused by cigarettes [88]. With regard to long-term carcinogenic effects, a recent qualitative risk assessment concluded that e-cigarettes are likely to cause cancer in humans, particularly lung and oral cancers [89].
A notable health event that highlighted safety concerns was the outbreak of E-cigarette or Vaping-Associated Lung Injury (EVALI) in the United States in 2019–2020. The outbreak was linked to vaping products containing vitamin E acetate

and other harmful additives. EVALI resulted in over 2,700 hospitalisations and 60 deaths in the US [90].
The phenomenon of dual use (i.e., the combined use of both e-cigarettes and conventional cigarettes) further complicates this issue. Rather than replacing cigarettes, many users adopt e-cigarettes alongside smoking [91, 92]. This pattern of use has been shown to pose an even greater risk than conventional smoking alone. A recent systematic review concluded that dual use poses greater cardiovascular and respiratory risks than smoking alone [88]. Furthermore, a recent case-control study found that combining e-cigarette use with smoking accelerates the risk of developing lung cancer, with dual users having a fourfold increased risk compared with conventional cigarette smokers [93].

1.4 Heated tobacco products

1.4.1 Launch of heated tobacco products

By the early 2000s, smoking prevalence and sales in high-income countries were declining steadily, reflecting the cumulative impact of comprehensive tobacco control interventions. As described earlier, the introduction of smoke-free legislation, tax increases, advertising bans and cessation support, together with the increasing global adoption of the WHO FCTC, contributed to a significant decrease in cigarette sales in many regions [43, 61, 94]. Meanwhile, the emergence of e-cigarettes introduced a new non-combustible nicotine delivery model to the market, providing a new way to consume nicotine.
In this rapidly evolving landscape, the tobacco industry was confronted with the prospect of substantial long-term revenue losses. Independent analyses suggest that major tobacco companies view the combination of regulatory pressure and changing consumer behaviour as a threat to the stability of the cigarette market [95, 96]. In response, the industry has moved to reposition itself within the growing electronic device sector, developing products that maintain nicotine dependence and preserve customer loyalty while allowing continued profits.
Heated tobacco products (HTP) emerged as a central element of this strategy. While they share technological similarities with e-cigarettes, such as the use of an electronic heating system to generate an inhalable aerosol, they differ fundamentally in that they contain processed tobacco rather than a nicotine solution [82, 97]. These characteristics enabled manufacturers to capitalise on the appeal of a novel “smoke-free” device while retaining the commercial advantages of selling a tobacco product. Furthermore, by presenting HTPs as reduced-risk alternatives, companies attempted to establish themselves as stakeholders in “harm reduction” debates.
Philip Morris International (PMI) was the first major company to commercialise a modern HTP device. IQOS, its device, was launched in December 2014, with

Milan (Italy) and Nagoya (Japan) selected as pilot cities for the European and Asian markets, respectively. IQOS has since expanded rapidly and is now available in most high-income countries. Other multinational tobacco companies soon followed suit with competing devices, including glo from British American Tobacco (BAT) and Ploom from Japan Tobacco International [97-99].

1.4.2 Composition and safety

These HTPs consist of two components: the electronic device (e.g, IQOS, glo), that heats the tobacco sticks designed specifically for each system (e.g, HEETS for IQOS, Neo for glo). The device uses controlled heating elements to reach temperatures typically ranging from 250 °C to 350 °C. While this is lower than the temperatures achieved during cigarette combustion, it is still sufficient to generate an inhalable aerosol containing nicotine and numerous chemicals. [100]. The tobacco sticks contain reconstituted tobacco, humectants (e.g., glycerol), flavour additives, and a polymer-based filter. Independent analyses have identified several toxic constituents in the sticks themselves and in the emissions produced when they are used, including nicotine, volatile organic compounds, carbonyls (such as formaldehyde and acrolein), polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines (TSNAs) and metals [101].
The technology of HTPs has evolved rapidly. Recent generations of devices, such as IQOS ILUMA, use an induction-heating system where the metallic blade is integrated into the tobacco sticks themselves (e.g., TEREA and DELIA). Some concerning cases have been reported in Italy and Japan of babies accidentally ingesting these sticks and the metal blade [102, 103].
Selected toxicants and carcinogens known to be released by conventional cigarettes are emitted by HTPs at substantially lower concentrations (around 10%). Nevertheless, they also generate substances that are not present, or are present at lower levels, in conventional cigarette smoke [101, 104]. Furthermore, the existing evidence does not permit definitive comparisons to be made regarding the long-term health risks associated with HTPs and conventional cigarettes, including their effect on cancer incidence and mortality.
In 2020, the U.S. Food and Drug Administration (FDA) authorised IQOS to be marketed as a Modified Risk Tobacco Product, but only with 'reduced exposure' claims, not 'reduced risk' claims. The FDA explicitly stated that there was insufficient evidence to conclude that IQOS reduces the risk of tobacco-related diseases. While this distinction has been widely criticised by independent tobacco-control experts for its potential to generate public misunderstanding, PMI has celebrated it as a 'milestone for public health', using the claim as part of its marketing strategy [105, 106].
In Italy, PMI formally requested that the Italian authorities evaluate the relative harmfulness of their novel tobacco product in 2019. The Italian Ministry of Health and the National Health Institute (ISS) concluded that it was not possible to

acknowledge a reduction in the toxic substances emitted by HTPs and claim a proportional reduction in health risk under the same conditions of use [107].

1.5 Other emerging nicotine products

1.5.1 Nicotine pouches

In recent years, a new category of nicotine-containing products has emerged alongside e-cigarettes and HTPs: nicotine pouches. Similar to Swedish snus in terms of how they are used, nicotine pouches contain a white nicotine powder rather than tobacco, enclosed in small, pre-portioned sachets. The pouch is placed between the upper lip and gum to allow nicotine to be absorbed through the oral mucosa [108, 109].

Unlike snus, which is banned in most EU member states except Sweden, the regulation of nicotine pouches is far less restrictive. Consequently, they are being distributed across many high-income countries, often outpacing the development of coherent regulatory frameworks. Major tobacco manufacturers have invested in nicotine pouches, creating their own brands such as Lyft by British American Tobacco, Velo by RJ Reynolds Vapor Company, Zyn by Swedish Match, Dryft by Kretek International, and Nordic Spirits by Japan Tobacco International [109]. These products are typically sold in colourful, minimalist cans and are available in a wide variety of flavours, which contribute to their polished, lifestyle-oriented image [109, 110].

The rapid and unregulated uptake of these products has raised several public health concerns. Their discreet mode of use allows them to be consumed in settings where smoking or vaping would be prohibited, and their appealing, flavourful presentation makes them attractive to adolescents. Consequently, some countries, such as France and Belgium, have banned the sale of nicotine pouches [111].

1.5.2 Nicotine sticks

Another category of emerging nicotine products is nicotine sticks, which are designed to be used with the same electronic devices as HTPs. Unlike traditional HTP sticks, which contain processed tobacco, nicotine sticks are tobacco-free and instead use alternative materials infused with nicotine and flavouring agents. They closely resemble tobacco-containing sticks in terms of appearance and mode of use, but their composition enables manufacturers to circumvent existing tobacco regulations.

Indeed, nicotine sticks were introduced in response to the European Union's Commission Delegated Directive (EU) 2022/2100, which extended the ban on characterising flavours in tobacco products to include HTPs [112]. This directive

was prompted by a substantial body of evidence indicating that flavours significantly increase the appeal of nicotine products among young people, reducing their perception of risk and increasing susceptibility to experimentation and sustained use [113, 114]. In response to the EU flavour ban, the tobacco industry quickly changed its product offering. While removing flavoured tobacco sticks from countries that implemented the EU directive, companies introduced tobacco-free nicotine sticks in a variety of flavours. Examples include LEVIA sticks for IQOS ILUMA and VEO sticks for glo. Such products may be pre-flavoured or contain breakable flavour capsules that release additional aromas when crushed, mirroring earlier strategies used in the design of menthol cigarettes.

As nicotine sticks are a recently marketed product, there is currently very little scientific evidence regarding their chemical composition, toxicological profile and health risks. Their aerosol emissions, patterns of use and long-term safety have not yet been characterised by independent researchers. However, given their extensive range of flavours and the industry's marketing of these products as 'tobacco-free', they may increase their appeal to young people, potentially leading to nicotine dependence in populations that have not previously used tobacco products.

1.6 Epidemiology and public health impact of novel tobacco and nicotine products

1.6.1 Epidemiology of novel tobacco and nicotine products

In Europe, the use of e-cigarettes expanded rapidly after their introduction around 2010 [115]. After this initial growth, the proportion of regular adult e-cigarette users remained relatively stable, rising only marginally from 1.5% in 2014 to 1.8% in 2017, with substantial heterogeneity across countries [116]. According to the 2024 Eurobarometer survey, more than one in ten Europeans had ever tried an e-cigarette: 8% reported having experimented once or twice, 3% were former users, and 3% were current users [117].

Evidence on HTPs is more limited but growing. Early investigations, primarily from Japan [99, 118, 119] and the United States [120], documented rapid market uptake and raised concerns regarding the potential public health implications of these products. In Europe, analyses from national representative surveys in Italy and the UK reported notable interest in HTPs among non-smokers [98] and adolescents [121], alongside a low but increasing prevalence of use [98]. Sales-based data similarly confirmed a marked upward trend in Italy up to 2018 [97]. In the 2024 Eurobarometer, nearly 1 in 10 Europeans had tried HTPs, with 2% being current users.

Overall, e-cigarettes remain slightly more commonly used than HTPs across Europe. However, while e-cigarette uptake appears to have plateaued in several countries [116], the popularity of HTPs continues to rise steadily [97], suggesting a shifting landscape in nicotine consumption patterns.
Regarding nicotine pouches, the 2024 Eurobarometer reported that 4% of Europeans had tried these products at least once, although use varied considerably between countries [117]. Current use remains relatively low among European adults.

1.6.2 The Italian context

E-cigarettes have been available in Italy since 2010. Their regular use increased from 0.4% in 2014–2015 to 1.8% in 2016–2017 [67, 68]. The 2024 Eurobarometer reported a prevalence of 3% current e-cigarette use among Italian adults, indicating a sustained presence in the market. Regarding HTPs, current use was reported at 4%, making it one of the highest prevalence rates in the region [117].

1.6.3 Smoking cessation and “gateway” effect

The public health impact of novel tobacco and nicotine products (NTNPs) can be broadly framed around two opposing factors: their potential contribution to smoking cessation, and their potential to attract non-smokers — particularly young people — thereby increasing nicotine dependence and potentially leading to cigarette smoking. These contrasting dynamics lie at the heart of the current scientific and policy debate.
Manufacturers have emphasised the first dimension, presenting NTNPs as “harm reduction” tools and suggesting that smokers who switch from conventional cigarettes may lower their risk of smoking-related diseases. For such claims to have meaningful population-level benefits, however, several conditions would need to be met. Firstly, the efficacy of these products for smoking cessation would need to be clearly and clinically demonstrated, ideally outperforming existing evidence-based methods. Secondly, there would need to be robust, independent toxicological and epidemiological evidence that these products pose substantially lower health risks than conventional cigarettes. Thirdly, individuals initiating the use of these products should avoid long-term dual use, given the associated exacerbated health risks. Finally, individuals switching from smoking should eventually discontinue use of all nicotine products, rather than remaining chronically dependent on alternative sources of nicotine.
Conversely, there are growing concerns about the uptake of NTNPs among people who have never smoked before. The industry's marketing strategies, characterised by appealing flavours, sleek designs and youth-oriented branding, have not consistently targeted adult smokers with a history of unsuccessful quit attempts. Instead, they have reached a wider, much younger demographic.

Increased nicotine exposure among young people poses significant public health risks due to the adolescent brain's neurobiological vulnerability to nicotine addiction and its long-term behavioural consequences.
Of particular concern is the possibility of a “gateway effect”, whereby non-smoking adolescents who start using NTNPs subsequently start smoking conventional cigarettes. This pattern is concerning because it could undermine decades of progress in reducing smoking prevalence and impede the broader pursuit of a tobacco endgame.

1.7 The interference of the tobacco industry on the scientific literature

1.7.1 Historical role of the tobacco industry in manipulating scientific research

For several decades, the tobacco industry actively opposed the emerging scientific consensus on the health harms of cigarette smoking [39]. Tobacco companies adopted coordinated strategies aimed at delaying regulatory action and preserving market stability. These strategies included the selective dissemination of favourable findings, the suppression of unfavourable results, and the creation of apparent scientific controversy through industry-funded research and front organisations. Internal documents later disclosed through litigation clearly demonstrated that the generation of doubt was not incidental but constituted a deliberate corporate objective. Legal actions in the late twentieth century, played a pivotal role in exposing these practices and documenting the systematic nature of scientific manipulation by tobacco companies [42].
A substantial body of independent scientific research has demonstrated that tobacco industry–funded studies on cigarette smoking were unreliable and systematically aligned with commercial interests [122-126]. Affiliation with the tobacco industry was strongly associated with study conclusions, with tobacco-sponsored research being far more likely to minimise or deny the harmful effects of smoking [123]. Rather than contributing to knowledge, tobacco companies used scientific publications strategically to influence public opinion, litigation outcomes, and regulatory debates [122]. It has been established that the tobacco industry's involvement in research on smoking has consistently produced biased evidence that serves to protect cigarette sales rather than public health.

1.7.2 Tobacco industry influence in research on NTNPs

In light of the tobacco industry's well-documented historical manipulation of scientific research to defend conventional cigarettes, it is reasonable to question whether similar dynamics are occurring today with regard to NTNPs. This is a particularly relevant concern given the renewed emphasis placed by manufacturers on “harm reduction” narratives, which were previously promoted

with “light” cigarettes and snus and are now centred on e-cigarettes, HTPs and nicotine pouches.

Over the past decade, several independent studies and systematic reviews have explicitly examined the association between tobacco industry involvement and the conclusions of research on NTNPs. Collectively, this body of evidence indicates that studies funded or influenced by the tobacco industry are significantly more likely to report favourable conclusions regarding the safety or reduced harm of e-cigarettes and HTPs compared with independent research [127-130]. Importantly, these patterns mirror those observed in cigarette smoking in the twentieth century, suggesting a continuity of industry strategies rather than a rupture.

Following decades of scandals and mounting evidence of misconduct, the tobacco industry has lost a great deal of credibility within the scientific community. In response, a more recent strategy has involved indirectly funding research through organisations that present themselves as independent, such as the Foundation for a Smoke-Free World (FSFW), which was created with funding from PMI [130]. The FSFW has, in turn, established and funded additional research entities, such as the Centre of Excellence for the Acceleration of Harm Reduction (CoEHAR). This research centre is focused on the promotion of NTNPs, thereby further complicating the tracing of tobacco industry funding and obscuring the boundaries between independent research and industry influence. [131].

The shift towards intermediary funding mechanisms complicates the identification of independence in NTNP research. Networks of indirect, opaque or inadequately disclosed financial relationships can obscure industry influence, allowing commercial interests to shape scientific narratives under the guise of neutrality. Rigorous scrutiny of funding sources and conflicts of interest is therefore essential in order to accurately interpret the current evidence base on NTNPs, and to safeguard the integrity of public health research.

1.8 Aims of this dissertation

1.8.1 Rationale

The rapid emergence and spread of NTNPs has sparked heated debate about their potential impact on human health and on tobacco control. This debate is inherently complex, as it encompasses multiple interrelated issues, including: i) the issue of product safety; ii) the relative safety of NTNPs compared with conventional cigarettes; iii) the marked heterogeneity of the NTNP market, with devices differing widely, and evolving continuously at a pace that outstrips scientific research; iv) NTNPs being adopted in contexts where smoking is prohibited, thus supplementing rather than replacing cigarette consumption; v)

the possible gateway effect among adolescents and young adults, whereby initial experimentation with NTNPs may lead to subsequent uptake of cigarette smoking; vi) relapse among former smokers, and more broadly, vii) their contribution to the persistence and normalization of nicotine addiction at a population level.
An additional layer of complexity arises from the tobacco and nicotine industry's active involvement in promoting an “harm reduction” narrative.
For all these reasons, there is an urgent need for independent research that can evaluate NTNPs rigorously from both a human health and a population-level perspective. This research must consider not only the direct health effects of these products, but also their wider impact on tobacco control. It is equally important to systematically monitor tobacco and nicotine industry involvement in the scientific literature to ensure that public health policies are informed by robust, conflict-free evidence.

1.8.2 Objectives

The present dissertation aims to provide new, fully independent epidemiological evidence on the prevalence and determinants of NTNP use in Italy. Specific attention is given to describing patterns of use among different population groups, evaluating the impact of these products on human health and determining the extent to which the tobacco industry is involved in the current scientific literature on NTNPs.
The specific objectives of the dissertation are as follows:

1) Patterns of use of heated tobacco products (Chapter 2)
2) Prevalence and patterns of electronic cigarette and heated tobacco product use among Italian adults in 2024 (Chapter 3)
3) Tobacco and nicotine product use among students aged 11-17 years (Chapter 4)
4) Adverse events associated with dual and poly use of conventional cigarettes, electronic cigarettes, and heated tobacco (Chapter 5)
5) The role of novel nicotine-containing products on SARS-CoV-2 infection and COVID-19 progression (Chapter 6)
6) Attitudes towards tobacco control policies in Italy (Chapter 7)
7) Conflict of interest in research on novel tobacco and nicotine products (Chapter 8)

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Chapter 2

Patterns of Use of Heated Tobacco Products: a Comprehensive Systematic Review

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2.1 Abstract

Introduction: Relative or absolute safety of heated tobacco products (HTPs) remains unknown, while independent literature suggests that these products do not favor tobacco control. We conducted a comprehensive systematic review and meta-analysis to evaluate HTP usage patterns and the effect of HTP use on conventional tobacco smoking (use transitions).

Methods: We used Pubmed/MEDLINE, Embase, and the Cochrane Library to identify all articles published up to February 2022 on HTP use. For the present review, we included all representative cross-sectional studies dealing with HTP use, and all prospective cohort studies or cross-sectional studies on conventional tobacco smoking transitions due to HTP use. From 610 non-duplicate articles, 76 were eligible (71 cross-sectional and 5 prospective cohort studies).

Results: Compared with young adults, HTP use was less frequent among middle-aged (15 studies; pooled odds ratio [OR] 0.59; 95% confidence interval [CI], 0.48–0.74) and older adults (12 studies; OR 0.17; 95% CI, 0.07–0.38). HTP use was more frequent among former (6 studies; OR 2.73; 95% CI, 1.03–7.25) and current smokers (12 studies; OR 14.53; 95% CI, 6.34–33.31). Overall, 68.3% of HTP users were dual users (n=26). Eight studies (including 5 cohorts) showed that HTP users were more likely than non-users to start conventional cigarette smoking (2 studies; OR 6.31; 95% CI, 4.13–9.65), whereas current cigarette smokers using HTPs were less likely to quit (4 studies; OR 0.84; 95% CI, 0.80–0.89).

Conclusion: We found that HTPs are specifically popular among young generations. More than two out of three HTP users are dual users. Prospective studies consistently show that, in real life, HTPs are not effective smoking-cessation tools.

2.2 Introduction

Heated tobacco products (HTPs) are tobacco sticks heated by an electric device to produce an aerosol containing nicotine.[1-3] Philip Morris International (PMI) was the first transnational tobacco company to launch its HTP device, IQOS, in Italy and Japan in 2014.[4] This device is currently available for sale in a large majority of high-income countries worldwide.[5] Other best-selling HTP devices include Glo (by British American Tobacco [BAT]) and Ploom TECH (by Japan Tobacco International [JTI]), with both products being sold since 2016.

Although HTPs are promoted by the tobacco industry as a safer product compared to conventional tobacco, evaluation of their relative or absolute health effects is complex and thus far has been inconclusive. In fact, besides emitting lower concentrations of the same harmful substances produced by conventional cigarettes, HTPs release several other toxicological and potentially carcinogenic compounds that are not even emitted by conventional cigarettes.[6] Moreover, no prospective data on the association between HTP use and disease incidence and mortality are available so far. Therefore, the only evidence-based conclusion regarding HTP safety is that these products are not safe for health.

Whereas e-cigarettes showed a certain success as smoking-cessation aids in clinical settings,[7] no data on the effectiveness of HTPs are available from clinical trials.[8] More importantly, in real life, HTPs can pose major public health problems, since these products, as well as e-cigarettes,[9] appear to thwart — not favor — tobacco control.[10] Despite these facts, in many countries HTPs enjoy large fiscal and regulatory benefits compared to conventional cigarettes,[11] which substantially contributed to the spread of these products. A recent and comprehensive meta-analysis investigated the global prevalence of HTP use.[12] From 45 studies conducted in 42 different countries, the authors identified growing estimates for lifetime (4.87%; 95% confidence interval [CI], 4.16–5.63%) and current use (1.53%; 95% CI, 1.22–1.87%), and non-negligible estimates also for daily HTP use (0.79%; 95% CI, 0.48–1.18%).

To our knowledge, there is no systematic review and meta-analysis in the literature examining patterns of HTP use. To fill this gap, we conducted a comprehensive systematic review of the literature in order to investigate patterns of HTP use and the effect of the use of these products on conventional tobacco smoking (use transitions).

2.3 Methods

Systematic review

A systematic search of the scientific literature was conducted to retrieve all the available publications on HTPs (PROSPERO registration number:

CRD42020137394). The search was performed on February 23, 2022 in Pubmed/MEDLINE, Embase and the Cochrane Library (the search strings are reported in eTable 1) and lead to the identification of 610 non-duplicate publications on HTPs. The objective of the present systematic review was to evaluate HTP use patterns and the effect of HTP use on conventional tobacco smoking. For this aim we considered as eligible articles: 1) primary publications providing data on use of HTP from representative cross-sectional studies, plus 2) primary publications evaluating the effect of HTP use on conventional tobacco smoking from cross-sectional studies and prospective studies. Two independent reviewers screened the 610 publications through a two-stage procedure (first title and abstract, second full-text) to identify all eligible articles. We excluded 336 non-eligible studies (eg, chemical/toxicological studies, in vivo or in vitro studies, or study protocols), 157 non-pertinent papers (eg, original studies or reviews focused on tobacco products other than HTPs), 11 papers showing prevalence estimates of HTP use in samples not representative of the general populations or of specific subgroups (eg, smokers or teenagers), 7 duplicate studies (ie, same data reported in more than one article), and 19 original articles focusing exclusively on perceptions and attitudes. After the inclusion of one additional article from six reviews on the issue and a further relevant article on the topic from other sources, we obtained 76 eligible publications (eFigure 1). The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting guidelines (eTable 2).

For each eligible study, we extracted the following relevant information using a standardized form in Microsoft Excel (Microsoft Corp, Redmond, WA, USA): first author, year of publication, country and year of conduction of the fieldwork, sample size, target population (ie, general population or specific subgroup), and results of the study including the prevalence of use (overall and stratified by socio-demographic characteristics), the proportion of dual users among current HTP users, and various risk measures (including odds ratios [ORs], relative risk ratios [RRRs], relative risks [RRs], or prevalence ratios [PRs], adjusted or crude with their corresponding 95% CIs).

Meta-analyses

We conducted meta-analyses to provide pooled quantifications of specific aspects regarding the use of HTPs. In particular, we investigated the relationship between individual-level characteristics (ie, sex, age group, socio-economic status [SES], and use of conventional cigarette) and current use of HTPs. Moreover, the pooled estimate of the prevalence of dual users was analyzed. We used meta-analytic approaches only when considering articles on the general population, thus excluding studies limited to specific subgroups of the population, such as smokers or teenagers. Finally, we also projected pooled estimates of ORs of conventional cigarette smoking transitions as a consequence of HTP use.

Socio-demographic characteristics and smoking status

We included in this meta-analysis cross-sectional studies providing measures of association for the relationship between selected socio-demographic and smoking variables and the use of HTPs in the general population (ORs or their proxies) and corresponding 95% CIs, or raw data to compute the estimates and their confidence intervals. Adult study populations in various publications were re-classified into three categories: young adults (if the mean age of the group as reported in the original article was less than 40 years), middle-aged adults (mean age between 40 and 60 years), and older adults (mean age over 60 years). When necessary, we computed OR estimates to pool the ORs from various age categories using the Hamling method.[13] We also applied the same methodology to pool categories of SES or conventional cigarette smoking, or to change reference categories.

Dual use

For the purpose of this meta-analysis, we included cross-sectional studies providing prevalence estimates of dual use among HTP users and corresponding 95% CIs, or raw data to compute their estimates and 95% CIs. Dual users were defined as subjects reporting being current smokers of conventional cigarettes and current HTP users. When the information on current HTP use was not reported, we defined dual users as subjects reporting to be current conventional cigarette smokers and ever HTP users. We included one publication considering any type of tobacco product users, not limited to conventional cigarette smokers only.[14]

Use transitions

We considered cross-sectional or prospective cohort studies providing risk estimates (OR, RR, or PR) for various outcomes related to conventional cigarettes smoking transitions (eg, smoking cessation, initiation, relapse, product switching) according to individual's HTP use, and/or prevalence estimates of the proportion of HTP users that changed their habits of tobacco use. We provided pooled estimates of risk measures for starting smoking among never smokers, relapsing among former smokers, and quitting among current smokers, according to HTP use. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies and the adapted version of the NOS for cross-sectional studies.[15, 16] NOS score for cohort studies ranges from 0 (poor quality) to 9 (good quality) and considers information on three broad categories: selection (maximum 4 points), comparability (maximum 2 points), and exposure (maximum 3 points). NOS score for cross-sectional studies ranges from 0 (poor quality) to 7 (good quality) and considers information on selection (3 points), comparability (2

points), and outcome (2 points). In this meta-analysis, high-quality studies were defined as those with NOS scores ≥7 for cohort studies and NOS score scores ≥6 for cross-sectional studies. No low-quality study was excluded from the meta-analysis.

Statistical analysis

We reported the prevalence of ever and current HTP use for adults and teenagers. If estimates from the same populations were reported in various articles, we considered only OR or prevalence estimate from the most recent paper or, if the year of publication was the same, from the article with the most complete data. We used random-effects meta-analytics models to obtain pooled results (OR and prevalence estimates). We used the I2 statistic to check for heterogeneity among studies.[17] We performed stratified analysis by continent to check for geographic differences. For use transitions, we reported the main results provided by the original articles and summarized the evidence using a meta-analytic approach. We performed all statistical analyses using the software SAS (version 9.4; SAS Institute, Cary, NC, USAS) and R (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria).

2.4 Results

Systematic review

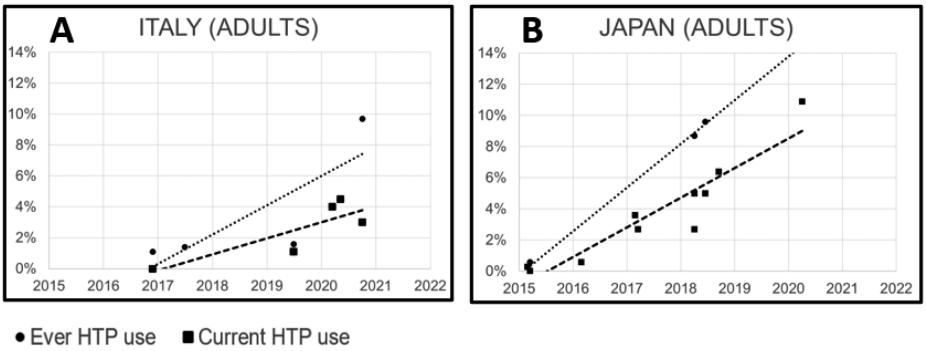
The 76 eligible original publications on HTP use, including 71 cross-sectional studies and 5 cohort studies, were conducted between 2016 and 2022 in Asia (41 studies), Europe (22 studies), North America (15 studies), Oceania (3 studies), or Central America (2 studies). Characteristics of all these studies are reported in eTable 3.

We found 59 prevalence estimates of ever HTP users (ie, individuals who tried HTPs at least once in their lifetime) and 67 prevalence estimates of current HTP users (ie, individuals who used HTPs at least once during the last 30 days) in the adult population (eTable 4). Corresponding numbers for studies based on teenagers were 14 and 18, respectively (eTable 5).

Among the 32 studies on adults, estimates of ever HTP use ranged from 0.1% in Japan (2015) to 23.9% in South Korea (2018) and estimates of current HTP use from 0.0% in Japan (2015) to 10.9% in Japan (2020). The only countries having three or more prevalence estimates in different years of current HTP use among adults were Japan (n=10), Italy (n=5), the United States (n=3) and the United Kingdom (n=5). The prevalence of HTP use increased substantially in the Japanese (annual percent change [APC] 2.1% between 2015 and 2020) and Italian general adult population (APC 1.0% between 2016 and 2020; Figure 1). In

other countries, as in the USA (APC -0.1%) and the United Kingdom (APC 0.0%) no evident change in the use of HTPs was detected over time (between 2016 and 2020, data not shown in figures). For several other countries, the prevalence estimates of HTP use were scarce and inconsistent, thus not allowing us to define a country-specific trend of HTP use through the years, particularly for young people. Among the 17 studies on teenagers, estimates of ever HTP use ranged from 0.7% in the United States (2019–2020) to 11.3% in Guatemala (2019) and estimates of current HTP use from 0.2% in the United States (2019–2020) to 2.9% in Guatemala (2019).

Figure 1. Trend of prevalence (%) of ever and current heated tobacco product use in the adult population in Italy (A) and Japan (B) from 2015 to 2021.



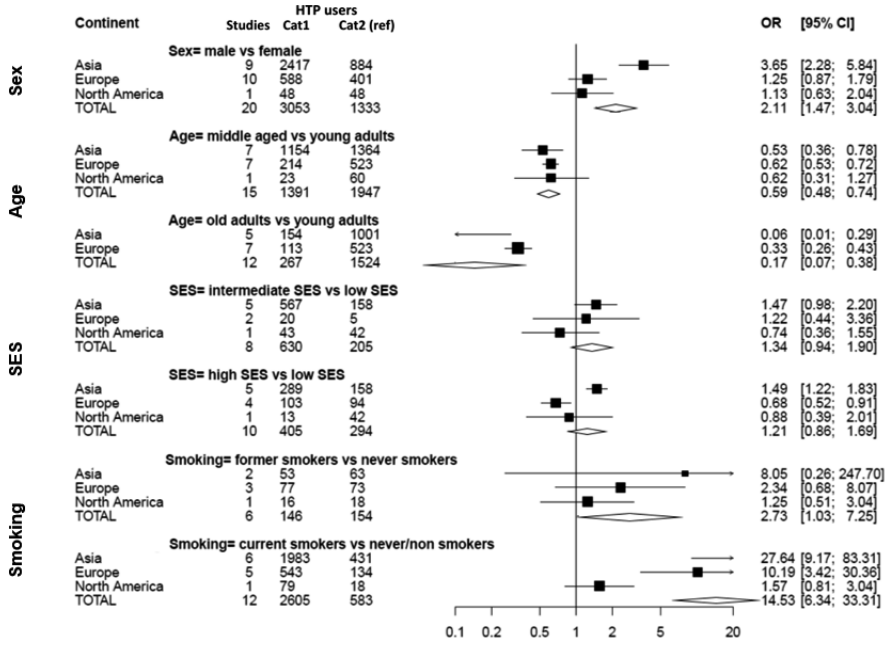
HTP: heated tobacco product.

Meta-analyses

Socio-demographic characteristics and smoking status

Twenty-two studies were included in the meta-analysis on the relationship between demographic and socio-economic factors and HTP use (Figure 2 and eFigures 2, eFigure 3, eFigure 4, eFigure 5, eFigure 6, eFigure 7 and eFigure 8). We found that current HTP use was significantly related to being male (20 studies; OR for male vs. female 2.11; 95% CI, 1.47–3.04), a young adult (15 studies; OR for middle-aged vs. young adults 0.59; 95% CI, 0.48–0.74 and 11 studies; OR for older vs. young adults 0.17; 95% CI, 0.07–0.38), and a former or current conventional cigarette smoker (6 studies; OR for former vs. never smokers 2.73; 95% CI, 1.03–7.25 and 12 studies; OR for current vs. never/non-smokers 14.53; 95% CI, 6.34–33.31). Globally, HTP use was not significantly associated with SES.

Figure 2. Forest plot of pooled odds ratios for current heated tobacco product use among adults according to different socio-demographic exposures (sex, age, socio-economic status, and smoking status), overall and stratified by continent

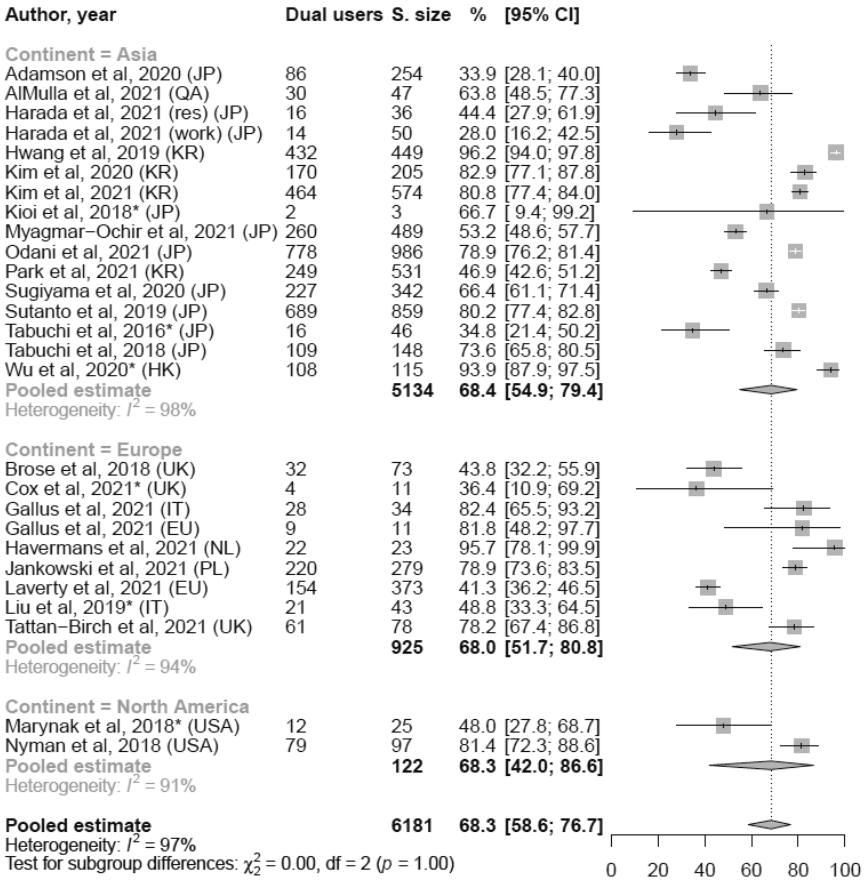


CI, confidence interval; HTP, heated tobacco product; OR, odds ratio; SES, socio-economic status.

Dual use

Twenty-six studies were included in the meta-analysis on the prevalence of dual users among HTP users. We found that globally 68.3% of HTP users were dual users (95% CI, 58.6–76.7%, Figure 3), with prevalence estimates among all included studies ranging between 28.0% (95% CI, 16.2–42.5%) and 96.2% (95% CI, 94.0–97.8%). The prevalence was consistent through continents, with a 68.4% prevalence of dual users in Asia (95% CI, 54.9–79.4%; 16 estimates from 15 studies), 68.3% in North America (95% CI, 42.0–86.62%; studies), and 68.0% in Europe (95% CI, 51.7–80.89%; studies).

Figure 3. Forest plot of study-specific and pooled prevalence (%) of dual use of heated tobacco products (HTP) and conventional cigarettes among adult HTP users, overall and stratified by continent



*in the study dual users were defined as current conventional cigarette smokers and ever HTP users; CI, confidence interval; EU, Europe (different countries); HK, Hong Kong; IT, Italy; JP, Japan; KR, South Korea; NL, Netherlands; PL, Poland; QA, Qatar; res, resident; UK, United Kingdom; USA, United States of America; work, work population.

Use transitions

We found eight articles showing data on conventional cigarettes smoking transitions according to HTP use (Table 1). Two prospective studies and one cross-sectional study consistently showed that among never smokers, HTP users were more prone to start conventional cigarette smoking than non-users. The pooled OR among never smokers was 6.31 (95% CI, 4.13–9.65; 2 studies; eFigure 9). Among former cigarette smokers, three prospective studies and one cross-sectional reported estimates on the association between current HTP use

and relapsing in smoking conventional cigarettes. The pooled OR of relapsing among former smokers for current HTP users vs non/never-users was 2.15 (95% CI, 0.89–5.21; 3 studies; eFigure 10). A potential favorable effect of HTPs as a smoking cessation tool was refuted in all the seven studies conducted on conventional tobacco smokers (four cohort studies and three cross-sectional). The pooled OR of quitting smoking among current smokers for current HTP users vs non/never-users was 0.84 (95% CI, 0.80–0.89; 4 studies; eFigure 11). Quality assessment of included cohort and cross-sectional studies is shown in eTable 6 and eTable 7, respectively. None of the cohort studies (0/5) or the cross-sectional studies (0/21) achieved a high-quality score on the Newcastle-Ottawa scale.

Table 1. Main results from eight original publications providing data on heated tobacco products (HTP) and conventional cigarettes use transitions included in the systematic review.

First author, year (reference)	Country	Year of data collection	Sample size	Population	Type of study	Type of endpoint	Endpoint	Main results
Gallus et al, 2022 [10]	Italy	2020 (~7 months of follow-up)	3,185	Adults	Prospective cohort study	Initiation	Among never smokers, RR of starting smoking conventional cigarettes for current vs never HTP users	RR of starting smoking= 5.80 (95% CI, 3.65–9.20)
						Relapse	Among former smokers, RR of relapsing for current vs never HTP users;	RR of relapsing= 3.32 (95% CI, 2.05–5.37)
						Cessation	Among current smokers, RR of continuing smoking for current vs never HTP users	RR of continuing smoking= 1.17 (95% CI, 1.10–1.23)
Kanai et al, 2021 [29]	Japan	2018 (~ 10 months of follow up)	158	Tobacco users at a manufacturing company	Prospective cohort study	Cessation	Among current smokers, RR of quitting smoking for current HTP users vs HTP non-users	RR of quitting smoking= 0.77 (95% CI, 0.61–0.97)
Luk et al, 2021 [30]	Hong Kong	2018 (~ 6 months of follow up)	1,213	Daily smokers	Prospective cohort study	Cessation	Among current smokers, PR of smoking abstinence at 3 months for current HTP users vs HTP non-users	PR of smoking abstinence at 3 months= 0.81 (95% CI, 0.43–1.52)
						Cessation	Among current smokers, PR of smoking abstinence at 6 months for current HTP users vs HTP non-users	PR of smoking abstinence at 6 months= 1.08 (95% CI, 0.63–1.85)
Matsuyama et al,	Japan	2019 (~ 12 month	5947	Former or never combusti	Prospective cohort study	Relapse	Among former smokers who recently quit, OR of	OR of relapsing= 0.59 (95% CI, 0.28–1.26)

2022 [31]		s of follow up)		ble cigarette smokers			relapsing for current HTP users vs HTP non-users	
						Relapse	Among former smokers who quit for one year or more, OR of relapsing for current HTP users vs HTP non-users	OR of relapsing= 2.80 (95% CI, 1.42–5.52)
						Initiation	Among never smokers, OR of starting smoking conventional cigarettes for current HTP users vs HTP non-users	OR of starting smoking= 9.95 (95% CI, 3.39–29.2)
Xia et al, 2022 [32]	Hong Kong	2016-2019 (~ 6 months of follow up)	579	Young Chinese smokers who want to quit	Prospective cohort study	Cessation	Among current smokers, RR of smoking abstinence at 1 week for current HTP users vs HTP non-users	RR of smoking abstinence at 1 week= 1.01 (95% CI, 0.79–1.28)
						Cessation	Among current smokers, RR of smoking abstinence at 1 month for current HTP users vs HTP non-users	RR of smoking abstinence at 1 month= 0.84 (95% CI, 0.66–1.07)
						Cessation	Among current smokers, RR of smoking abstinence at 3 months for current HTP users vs HTP non-users	RR of smoking abstinence at 3 months= 0.50 (95% CI, 0.29–0.86)
						Cessation	Among current smokers, RR of smoking abstinence at 6 months for current HTP users vs HTP non-users	RR of smoking abstinence at 6 months= 0.47 (95% CI, 0.24–0.91)
						Relapse	Among former smokers, RR of relapsing during the follow-up for current HTP users vs HTP non-users	RR of relapsing= 4.56 (95%-CI; 1.17–17.8)
Adamson et al, 2020 [33]	Japan	2018	4,154	Population aged 20+ living in Sendai, Tokyo and Osaka	Representative cross-sectional study	Cessation	Proportion of HTP dual users according to the change in the status of smoking conventional cigarettes or HTPs	79.2% of dual users in the previous 12 months are current conventional cigarette smokers; 4.1% are former tobacco users
Gallus et al, 2021 [34]	Italy	2019	3,120	Population aged 15+	Representative cross-sectional study	Initiation/ relapse, cessation	Proportion of HTP ever users according to the change in the status of smoking conventional cigarettes	19.1% of ever HTP users started or re-started smoking conventional cigarette; 14.6% quit smoking; 66.3% did not change their smoking habit

Koyama et al, 2021 [35]	Japan	2020	5,120	Tobacco users	Non-Representative cross-sectional study	Cessation	Among ever conventional cigarette smokers, PR of quitting smoking any type of tobacco for smokers who switched from conventional cigarettes to HTPs vs smokers who did not switch	PR of quitting smoking any type of tobacco= 0.15 (95% CI, 0.04–0.58)

CI, confidence interval; HTP, heated tobacco product; OR, odds ratio; PR, prevalence ratio; RR, relative risk.

2.5 Discussion

Our comprehensive systematic review and meta-analysis shows that HTP use among adults has increased substantially in Japan and Italy between 2016 and 2020, while in other European or American countries current use has not significantly changed. HTP users are more likely to be men, young adults, and current or former smokers. Moreover, two thirds of HTP users are dual users consuming both HTPs and conventional cigarettes. Current HTP use among the teenager population is also not negligible. Evidence from eight studies (including five prospective cohort studies) dealing with use transitions does not support these products as effective smoking cessation tools. In contrast, HTP users are more likely to start conventional cigarette smoking and less likely to quit conventional cigarettes.

In agreement with a previous systematic review on the issue, we observed a growing trend in HTP use in some countries, but not all.[12] We observed impressive increase trends in Japan and Italy between 2016 and 2020. Notably, these countries have an extremely high level of tobacco industry interference index [18] and were those chosen as pilot countries to launch the first HTPs for the Asian and Western markets, respectively.

Overall, we found that HTPs were more frequently used by men than women. However, this pattern was mainly present in studies from Asian countries. No difference in HTP use between men and women was observed in some countries in a more advanced stage of the tobacco epidemic,[19] including the United States and several European countries. This finding is in agreement with a systematic review on HTP use, showing that the prevalence of current use in men (5.8%; 95% CI, 3.6–8.5%) was higher than in women (1.6%; 95% CI, 1.0–2.4%) in the Western Pacific Region, but not in the European Region or the Americas Region [12]. This gender gap in HTP use mirrors the well-known gap for conventional tobacco products, although more pronounced for conventional cigarettes, particularly in Western Pacific countries, where only one in 18 tobacco users is female [20].

The most frequent consumers of HTPs are young adults. Our results are consistent with another systematic review in which the percentage of ever users was higher in the younger population (5.3%; 95% CI, 4.4–6.2% for adolescents and 2.5%; 95% CI, 0.8–5.0% for adults).[12] The prevalence of current use of these products among teenagers is not negligible in many countries, including Guatemala (2.9% in 2019), South Korea (2.6% in 2019), Taiwan (2.3% in 2018), and Italy (2.0% in 2018). Indeed, both the packaging and the technological components make these devices particularly attractive for teenagers [21, 22], and the wide variety of flavors is appealing to young non-smokers, similar to electronic cigarettes, as the World Health Organization warns.[23] Moreover, young people are the target population of the advertisements of these products, and kids and adolescents come into contact with uncontrolled HTPs advertisement on social media platforms [24, 25].

Socio-economic status does not emerge as a relevant influencing factor for HTP use in the global analysis, but we observed some differences between continents. We hypothesized that the high initial cost of these devices might discourage potential consumers with lower economic means. Indeed, some studies from the literature suggest that higher socio-economic classes were associated with the highest percentage of current HTP use [26-28]. From our meta-analysis, we show that this is valid in Asia but not in Europe, where people with higher SES are less likely to use HTPs than people with lower SES.

If HTPs were an effective smoking cessation tool, we would expect the large majority of HTP users to be ex-smokers who successfully quitted due to a complete switch from conventional cigarette to HTP. On the contrary, current smokers are by far the slice of population most frequently using HTPs. Accordingly, we found that two out of three HTP users are dual users. This is of great concern because among current smokers, HTPs likely represent a compensative measure for smoking in settings where conventional cigarettes are banned, thus increasing the occasions for daily nicotine intake. These products are less frequently used by ex-smokers. Since our evidence comes from cross-sectional studies, it is difficult to infer if HTP users among former smokers had profited or not from their HTP use to quit smoking. However, a study conducted in 11 European countries showed that half of the former smokers using HTPs had quit smoking before HTPs were launched in their local markets.[26] This indicates that a large proportion of former smokers using HTPs are not smokers who switched to HTPs to reduce their harm, but people who had already quit smoking and started using a tobacco product again with the entrance in commerce of HTPs. In order to assess how the prevalence of dual use changes in relation to the increase in the use of HTPs, future studies should evaluate the temporal trends of dual use in specific countries with a high prevalence of HTP use.

Eight studies [10, 29-35] (three cross-sectional and five cohort studies) provided data on cigarette smoking transitions according to HTP use, thus showing the

change in the use of conventional cigarette over time based on individual-level use of HTPs. Despite the high heterogeneity in the study measures (risk measures or prevalence estimates) and the study populations (smokers or non-smokers) among the few studies available on the issue, we were able to provide pooled estimates quantifying the effect of HTP use on conventional cigarette smoking. All the publications consistently showed that dual users of HTPs and conventional cigarettes were less prone to quit conventional tobacco than exclusive smokers. Furthermore, HTP users were more inclined to start conventional cigarette consumption than HTP non-users, and three prospective studies showed that among former smokers, HTP users were more likely to relapse, with the possible exception of recent quitters, for whom no statistically significant association was found. Specific data on changes in conventional cigarette smoking intensity among HTP users were not systematically reported in the included studies, and none of the prospective cohort studies focused on this issue. This factor should be analyzed in future studies on HTPs. The available evidence therefore confirms that HTPs represent a gateway to smoking initiation and rejects the hypothesis of HTPs as effective tools to quit conventional cigarette smoking.

To our knowledge, this is the most comprehensive systematic review and meta-analysis on the patterns and transitions of HTP use globally. Our search strategy might have some limitations, but we minimized them by building a broad search string, including various terms referring to HTPs and performing the search on various scientific databases. We considered only scientific articles published in peer-reviewed journals, excluding information available in the grey literature and in other official reports.

Some other limitations are inherent to the characteristics of the original studies included in our systematic review and meta-analysis. First, most of the studies are cross-sectional studies, so we could not infer the causal associations between specific factors on HTP use. Furthermore, the definition of HTP use was inconsistent among studies, likely contributing, together with the differences between study populations and socio-demographic characteristics influencing HTP use, to the high heterogeneity observed in each meta-analysis. The quality of the cross-sectional studies included in the meta-analysis on the association between HTP use and socio-demographic characteristics, and of the cohort studies included in the meta-analysis on use transitions was assessed using the NOS quality scale (and the adapted version for cross-sectional studies), which is the most widely recognized tool for assessing the quality of observational studies [15, 16]. None of the studies achieved a high-quality score. In fact, the NOS scale captures the quality of the report rather than the quality of the study, while the scoring of most of its items is somewhat subjective and can vary depending on the type of follow-up, exposure, and outcome measured. As a result, in some cases it is difficult to obtain high scores even when the studies are of good quality.

In conclusion, our systematic review shows robust evidence of frequent use of HTPs among current smokers, who continue smoking conventional cigarettes, and among younger individuals and adolescents. The widespread use of HTPs among young people contradicts tobacco companies' claims that these devices are designed only for heavy smokers, and confirms that the growing spread of HTP use represents a severe public health issue. More independent studies need to be conducted to obtain updated information to better understand the global trends and patterns of HTP use. The current evidence is strong enough to recommend to repeal the fiscal and regulatory benefits HTPs have compared to conventional cigarettes, to protect young adults and adolescents.

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Chapter 3

Prevalence and patterns of electronic cigarette and heated tobacco product use among Italian adults in 2024: a cross-sectional study

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3.1 Abstract

Introduction: Electronic cigarettes (EC) and heated tobacco products (HTP) have gained popularity worldwide, despite concerns about their safety. In Italy, updated national data on these devices remain scarce. The aim of this study is to estimate prevalence, patterns, determinants and trends of EC and HTP use among Italian adults in 2024.

Methods: A face-to-face cross-sectional survey was conducted in 2024 on a representative sample of 3,125 Italian individuals aged 15 years and older. Data were collected through interviewer-administered questionnaires and included self-reported information on conventional cigarette (CC), EC, and HTP use. We used multivariable logistic regression models to assess adjusted odds ratios (aOR) for EC and HTP use, including sex, age, educational level, and smoking status as covariates. Trends (2022-2024) were assessed using analogous surveys.

Results: In 2024, 2.3% (95% confidence intervals, CI: 1.7-2.8) of Italian adults used EC, and 4.5% (95% CI: 3.7-5.2) HTP. Use of both products declined with age (p-trend<0.001). Dual use with CCs was prevalent among EC (87.8%, 95% CI: 80.1-95.4) and HTP (92.5%, 95% CI: 88.1-96.8) users. Compared with current CC smokers, odds of EC and HTP use were lower in never (EC: aOR=0.04, 95% CI: 0.02-0.09; HTP: aOR=0.01, 95% CI: 0.00-0.03) and former smokers (EC: aOR=0.14, 95% CI: 0.04-0.48; HTP: aOR=0.18, 95% CI: 0.08-0.41). Use of HTP increased by 40% over two years (p for trend=0.085). Use of EC did not substantially change.

Conclusions: The widespread dual use and the increasing prevalence of HTP use in Italy highlight growing public health concerns. Instead of serving as cessation aids for smokers, these devices are frequently used by youth and alongside CCs.

3.2 Introduction

Tobacco use remains the world's leading preventable cause of death, responsible for more than 8 million deaths each year [1, 2]. In recent years, the industry has introduced novel nicotine delivery systems - electronic cigarettes (EC), heated tobacco products (HTP) and nicotine pouches - which are promoted as reduced-harm alternatives [3, 4]. In Italy - one of the world's first test markets for Philip Morris International's IQOS (a HTP device that was first launched there and in Japan in 2014) - adult smoking remains high [5], and uptake of EC and HTP has grown since they were introduced to the market [6]. Nicotine pouches are pre-filled sachets containing white nicotine powder, designed to be placed between the lip and gum for consumption [7]. Originally developed in Scandinavia, they are now being distributed globally by major tobacco manufacturers [7]. Monitoring the prevalence of these products and the determinants of their use in the Italian population is crucial in this context.

Despite the tobacco industry claims, a growing body of evidence from independent studies warns about the health effects of novel nicotine-containing products [2], particularly when combined with conventional cigarette (CC) smoking (dual use) [8-10]. A recent systematic review concluded that EC use does not provide substantial harm reduction for all cigarette-caused diseases, while dual use poses greater health risks than CC smoking [8]. According to a recent qualitative risk assessment, ECs are likely to be carcinogenic to humans, with probable risks of lung and oral cancer [10]. A recent case-control study found that the addition of EC use to smoking accelerated the risk of developing lung cancer, with dual users having a fourfold increased risk of lung cancer compared with CC smokers [9]. Although clinical trials in controlled settings suggest that ECs can support quitting cigarette smoking, real-world evidence suggests that these devices do not improve smoking cessation rates. In fact, smokers who adopt ECs or HTPs are less likely to quit smoking than those who do not, and non-smokers who start using novel products are more likely to start CC smoking [11-15]. Of particular concern is the rapid uptake among adolescents and young adults, groups highly susceptible to nicotine addiction and potential 'gateway' progression, fuelled by targeted marketing by the EC and the tobacco industry.

In Italy, novel tobacco and nicotine products are subject to substantially lower tax rates than CC, resulting in a significant annual loss of tax revenue [16]. Furthermore, the indoor smoking bans established by Law 3/2003 (the Sirchia Law) do not apply to ECs and HTPs, permitting their use in bars, restaurants, on public transport and in other enclosed public spaces [17]. Advertising restrictions for ECs and HTPs are similarly weak. Unlike CCs, ECs and HTPs are not subject to a comprehensive advertising ban, and promotional campaigns often feature messaging and imagery that appeal to younger audiences [18]. This regulatory vacuum contributes to the normalisation and spread of these products, particularly among young people. Findings from the Global Youth Tobacco

Survey (GYTS) survey suggest that Italy is among the top countries for early experimentation with ECs, with more than half of adolescents aged 13-15 having tried these products [19]. This concerning landscape highlights the importance of systematically monitoring both the prevalence and determinants of novel product use in the Italian population, as well as evolving trends in recent years. Therefore, this study aimed to provide updated national estimates of the prevalence and patterns of use of ECs and HTPs among Italian adults in 2024. We further investigated socio-demographic and behavioural determinants of their use and examined trends over the period 2022–2024.

3.3 Methods

The data used in this study come from a cross-sectional survey conducted in Italy between March and September 2024 by the Istituto di Ricerche Farmacologiche Mario Negri (Milan), with fieldwork carried out by BVA DOXA, the Italian branch of the Worldwide Independent Network/Gallup International Association (Milan). Regarding selection criteria, the sample was designed to be representative of the Italian population aged 15 years and older, including participants selected to reflect the national distribution by sex, age, geographic area, and socioeconomic characteristics. The Ethics Committee of Istituto Neurologico Carlo Besta–Milano acknowledged the collection of anonymous data in face-to-face population-based, observational, cross-sectional studies (File number 37, 2017).
The study used a multistage representative sampling approach to select participants, with recruitment process designed to preserve the representativeness of the final sample. Data were collected by trained interviewers in the context of a computer-assisted personal interview (CAPI) in participants' house. Detailed methodology of the survey administration is described in previous papers [5]. The trend analysis included data from analogous DOXA surveys conducted in 2022 and 2023 in collaboration with the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) [20, 21]. These surveys used an analogous sampling and questionnaire methodology and were based on a representative sample of the Italian adult population.
The questionnaire collected information on the use of CC, EC and HTP. Current CC smokers were defined as those who reported having smoked 100 or more cigarettes in their lifetime and who were currently smoking cigarettes or had quit within the past year. Never CC smokers were defined as individuals who reported having smoked fewer than 100 cigarettes in their lifetime. Former CC smokers were those who had smoked 100 or more cigarettes in their lifetime but had not smoked for at least one year. Individuals were categorised as EC users if they reported current use (daily or occasional) of any type of EC, including disposable, cartridge-based or rechargeable EC. Former EC users were those who reported having used e-cigarettes in the past, while never users were those who reported never having used or not knowing these products. For HTP use, individuals were

categorised as users if they reported current use (daily or occasional) of any type of HTP, such as IQOS, glo or Ploom. Former HTP users were those who reported having used these products in the past, and never users were those who reported never having used or not knowing them. Data on the intensity of EC (puffs/day) and HTP (sticks/day) were also collected. Dual use was defined as the combined current use of CC and EC and/or HTP. Poly use was defined as the combined current use of EC, HTP and CC. The use of nicotine pouches was investigated among current CC smokers.
Sex was categorized as male or female. Age groups were defined as 15–29, 30–49, 50–64, and 65 years and over. Geographic area was classified into Northern, Central, and Southern Italy (including Islands). Participants' level of education was classified as low for those who completed middle school or less, intermediate for high school graduates, and high for university graduates or beyond. The variables sex, age, educational level, and smoking status were included as potential confounders.

Statistical Analysis

Statistical weights were generated and used in the data analysis phase to ensure representativeness of the Italian population aged 15 years and over. We used descriptive statistics (i.e., means and percentages) to analyse qualitative variables. To assess the independent associations between selected socio-demographic characteristics and EC and HTP use, while controlling for potential confounders, we used multivariable unconditional multiple logistic regression models including terms for sex, age, educational level and smoking status. We estimated adjusted odds ratios (aOR) and corresponding 95% confidence intervals (CI) for EC use versus EC non-use, and HTP use versus HTP non-use. Statistical significance was defined as a p-value below the conventional threshold of 0.05. All statistical analyses were performed using SAS (SAS version 9.4, SAS Institute) and R (R version 4.4.3).

3.4 Results

Detailed socio-demographic characteristics of the 3,125 Italian adults (48.5% men and 51.5% women; mean age: 50.1 years) participating in the survey are provided in Supplementary Table 1. No missing data were reported for the variables included in the analysis. In 2024, the prevalence of current cigarette smoking was 26.6% (95% CI 25.0-28.1). Regarding novel product use, 2.3% (95% CI 1.7-2.8) of Italian adults reported current EC use, and 4.5% (95% CI 3.7-5.2) reported current HTP use (Table 1). Average daily intensity was 13.3 cigarettes/day (standard deviation, SD=6.0) for CC smokers, 40.2 puffs/day (SD=67.5) for EC users, and 9.3 sticks/day (SD=5.8) for HTP users.

Table 1. Tobacco and nicotine product use among 3125 Italian adults included in the study, overall and stratified by sex. Italy, 2024.

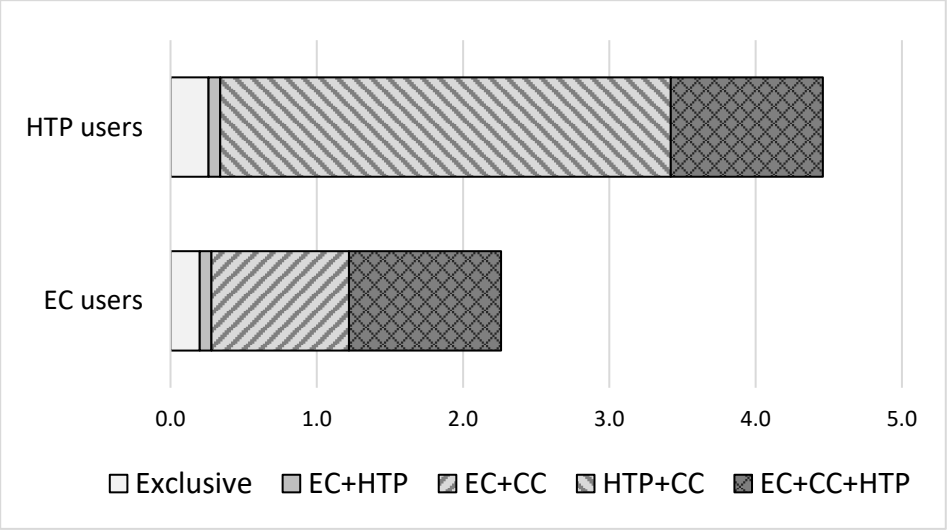
	Total	Men	Women	Age 15-29 years	Age 30-49 years	Age 50-64 years	Age ≥65 years
N	3125	1515	1610	479	892	895	860
Smoking status, % (CI)							
Never	61.7 (60.0-63.4)	53.7 (51.2-56.2)	69.2 (67.0-71.5)	72.3 (68.3-76.3)	59.4 (56.2-62.6)	56.9 (53.6-60.1)	63.2 (60.0-66.4)
Former	11.7 (10.6-12.9)	15.1 (13.3-16.9)	8.5 (7.2-9.9)	1.6 (0.5-2.7)	9.2 (7.3-11.1)	12.6 (10.4-14.8)	19.1 (16.5-21.7)
Current	26.6 (25.0-28.1)	31.1 (28.8-33.5)	22.3 (20.3-24.3)	26.1 (22.2-30.0)	31.4 (28.4-34.5)	30.5 (27.5-33.5)	17.7 (15.2-20.3)
Intensity, mean cigarettes per day (SD)	13.3 (6.0)	14.0 (6.2)	12.4 (5.7)	10.8 (6.9)	13.4 (5.3)	13.4 (5.8)	14.9 (6.4)
EC use, % (CI)							
Never	95.5 (94.8-96.2)	94.3 (93.1-95.4)	96.6 (95.7-97.5)	93.9 (91.7-96.0)	93.3 (91.7-94.9)	95.9 (94.5-97.2)	98.3 (97.4-99.1)
Past	2.3 (1.7-2.8)	3.3 (2.4-4.2)	1.3 (0.7-1.8)	3.0 (1.4-4.5)	3.4 (2.3-4.6)	1.4 (0.6-2.1)	1.6 (0.7-2.4)
Current	2.3 (1.7-2.8)	2.4 (1.7-3.2)	2.1 (1.4-2.8)	3.2 (1.6-4.7)	3.3 (2.1-4.4)	2.8 (1.7-3.9)	0.2 (0.0-0.4)
Intensity, mean puffs per day (SD)	40.2 (67.5)	50.2 (77.8)	29.3 (54.3)	108.1 (126.1)	29.3 (42.8)	15.3 (13.3)	28.2 (33.7)
HTP use, % (CI)							
Never	93.9 (93.0-94.7)	92.9 (91.6-94.2)	94.8 (93.7-95.9)	89.0 (86.2-91.8)	90.5 (88.6-92.4)	94.7 (93.3-96.2)	99.2 (98.6-99.8)
Past	1.7 (1.2-2.1)	2.2 (1.4-2.9)	1.2 (0.7-1.8)	1.7 (0.5-2.9)	2.8 (1.7-3.9)	1.6 (0.8-2.5)	0.6 (0.1-1.0)
Current	4.5 (3.7-5.2)	5.0 (3.9-6.1)	4.0 (3.0-4.9)	9.3 (6.7-11.9)	6.7 (5.1-8.4)	3.6 (2.4-4.9)	0.3 (0.0-0.7)
Intensity, mean sticks per day (SD)	9.3 (5.8)	10.3 (6.2)	8.2 (5.2)	8.8 (5.9)	10.0 (6.0)	8.2 (5.3)	14.5 (4.3)

CI: confidence intervals; EC: electronic cigarettes; HTP: heated tobacco product; SD: standard deviation.

Among men, 2.4% (95% CI: 1.7-3.2) reported current EC use and 5.0% (95% CI: 3.9-6.1) reported current HTP use; among women, the corresponding figures were 2.1% (95% CI: 1.4-2.8) and 4.0% (95% CI: 3.0-4.9), respectively. By age group, current EC use was reported by 3.2% (95% CI: 1.6-4.7) of participants aged 15-29, 3.3% (95% CI: 2.1-4.4) of those aged 30-49, 2.8% (95% CI: 1.7-3.9) of those aged 50-64, and 0.2% (95% CI: 0.0-0.4) of those aged 65 and over. For HTP use, the corresponding figures were 9.3% (95% CI: 6.7-11.9), 6.7% (95% CI: 5.1-8.4), 3.6% (95% CI: 2.4-4.9), and 0.3% (95% CI: 0.0-0.7), respectively.

Among those reporting current EC use, 8.6% (95% CI 2.1-15.2) used EC only, 3.6% (95% CI 0.0-7.9) combined them exclusively with current HTP use, while 87.8% (95% CI 80.1-95.4) were current dual users of EC and CC (46.0% were poly-users of EC, HTP and CC; Figure 1). Among HTP users, 5.7% (95% CI 1.9-9.6) used HTP exclusively, 1.8% (95% CI 0.0-4.1) combined HTP exclusively with EC, and 92.5% (95% CI 88.1-96.8) were dual users of HTP and CC (23.3% used all three products). Overall, 5.1% of Italian adults aged 15 years and over reported dual use of CC with either EC and/or HTP. This prevalence was highest among those aged 15-29 (9.3%) and 30-49 (7.7%), and lowest among those aged 65 and over (0.3%). None of the CC smokers reported using nicotine pouches.

Figure 1. Prevalence of exclusive, dual, and poly-use among electronic cigarette and heated tobacco product users in the Italian adult population (age 15 years and over), based on a representative sample of 3,125 Italian adults. Italy,2024.



CC: conventional cigarettes; EC: electronic cigarettes; HTP: heated tobacco products.

The multivariable analysis of factors related to current EC use and current HTP use is shown in Table 2. Increasing age was significantly related with a lower EC use (p for trend<0.001). Compared with the youngest age group (15-29 years), the likelihood of EC use did not significantly differ for those aged 30-49 years (aOR=0.84; 95% CI: 0.43-1.61), and those aged 50-64 years (aOR=0.70; 95% CI: 0.36-1.37), but was significantly lower for those aged 65 and over (aOR=0.06; 95% CI: 0.01-0.34). Geographic area was significantly associated with EC use, with lower odds observed in Central compared with Northern Italy (aOR=0.43; 95% CI: 0.19-0.98), while no significant difference was found between Southern/Islands and Northern Italy (aOR=0.95; 95% CI: 0.56-1.61). Both never and former smokers reported significantly lower EC use compared with current smokers (aOR=0.04; 95% CI: 0.02-0.09 for never smokers; aOR=0.14; 95% CI: 0.04-0.48 for former smokers). Finally, HTP users were more likely to use EC than HTP non-users (aOR=7.65; 95% CI: 4.36-13.42).

Compared with the youngest age group (15-29 years), HTP use was less common among those aged 30-49 years (aOR=0.46; 95% CI: 0.29-0.74), among those aged 50-64 years (aOR=0.23; 95% CI: 0.14-0.39), and among those aged 65 and over (aOR=0.03; 95% CI: 0.01-0.11), with a significant downward trend by age (p for trend<0.001). High education (university degree or higher) was related with higher HTP use compared to lower (middle school or lower) educational level (aOR=2.07; 95% CI: 1.06-4.05; p for trend=0.039). Compared

with current smokers, never smokers (aOR=0.01; 95% CI: 0.00-0.03) and former smokers (aOR=0.18; 95% CI: 0.08-0.41) reported significantly lower HTP use. Finally, EC users were more likely to use HTP compared with EC non-users (aOR=7.99; 95% CI: 4.53-14.11).

Table 2. Adjusted odds ratios (aOR) for current use of electronic cigarettes (EC) and heated tobacco products (HTP), according to selected characteristics among 3,125 Italian adults. Italy, 2024.

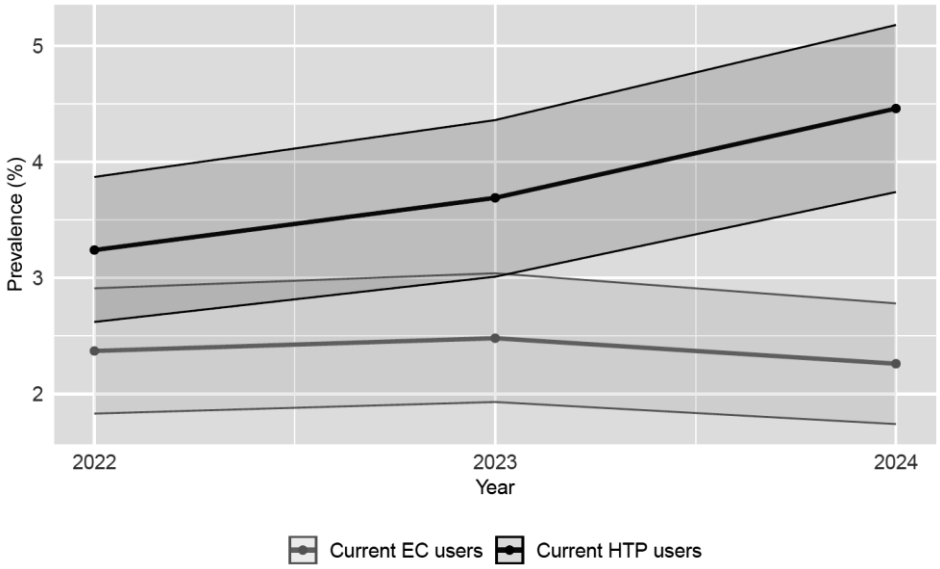
	EC users (%)	EC use vs EC non-use aOR (95% CI)	HTP users (%)	HTP use vs HTP non-use aOR (95% CI)
Total	2.3	-	4.5	-
Sex				
Male	2.4	1.00 (ref)	5.0	1.00 (ref)
Female	2.1	1.28 (0.78-2.09)	4.0	1.34 (0.92-1.96)
Age group (years)				
15-29	3.2	1.00 (ref)	9.3	1.00 (ref)
30-49	3.3	0.84 (0.43-1.61)	6.7	**0.46 (0.29-0.74)**
50-64	2.8	0.70 (0.36-1.37)	3.6	**0.23 (0.14-0.39)**
≥65	0.2	**0.06 (0.01-0.34)**	0.3	**0.03 (0.01-0.11)**
p for trend		**<0.001**		**<0.001**
Education[a]				
Low	1.3	1.00 (ref)	1.7	1.00 (ref)
Intermediate	2.4	0.92 (0.47-1.78)	5.6	1.71 (0.96-3.05)
High	3.6	1.34 (0.62-2.89)	6.3	**2.07 (1.06-4.05)**
p for trend		0.409		**0.039**
Geographic area				
Northern Italy	2.3	1.00 (ref)	4.3	1.00 (ref)
Central Italy	1.2	**0.43 (0.19-0.98)**	4.3	0.84 (0.51-1.41)
Southern Italy and islands	2.8	0.95 (0.56-1.61)	4.8	0.80 (0.52-1.22)
Smoking status				
Never	0.3	**0.04 (0.02-0.09)**	0.2	**0.01 (0.00-0.03)**
Former	0.7	**0.14 (0.04-0.48)**	1.9	**0.18 (0.08-0.41)**
Current	7.5	1.00 (ref)	15.5	1.00 (ref)
EC use				
Non-user	-	-	3.4	1.00 (ref)
User	-	-	49.8	**7.99 (4.53-14.11)**
HTP use				
Non-user	1.2	1.00 (ref)	-	-
User	25.2	**7.65 (4.36-13.42)**	-	-

CI: confidence intervals; EC: electronic cigarette; HTP: heated tobacco product. aORs are estimated through unconditional multivariable logistic regression models adjusted for sex, age group, education and smoking status. Statistically significant estimates at 0.05 level are reported in bold. a Low for middle school or less, intermediate for high school graduates, high for university graduates or beyond.

Figure 2 illustrates the trends in current use of EC and HTP over the last three years in the Italian adult population. Regarding EC use, the prevalence was 2.4%

(95% CI 1.8-2.9) in 2022, 2.5% (95% CI 1.9-3.0) in 2023, and 2.3% (95% CI 1.7-2.8) in 2024. For HTP use, the prevalence increased from 3.2% (95% CI 2.6-3.9) in 2022 to 3.7% (95 % CI 3.0-4.4) in 2023, reaching 4.5% (95% CI 3.7-5.2) in 2024 (p for trend=0.085).

Figure 2. Trends of electronic cigarette (EC) and heated tobacco product (HTP) current use in the Italian adult population (age 15 years and older), based on a representative sample of 3,125 Italian adults, with 95% confidence interval. Italy, 2022-2024*.



*Data for 2022 and 2023 were collected through different surveys.

3.5 Discussion

This study provides an updated overview of novel tobacco and nicotine product use in Italy in 2024. The vast majority of EC and HTP users also smoke CCs, and the prevalence of dual and poly-use is high. These products are more prevalent among younger adults than among older adults. There has been a consistent, albeit not statistically significant, upward trend in the prevalence of HTP use, with an increase of 40% over the past two years. The use of EC has been stable.

The large majority of EC and HTP users in the Italian adult population are current smokers, these products are predominantly used concurrently with CCs. In our sample, about nine out of ten EC and HTP users also smoked CCs, suggesting that these devices may not be functioning as intended cessation aids in real-world conditions, but rather as complementary nicotine sources. Emerging evidence suggests that dual users face greater health risks than those who only smoke CCs [8, 9]. This widespread pattern of dual use raises concerns and highlights the need for policies to curb the spread of these products.

Our findings show that EC and HTP use is more common among younger age groups, with significantly lower use among older adults. These results are consistent with an increasing body of international literature suggesting that novel nicotine products are not primarily adopted by older smokers seeking cessation alternatives, but rather by younger individuals [12, 22-24]. A recent systematic review of existing research on HTP use found that, in 15 studies, prevalence was consistently higher among individuals under 40 years of age compared to older adults [12]. The widespread use of these products among adolescents and young adults is a pressing and concerning public health issue.

The tobacco industry claims that the overwhelming majority of HTP consumers are older adults, with over four out of five users reporting to be aged 30 years or more [25]. However, our data show that fewer than two in five EC users and approximately one in four HTP users in Italy are over the age of 50 - an age group where hardcore smokers, i.e., those who could potentially benefit most from smoking cessation interventions, are concentrated. This discrepancy is further underscored by the notable absence of underaged kids in our cohort, given that independent evidence shows that significant numbers of adolescents and children use these products, also in Italy [26]. Therefore, if data on younger individuals had been included, the proportion of users aged over 50 would have been even smaller. These findings emphasise the discrepancy between industry assertions and independent epidemiological evidence.

The observed upward trajectory in HTP use, showing a marked relative increase in 2 years, signals a potentially widening public health challenge if left unaddressed. As these products are being adopted disproportionately by younger adults, continued market growth can be anticipated in the coming years, which would further entrench nicotine dependence in the Italian population. The growing popularity of HTPs could renormalize tobacco use and reverse decades of progress in tobacco control.

These products are not adequately regulated in Italy. Unregulated marketing, ranging from product advertising to social media promotions, explicitly targets adolescents and young adults, increasing curiosity and experimentation among youth and non-smokers [27, 28]. There is a growing public demand for stronger regulation, with the vast majority of Italians in favour of extending existing smoke-free laws to novel nicotine products [29, 30]. By contrast, countries such as Denmark and Finland already include ECs and HTPs in tobacco control measures, applying advertising bans, plain packaging, and flavour restrictions [31]. The European Commission has recommended extending smoke-free environments by banning CCs, ECs and HTPs also from outdoor areas, as part of the EU's "Beating Cancer Plan" [32]. Therefore, Italian policymakers should prioritise harmonising regulations so that ECs and HTPs are treated equally to CCs.

None of the CC smokers reported using nicotine pouches. This result highlights that these products have not yet been adopted by adults in Italy. However, recent

data from the European School Survey Project on Alcohol and Other Drugs (ESPAD) revealed that one in 25 students had used nicotine pouches in the past year (2024) [33]. Therefore, nicotine pouches seem to be just another nicotine product targeting youth and non-smokers instead of adult smokers in Italy. Further surveys should monitor nicotine pouch use in both the young and adult populations.

The present study has some limitations. Its cross-sectional design inherently precludes any inference of causality. The self-reported nature of the data introduces the potential for information bias, such as underreporting of smoking habits. However, the face-to-face interview approach with trained interviewers likely helped to minimise this bias. In addition, despite adjustment for key confounders, the possibility of residual confounding cannot be excluded. Another limitation of this study is that, for all tobacco and nicotine products, the exact time since cessation was not assessed, preventing a more accurate classification of former smokers and users. The modest number of EC and HTP users in our sample potentially constrained the power of some subgroup analyses. However, the sample was calibrated to mirror the Italian adult population, thereby enabling the findings to be generalised to the Italian population. Future research should consider representative samples of minors and adolescents to better characterise the prevalence and determinants of novel product use in younger age groups. The 2022 and 2023 surveys were conducted by a different research group; however, the questionnaire structure and key items were maintained to ensure comparability with the 2024 survey. The results on the prevalence of use may be affected by social desirability bias, whereby respondents tend to answer questions in a way that they perceive to be politically or socially correct. This can result in underreporting of self-reported behaviours relating to tobacco and nicotine use. In addition, since interviews with minors might have been conducted in the presence of an adult parent or relative, underreporting among younger participants cannot be ruled out. These biases may have led to an overall underestimation of the prevalence of use, suggesting that the actual consumption of these products - particularly among younger individuals - could be even higher.

Conclusion

The growing prevalence of EC and HTP use - particularly among younger age groups - together with the alarmingly high rate of dual use with CCs observed in our data, strengthens concerns that these products may neither serve as effective cessation tools in Italy nor be primarily adopted by older adult smokers, contrary to tobacco industry claims [11-15]. Instead, they appear to be more commonly used by younger individuals, often alongside CCs. Further research, including longitudinal studies, is needed to clarify usage trajectories and potential health implications.

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Supplementary Materials available online at:

https://www.tobaccopreventioncessation.com/Prevalence-and-patterns-of-electronic-cigarette-and-heated-tobacco-product-use-among,213721,0,2.html

Chapter 4

Tobacco and nicotine product use among students aged 11-17 years: a cross-sectional study from Italy

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Submitted

4.1 Abstract

Introduction: The rapid expansion of novel tobacco and nicotine products, including electronic cigarettes (e-cigarette), heated tobacco products (HTP) and nicotine pouches, has raised concerns about their uptake among adolescents. This study aimed to provide updated data on the prevalence and patterns of tobacco and nicotine product use among underage students in Italy, and to examine associated sociodemographic and behavioural factors.

Methods: A cross-sectional survey (November 2024–May 2025) was conducted among middle and high school students from 5 regions of northern, central and southern Italy. Ever and last-month use of cigarettes, e-cigarettes, HTP and nicotine pouches were assessed. Dual use was defined as use of conventional cigarettes plus another nicotine product. Prevalence estimates were calculated, and multivariable logistic regression models were used to assess factors related to last-month use, reporting adjusted odds ratios (aOR) and 95% confidence intervals (CI).

Results: A total of 7,390 students aged 11-17 years were included. Overall, 18.0% reported last-month cigarette smoking, 21.9% e-cigarette use, 15.8% HTP use and 2.4% nicotine pouch use; 27.7% reported use of at least one nicotine product and 15.8% dual use. Among high school students, 5.9% reported daily e-cigarette use and 4.5% reported daily HTP use. In multivariable analyses, alcohol use was related to all nicotine products (aOR range 6.73-11.07). Cigarette smoking was related to the use of e-cigarettes (aOR=23.45; 95% CI: 20.02-27.47), HTP (aOR=30.76; 95% CI: 25.94-36.48) and nicotine pouches (aOR=36.40; 95% CI: 22.96-57.71).

Conclusions: Nicotine and tobacco product use is widespread among underage students in Italy. Notably, e-cigarettes and HTPs are used more frequently by high school students -who are legally prohibited from purchasing these products- rather than by the adult population. These findings suggest that novel tobacco and nicotine products are related to sustained and diversified nicotine use among children and adolescents, underscoring the need for strengthened regulation, prevention and ongoing surveillance.

4.2 Introduction

Tobacco use remains the world's leading preventable cause of death, accounting for over 8 million deaths worldwide each year.[1, 2] In recent years, the tobacco and nicotine market has expanded beyond conventional cigarettes with the introduction of novel nicotine products, such as electronic cigarettes (e-cigarette), heated tobacco products (HTP), and nicotine pouches. E-cigarettes are battery-operated devices that aerosolise a liquid containing nicotine,[3] HTPs heat processed tobacco to release an inhalable aerosol,[4] and nicotine pouches are smokeless, oral products that deliver nicotine through the oral mucosa.[5] While these products have been promoted as innovative alternatives to conventional cigarette smoking, their rapid diffusion has raised growing concerns regarding their health effects and the uptake among adolescents and minors, a population particularly vulnerable to nicotine addiction.[6, 7]

Novel nicotine products have been widely promoted by the tobacco industry through the "harm reduction" narrative. This narrative claims that these products are intended primarily to help adult smokers quit and substantially reduce the health risks associated with conventional cigarette smoking.[8, 9] However, this narrative largely relies on industry-funded evidence,[10, 11] while an increasing body of independent research has cast doubt on both the extent of the proposed risk reduction and the effectiveness of these products as smoking cessation tools.[12] Emerging evidence suggests that, in real-world settings, using novel nicotine products does not lead to better smoking cessation outcomes and may instead lead to long-term nicotine dependence.[13, 14] Furthermore, there are concerns about a potential gateway effect whereby non-smokers, often adolescents and young adults, initiate nicotine use through these products and then transition to conventional cigarettes.[13, 15, 16] Of particular concern is the "dual use" of novel products alongside conventional cigarettes, which has been found to increase the risk of smoking-related diseases, including lung cancer, compared with smoking conventional cigarettes exclusively.[17, 18]

There is growing concern about the uptake of novel nicotine products among children and adolescents, driven by several interrelated factors. These products are heavily promoted through aggressive marketing strategies, particularly on social media platforms, where advertising frequently targets younger audiences and often involves influencers promoting product use.[19, 20] Manufacturers use branding, terminology and product designs that appeal to young people rather than adult smokers.[6, 21] Moreover, many of these products are available in a wide range of flavours and colours, features known to increase their appeal to children and adolescents, but which are irrelevant for smoking cessation.[22] The ease of use and discreet nature of these devices, compared with conventional cigarettes, further facilitates their use in settings where smoking is prohibited and allows minors to more easily conceal consumption from parents and teachers. In response to these concerns, some countries have introduced regulatory

measures, such as banning characterising flavours [23] or restricting specific products, including disposable electronic cigarettes and nicotine pouches.[24, 25] In contrast, weaker regulation compared with that for conventional cigarettes may facilitate the diffusion of novel nicotine products among young people in other countries.

Italy represents a relevant setting for the study of novel nicotine products. It was one of the first test markets for Philip Morris International's IQOS, a HTP that was firstly introduced in Italy and Japan in 2014.[4] In the last decade the country has experienced the diffusion of e-cigarettes and HTPs and, more recently, nicotine pouches have also entered the Italian market.[26] Recent estimates indicate that 2.3% and 4.5% of Italian adults use e-cigarettes and HTPs respectively, with a higher prevalence among young people and current cigarette smokers.[27] Meanwhile, nicotine pouch use remains uncommon in the adult population.[27] The regulatory framework may have contributed to this diffusion. The indoor smoking ban introduced by Law 3/2003 (the "Sirchia Law"[28]) applies to conventional cigarettes but has never been explicitly extended to e-cigarettes or HTPs. This allows their use in indoor public spaces where smoking is otherwise prohibited, thereby favouring their social acceptability. Although the sale of nicotine-containing products to minors is prohibited in Italy, weak enforcement and a permissive regulatory environment have created a context of potential risk for underage individuals, facilitating access and use of these products among adolescents.

Evidence from national and international surveillance systems indicates that tobacco and nicotine product use among adolescents in Italy is widespread. Recent reports from the Italian National Institute of Health (ISS), together with data from the European School Survey Project on Alcohol and Other Drugs (ESPAD) surveillance system, consistently show that a substantial proportion of students report using e-cigarettes, HTPs and, to a lesser extent, nicotine pouches.[29, 30] Although these data have not been published in peer-reviewed scientific journals, they highlight the importance of having up-to-date information on tobacco and nicotine product use among Italian minors. A recent peer-reviewed article presenting results from the 2022 Global Youth Tobacco Survey (GYTS) conducted in eight Italian regions has also provided important insights into novel product use among adolescents aged 13-15 years.[31] However, the narrow age range considered underscore the need for up-to-date and comprehensive evidence on tobacco and nicotine product use among Italian youth.

The aim of the present study is therefore to provide updated evidence on the prevalence of tobacco and nicotine products among underage students in Italy. The study will investigate patterns of use, and the socio-demographic and behavioural factors related to them.

4.3 Methods

The data analysed in this study were collected as part of the project “Use of tobacco and other nicotine-containing products among Italian students”, which was promoted by the Italian League Against Cancer (Lega Italiana per la Lotta contro i Tumori, LILT) Milano Monza Brianza. The project was designed to investigate the use of tobacco and nicotine products among children and teenagers in Italy. This observational, cross-sectional study involved students attending lower and upper secondary schools (middle and high schools) that participated in the networks of several LILT branches across Italy. Data were collected through a self-administered electronic questionnaire completed by students during school hours. The survey was administered between November 2024 and May 2025. We enrolled a total of 8,316 students. For the purposes of this study, only data from students under the age of 18 were included (88.9% of the total sample; n=7,390).
The questionnaire collected information on socio-demographic and behavioural characteristics. Socio-demographic variables included gender, age, school year, type of school (lyceum, technical or vocational), region of residence and birthplace (Italy or other country). Behavioural variables investigated the use of tobacco and nicotine products, including conventional cigarettes, e-cigarettes, HTPs and nicotine pouches, as well as the consumption of alcoholic beverages and energy drinks.
For each product, “ever use” was defined as having tried the product at least once in the lifetime, while “use in the last month” was defined as having used the product on at least one day in the past 30 days. For nicotine-containing products, an additional composite variable (at least one nicotine product) was created to identify students reporting use of at least one among conventional cigarettes, e-cigarettes, HTPs or nicotine pouches. Dual use was defined as the concomitant use of conventional cigarettes and at least one other nicotine-containing product.

Statistical analysis

Descriptive statistics were used to analyse all variables. Prevalence estimates were calculated for all socio-demographic and behavioural variables. For tobacco and nicotine product use, the prevalence of last-month use was additionally examined, stratified by selected socio-demographic characteristics.
Multivariable logistic regression models were then employed to investigate the relationship between tobacco and nicotine product use and potential determinants of use, such as gender, school year, birthplace, alcohol drinking, energy drink consumption, and cigarette use in the last month. Separate models were fitted for last-month use of conventional cigarettes, e-cigarettes, HTPs, nicotine pouches, use of at least one nicotine product and dual use. Relationships were expressed using adjusted odds ratios (aOR) with corresponding 95%

confidence intervals (CI). All models were adjusted for gender and school year. All statistical analyses were performed using SAS (SAS version 9.4, SAS Institute).

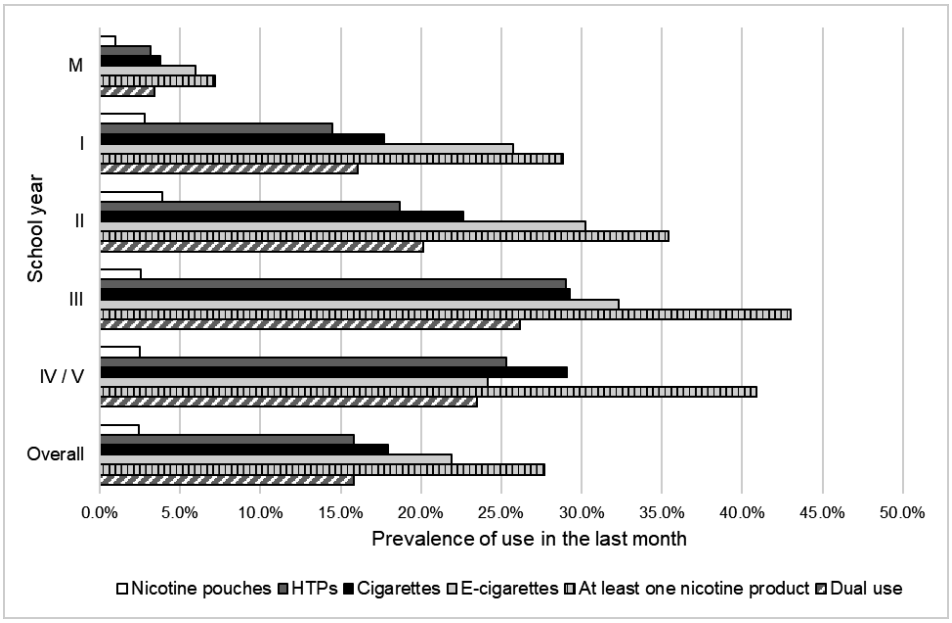
4.4 Results

A total of 7,390 students aged 11-17 were included in the analysis (Supplementary Table 1). Slightly more than half of participants were female (51.8%), 46.0% were male and 2.2% identified as “other” or did not report their gender. Nearly one-third of students attended middle school (29.9%), while the remaining were enrolled in high school: 18.6% in the first year, 23.1% in the second year, 18.1% in the third year, and 10.4% in the fourth or fifth year. The majority of participants were from Lombardy (62.8%), while the remaining were from four other Italian Regions (Sardinia 15.0%; Molise 14.5%; Tuscany 5.9%; Campania 1.8%). Most students were born in Italy (94.2%), while 5.8% reported being born abroad.

Overall, 32.3% of students reported they ever smoked conventional cigarettes, 18.0% reported cigarette use in the last month, and 3.8% daily cigarette use. Ever use of e-cigarettes was reported by 41.5% of participants, while 21.9% reported use in the past 30 days, and 4.3% daily use. For HTPs, 29.3% of students reported ever use, 15.8% reported last-month use, and 3.3% daily use. For nicotine pouches, ever use was reported by 5.1%, use in the last month by 2.4%, and daily use by 0.2% of the students. Considering overall nicotine exposure, 45.1% of students reported ever use of at least one nicotine product, 27.7% reported use of at least one nicotine product in the last month, and 8.9% daily use. Dual use was reported by 30.5% of students as ever use, by 15.8% in the last month, and by 1.8% as daily use.

The prevalence of last-month use of nicotine products varied by school year (Figure 1). Conventional cigarette use ranged from 3.7% in middle school to 29.3% in the third year and 29.1% in the fourth–fifth year of high school. E-cigarette use was highest in the third year of high school (32.4%). HTP use increased from 3.1% in middle school to a maximum of 29.0% in the third year of high school. Nicotine pouch use ranged from 1.0% in middle school to a peak of 3.9% in the second year of high school. Overall, use of at least one nicotine product in the last month was higher among high school students (28.9% to 43.0%) compared with middle school students (7.2%). The highest prevalence was observed among third-year high school students (43.0%). A similar pattern was observed for dual use, ranging from 3.4% in middle school to a peak of 26.2% in the third year of high school. Among high school students, 5.1% reported daily cigarette smoking, 5.9% reported daily e-cigarette use, 4.5% reported daily HTP use, and 0.3% reported daily nicotine pouch use.

Figure 1. Prevalence of nicotine and tobacco product use in the last month among 7,390 Italian students aged 11-17 included in the study, overall and stratified by school year.



Dual use: use of conventional cigarettes and at least one more nicotine product; e-cigarettes: electronic cigarettes; HTPs: heated tobacco products; M: middle school (n=2209); I: first year of high school (n=1372); II: second year of high school (n=1710); III: third year of high-school (n=1334); IV / V: fourth or fifth year of high school (n=765).

Regarding other behavioural characteristics, 68.4% of students reported ever consumption of alcoholic beverages, and 40.7% reported alcohol use in the last month. Regarding energy drink consumption, 71.1% of participants reported ever use, and 40.9% reported use in the past month.

Results from the multivariable logistic regression models on the relationship between different socio-demographic and behavioural factors and last-month use of nicotine products are reported in Table 1.

Table 1. Tobacco and nicotine product use in the last month among 7,390 Italian students aged 11-17 included in the study, according to socio-demographic and behavioural characteristics.

	Tot	Use in the last month											
		Conventional cigarettes		Electronic cigarettes		Heated tobacco products		Nicotine pouches		At least one nicotine product		Dual use	
	N	N (%)	aOR[a] (95% CI)	N (%)	aOR (95% CI)	N (%)	aOR (95% CI)	N (%)	aOR (95% CI)	N (%)	aOR (95% CI)	N (%)	aOR (95% CI)
Total	7390	1326 (18.0)	-	1618 (21.9)	-	1169 (15.8)	-	178 (2.4)	-	2047 (27.7)	-	1169 (15.8)	-
Gender													
Male	3339	590 (17.4)	ref	698 (20.6)	ref	433 (12.8)	ref	124 (3.7)	ref	854 (25.1)	ref	522 (15.4)	ref
Female	3826	694 (18.1)	0.99 (0.87-1.12)	874 (22.9)	1.12 (0.99-1.25)	705 (18.4)	1.48 (1.29-1.69)	44 (1.2)	0.30 (0.21-0.43)	1135 (29.7)	1.20 (1.08-1.34)	609 (15.9)	0.98 (0.86-1.12)
Other	165	42 (25.5)	1.54 (1.06-2.25)	46 (27.9)	1.39 (0.96-1.99)	31 (18.8)	1.51 (0.99-2.29)	10 (6.1)	1.58 (0.81-3.07)	58 (35.2)	1.54 (1.09-2.17)	38 (23.0)	1.56 (1.06-2.30)
School year[b]													
M	2209	82 (3.7)	ref	131 (5.9)	ref	69 (3.1)	ref	21 (1.0)	ref	158 (7.2)	Ref	74 (3.4)	ref
I	1372	243 (17.7)	5.58 (4.30-7.24)	354 (25.8)	5.50 (4.44-6.81)	199 (14.5)	5.22 (3.93-6.93)	38 (2.8)	3.06 (1.78-5.24)	396 (28.9)	5.25 (4.30-6.41)	221 (16.1)	5.53 (4.21-7.27)
II	1710	387 (22.6)	7.54 (5.89-9.67)	517 (30.3)	6.87 (5.60-8.43)	320 (18.7)	7.18 (5.49-9.40)	66 (3.9)	4.11 (2.50-6.76)	606 (35.4)	7.12 (5.89-8.61)	345 (20.2)	7.25 (5.59-9.40)
III	1334	391 (29.3)	10.76 (8.38-13.82)	431 (32.4)	7.54 (6.11-9.31)	387 (29.0)	12.49 (9.56-16.33)	34 (2.6)	2.92 (1.68-5.06)	574 (43.0)	9.72 (8.00-11.81)	349 (26.2)	10.25 (7.89-13.32)
IV / V	765	223 (29.2)	10.70 (8.17-14.03)	185 (24.2)	5.00 (3.93-6.38)	194 (25.4)	10.18 (7.61-13.60)	19 (2.5)	3.03 (1.61-5.67)	313 (40.9)	8.84 (7.11-10.98)	180 (23.5)	8.91 (6.69-11.86)
Birthplace													
Italy	6961	1260 (18.1)	ref	1518 (21.8)	Ref	1120 (16.1)	ref	157 (2.3)	ref	1938 (27.9)	Ref	1104 (15.9)	Ref
Other	429	66 (15.4)	0.88 (0.66-1.16)	100 (23.3)	1.15 (0.90-1.46)	49 (11.4)	0.72 (0.53-0.99)	21 (4.9)	2.16 (1.34-3.47)	109 (25.4)	0.95 (0.75-1.20)	65 (15.2)	1.01 (0.76-1.34)
Alcohol (last month)													
No	4334	238 (5.5)	Ref	356 (8.2)	ref	192 (4.4)	Ref	20 (0.5)	ref	451 (10.4)	Ref	201 (4.6)	Ref
Yes	2970	1065 (35.9)	7.07 (6.05-8.28)	1240 (41.8)	6.73 (5.86-7.73)	957 (32.2)	7.74 (6.52-9.19)	155 (5.2)	11.07 (6.81-17.99)	1561 (52.6)	7.40 (6.51-8.41)	950 (32.0)	7.31 (6.18-8.64)
Energy drink (last month)													
No	4317	508 (11.8)	ref	563 (13.0)	Ref	483 (11.2)	Ref	28 (0.7)	ref	811 (18.8)	Ref	427 (9.9)	Ref
Yes	2984	795 (26.6)	2.97 (2.60-3.40)	1034 (34.7)	3.97 (3.50-4.51)	66 (22.4)	2.75 (2.39-3.17)	147 (4.9)	6.26 (4.13-9.48)	1202 (40.3)	3.52 (3.13-3.97)	724 (24.3)	3.14 (2.73-3.62)
Conventional cigarettes (last month)													
No	6062	-	-	621 (10.2)	Ref	300 (4.9)	Ref	25 (0.4)	ref	-	-	-	-
Yes	1326	-	-	997 (75.4)	23.45 (20.02-27.47)	869 (65.6)	30.76 (25.94-36.48)	153 (11.6)	36.40 (22.96-57.71)	-	-	-	-

[a]aOR: adjusted odds ratios estimated through unconditional logistic regression models after adjustment for gender and school year; CI: confidence interval; [b] School year defined as: M: middle school; I: first year of high school; II: second year of high school; III: third year of high-school; IV / V: fourth or fifth year of high school.

Gender

Compared with males, females had higher odds of HTP use (aOR=1.48; 95% CI: 1.29-1.69) and use of at least one nicotine product (aOR=1.20; 95% CI: 1.08-1.34), and lower odds of nicotine pouch use (aOR=0.30; 95% CI: 0.21-0.43). Students reporting “other” gender identity, compared with males, had higher odds of cigarette smoking (aOR=1.54; 95% CI: 1.06-2.25), use of at least one nicotine

product (aOR=1.54; 95% CI: 1.09-2.17), and dual use (aOR=1.56; 95% CI: 1.06-2.30).

School year

Compared with middle school students, all high school years were significantly related to higher odds of use across outcomes. The highest aOR was observed in third-year students for cigarette smoking (aOR=10.76; 95% CI: 8.38-13.82), for e-cigarettes (aOR=7.54; 95% CI: 6.11-9.31), for HTP (aOR=12.49; 95% CI: 9.56-16.33), for use of at least one nicotine product (aOR=9.72; 95% CI: 8.00-11.81) and for dual use (aOR=10.25; 95% CI: 7.89-13.32). For nicotine pouches, the highest aOR was observed in the second year of high school (aOR=4.11; 95% CI: 2.50-6.76).

Birthplace

Compared with students born in Italy, those born abroad had lower odds of HTP use (aOR=0.72; 95% CI: 0.53-0.99) and higher odds of nicotine pouch use (aOR=2.16; 95% CI: 1.34-3.47).

Alcohol and energy drinks

Compared with students who did not report alcohol use in the last month, those who did had higher odds of use across all outcomes, with aORs ranging from 6.73 for e-cigarette use to 11.07 for nicotine pouch use. Compared with those who did not report energy drink use, students that did had higher odds of nicotine product use, with aORs ranging from 2.75 for HTP use to 6.26 for nicotine pouch use.

Conventional cigarettes

Last-month cigarette smoking was associated with higher odds of e-cigarette use (aOR=23.45; 95% CI: 20.02-27.47), HTP use (aOR=30.76; 95% CI: 25.94-36.48), and nicotine pouch use (aOR=36.40; 95% CI: 22.96-57.71).

4.5 Discussion

This study, conducted among underage students in Italy, shows that more than one in four reported having used at least one nicotine product in the last month, despite the legal ban on selling to minors. Conventional cigarettes, e-cigarettes and HTPs were all widely used, with a substantial proportion of students reporting dual use. Additionally, a non-negligible prevalence of nicotine pouch use was also reported.

Europe has the highest prevalence of current smokers in adolescence, with Italy ranking first for all tobacco products according to the World Health

Organization.[32] The spread of novel nicotine products among minors is of particular concern. Italy has long represented a particularly critical context in Europe with regard to youth smoking and e-cigarette use, consistently reporting higher prevalence estimates than many other countries.[33-35] In the Italian adult population, according to a recent cross-sectional survey, current e-cigarette and HTP users (daily or occasional) are 2.3% and 4.5% of adults, respectively.[27] Among underage high school students in our study, daily use of e-cigarette and HTP reached 5.9% and 4.5% respectively, with peaks of use in the last month at 32.3% for e-cigarettes and 29.0% for HTPs in the third year of high school. Similarly, nicotine pouches appear to be emerging among minors, while remaining largely uncommon in the adult population.[27] Overall, these findings indicate that all novel tobacco and nicotine products are more common among high school students who are legally prohibited from purchasing these products than among the adult population.

Notably, the emergence of novel nicotine products has not replaced conventional cigarette smoking among adolescents in Italy. On the contrary, cigarette use remains substantial, reaching prevalence comparable to those observed in the adult population already by the third year of high school.[36] Moreover, the vast majority of adolescent cigarette smokers reported combining cigarettes with other nicotine products, resulting in dual or poly-use patterns. Such patterns have been demonstrated to be associated with greater health risks compared with exclusive cigarette smoking, including higher risk of cardiovascular disease and lung cancer.[17, 18] These patterns of widespread poly use are largely unprecedented in the adult population and outline a different prospective scenario, potentially posing new and complex challenges for tobacco control strategies and public health policies in the coming decades.

Comparisons with other research in different settings highlight differences in youth tobacco and nicotine use. A recent U.S. National Youth Tobacco Survey report found overall prevalence of current nicotine and tobacco product use among middle and high school students—particularly HTPs and cigarettes—to be substantially lower than in our Italian sample, although nicotine pouch use prevalence was similar.[37] On the other hand, we found similarities with recent data from national Italian surveys. Data from the Global Youth Tobacco Survey (GYTS) conducted in eight Italian regions among 13–15-year-olds reported current smoking prevalence of approximately 18% for cigarettes, 20% for e-cigarettes, and 16% for HTPs, closely aligning with the corresponding age group estimates in our study.[31] The GYTS analysis also documented rising prevalence of poly-product use among adolescents, a pattern consistent with the dual and multiple product use observed in our analysis. Recent estimates from the ISS reported that 30.2% of adolescents aged 14-17 years had used at least one nicotine product, a figure that is consistent with the prevalence observed in our study.[29]

The multivariable logistic analysis allowed us to examine a range of sociodemographic and behavioural factors potentially associated with nicotine product use. Historically, cigarette smoking has been more prevalent among males than females, although this gap has progressively narrowed in many Western countries. [38, 39] For novel tobacco and nicotine products, gender differences appear less consistent among young people.[31, 40] In our sample, girls did not report lower use than boys: cigarette and e-cigarette use were comparable, and HTP use was more frequent among females, while nicotine pouch use remained more common among males. In line with previous literature,[41, 42] students who did not identify as male or female showed higher odds of nicotine product use, including a significant association with dual use. Taken together, these findings highlight the need for gender-sensitive prevention strategies that address evolving patterns of nicotine consumption among adolescents. With regard to birthplace, students born abroad had lower odds of HTP use but higher odds of nicotine pouch use compared with those born in Italy, while no significant differences emerged for the other products.

Use of nicotine products was strongly associated with alcohol consumption, another behaviour for which sales to minors are legally prohibited in Italy, yet widely reported. Students who had consumed alcohol in the last month had between 7 to 11 times higher odds of using nicotine and tobacco products. The combined and potentially synergistic action of these risk behaviours during adolescence may contribute to substantial long-term health consequences.[43, 44] Energy drink consumption in the last month was also significantly associated with all nicotine product outcomes. These findings suggest that school-based prevention and education programmes should address multiple co-occurring risk behaviours simultaneously, targeting tobacco and nicotine products together with alcohol and energy drink consumption in order to reduce early initiation and prevent the consolidation of harmful patterns during adolescence.

A very strong relation was observed between cigarette smoking and the use of novel tobacco and nicotine products. Students who reported cigarette smoking had 24 to 37 times higher odds of using e-cigarettes, HTP and nicotine pouches compared with non-smokers. Exclusive use was uncommon, while most adolescent smokers reported concurrent use of multiple products. It is plausible that, depending on the context, minors alternate between using these products and cigarette smoking, using novel products in situations where cigarette smoking is not permitted. Such patterns entail multiple risks, as they may increase and diversify exposure to nicotine and other harmful substances, potentially reinforcing dependence and complicating future cessation. These findings raise concerns about the immediate health of adolescents and future public health, and challenge the claim that these products are “harm reduction” tools in the real world.

This study has some limitations that should be acknowledged. First, the sample was not nationally representative, and therefore the findings cannot be directly generalized to all underage students in Italy. However, the prevalence estimates observed are closely aligned with those reported by other national surveillance systems and surveys, supporting the overall consistency and plausibility of our results. Second, the cross-sectional design precludes any inference on causal relationships between nicotine product use and the sociodemographic and behavioural factors examined. Therefore, any observed association should be interpreted as co-occurrence rather than causation. At the same time, the study has several strengths. It provides detailed and updated data on the use of multiple tobacco and nicotine products among a large sample of underage students, including age-stratified estimates that allow a granular description of patterns of use. The simultaneous assessment of conventional cigarettes, e-cigarettes, HTP and nicotine pouches enables a comprehensive overview of concurrent and dual use. Finally, the application of multivariable logistic regression models allowed the identification of factors associated with product use, offering relevant insights to inform prevention and policy strategies.

In our survey on underaged Italian students, nicotine product use was widely spread, with the use of novel tobacco and nicotine products substantially higher than in the adult population. Our findings support the evidence suggesting that, while promoted as alternatives for adult smokers, novel tobacco and nicotine products may be playing a role in the development of a new generation of young nicotine users. Continuous monitoring of prevalence, patterns of use and associated determinants is essential to promptly identify emerging trends and guide evidence-based interventions.

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Supplementary Materials will be available online after publication.

Chapter 5

Adverse events associated with dual and poly use of conventional cigarettes, electronic cigarettes, and heated tobacco: a cross-sectional study of Italian adults

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5.1 Abstract

Introduction: Electronic cigarettes (EC) and heated tobacco products (HTP) face growing scepticism regarding their safety and effectiveness in promoting conventional cigarettes (CC) cessation. Understanding patterns of use of these products and their health effects is essential on a public health perspective. The primary objective of this study is to investigate the adverse events associated with the exclusive and combined use of these products.

Methods: Between October 2023 and March 2024, a cross-sectional sample of 22,428 Italian adults was recruited through an online panel. Participants completed a structured self-reported questionnaire on their use of CC, EC, and HTP and any adverse events -including dry cough, sore throat and dry mouth- experienced during or after each product use. We used multivariable logistic regression models to assess adjusted odds ratios (aOR) of reporting at least one CC-related adverse event in dual/poly users (CC plus EC and/or HTP) versus CC-only smokers.

Results: CC use was reported by 75·6% of EC users and 80·3% of HTP users. At least one product-specific adverse events were reported by 68·2%, 44·7% and 44·5% of CC, EC and HTP users, respectively. Compared to CC-only smokers, CC smokers also using EC (aOR: 1·32, 95% confidence interval; 95%CI: 1·17-1·50), also using HTP (aOR: 1·14, 95%CI: 1·01-1·30) and also using EC and HTP (aOR: 1·50, 95%CI: 1·29-1·75) had a higher likelihood of experiencing at least one CC-related adverse event.

Conclusions: The combination of CCs with ECs and/or HTPs increases the likelihood of adverse events related to CC smoking. To these figures we must add the far from negligible number of adverse events due to EC or HTP use. Our findings are consistent with the growing evidence of a higher harm for dual users compared to CC-only smokers, suggesting that EC and HTP may undermine rather than support tobacco control efforts.

5.2 Introduction

Tobacco smoking remains one of the leading causes of preventable morbidity and mortality worldwide, accounting for 8 million deaths per year.[1, 2] Over the last decades, novel nicotine and tobacco containing products such as electronic cigarettes (EC) and heated tobacco products (HTP) have been introduced to the market and marketed as safer options for smokers unable to quit conventional cigarettes (CC).[3, 4] Understanding the patterns of use of these products is crucial for public health, as the combined use of CCs and novel products could exacerbate health risks by exposing users to multiple sources of harm. Therefore, assessment of the short and long-term health effects of these products is essential to inform evidence-based regulatory decisions and public health strategies.

Contrary to their intended role as cessation tools for adult smokers, novel tobacco and nicotine products have gained considerable popularity among younger populations, including non-smokers, who initiate nicotine dependence by using these products.[5-7] Moreover, studies consistently show that a significant proportion of users are dual users, combining these products with conventional cigarettes. [5, 8-10] Evidence from many independent longitudinal studies suggests that these products are not effective in smoking cessation and that dual users are more likely to continue smoking CCs.[7, 11, 12] The health risks associated with smoking are well documented and include a wide range of serious conditions, from cardiovascular diseases to cancer.[1, 2] For novel tobacco products, the World Health Organization (WHO), supported by several independent studies, has highlighted the potential risks associated with exposure to harmful substances present in aerosols and emissions.[1, 13-16]

Detailed analyses of patterns of use of ECs and HTPs - exclusively and in combination with CCs - are needed to assess in detail how users approach these products and, in particular, to understand how short-term effects such as adverse events vary with different patterns of product use (e.g., exclusive, dual or poly use). In addition, longitudinal data on the medium- and long-term effects of exclusive and combined use of these products remain scarce, with the first observational studies showing an increased risk of lung cancer and other diseases in EC users and dual users.[16, 17] Such data are essential to assess their long-term effects and public health implications.

In this study, we recruited a large sample of Italian adults, including both smokers and non-smokers, to assess the patterns of use of tobacco and nicotine products and to compare the prevalence and burden of self-reported short-term adverse events across exclusive, dual and poly users. Detailed analyses of EC and HTP use patterns are needed not only to describe how these products are used in real-world settings, but also to evaluate whether different patterns of use (exclusive, dual or poly use) are associated with differences in the burden of short-term adverse symptoms. Since dual use has become widespread among

EC and HTP users, understanding its health implications is particularly relevant from a public health perspective. The present analysis represents the baseline of a longitudinal study that will provide the opportunity to investigate not only the short-term adverse effects associated with the use of these products, but also the development of medium- and long-term health outcomes.

5.3 Methods

The present study is based on cross-sectional data collected at baseline from a longitudinal study of Italian adults. Between October 2023 and March 2024, a sample of adults aged 18–93 years was recruited via Computer-Assisted Web Interviewing (CAWI) from the DOXA (a market research company) online panel. The study sample was based on a non-probability, convenience sampling approach. The study protocol was approved by the Ethics Committee of Mario Negri Institute (Ethics Committee of Fondazione IRCCS Istituto Neurologico Carlo Besta, ID: 09, date: 9 November 2022). The inclusion criteria were an age of at least 18 years and residence in Italy. This baseline sample serves as the foundation for a prospective cohort study that will follow participants over the coming years, allowing future analyses of trends in tobacco and nicotine product use and related health outcomes.
Baseline data collection included information on tobacco and nicotine product consumption (full questions in Supplementary Box 1), covering patterns of use for each product (CC, EC and HTP), as well as the combination of these products. Patterns of use were categorized into exclusive use (CC-only, EC-only or HTP-only), dual use (combined use of two products), and poly use (combined use of the three products). Individuals included in the study were characterized according to their consumption of CC, EC, and HTP. Participants were asked to report any adverse effects they experienced during or after using each specific device. For each product, users (i.e., current smokers for CC, and both occasional and regular current users for EC and HTP) were asked whether they experienced one or more adverse events. The list of symptoms was adapted from a previously published questionnaire developed to investigate adverse events associated with e-cigarette use, either during or after its use:[18] dry cough, sore throat, mouth dryness, vertigo, headache, constriction of the respiratory tract, mouth irritation, nausea, dizziness, burns to the lips, or mouth ulcers. Participants could also report other symptoms that were not included in the list. Although originally developed in that context, the selected symptoms represent common acute manifestations reported after the use of cigarettes and other nicotine-containing products and were therefore considered suitable for comparing the overall burden of short-term adverse events across different patterns of nicotine product use. This approach, based on symptom-specific questions rather than open-ended reporting, was designed to improve data consistency and comparability. The main outcomes considered in the

analyses were the reporting of at least one adverse event and the mean number of different adverse events reported.

Statistical analysis

Descriptive analyses -proportions for categorical variables, means and standard deviations (SD) for continuous variables- were conducted to characterize our sample, focusing on the socio-demographic variables -including sex (male, female), age (18-24, 25-44, 45-64, 65+), marital status (married/cohabiting, divorced/separated, widowed, single), economic status (above the Italian mean, on average, below the Italian mean), and education level (middle school or lower, high school, university degree or higher)- and behavioral variables on tobacco and nicotine products consumption. The frequencies of exclusive and combined use of CC, EC and HTP were assessed to determine patterns of product consumption, including dual and poly use. The frequencies of adverse events experienced during or after product use, were assessed by consumption type (exclusive use, dual use, or poly use) to highlight whether different patterns of use influenced the number of different adverse events reported. Since the number of adverse events was not normally distributed, a negative binomial model was performed to compare the mean number of different adverse events associated with CC use between exclusive CC smokers and CC smokers who also used ECs or HTPs. A multivariable logistic regression model adjusted for possible confounders such as age, sex and smoking intensity (i.e., number of CC smoked per day) was used to calculate adjusted odds ratios (aOR) of experiencing at least one type of adverse event according to use patterns, comparing exclusive CC smokers with dual users of CC plus EC and/or HTP. These analyses aimed to identify significant differences in adverse event reporting based on usage patterns. All statistical analyses were performed using SAS (version 9.4).

5.4 Results

Our sample included 22,428 Italian adults (9,792 men and 12,636 women) with a mean age of 47·9 years (Supplementary Table 1). Overall, 42·7% of participants reported to be never CC smokers, 24·8% former smokers and 32·5% current smokers. Regarding ECs, 78·6% of participants had never used them, 9·1% were former users and 12·3% were current users, including 7·2% occasional users and 5·1% regular users. Finally, 81·7% of participants reported never using HTPs, 7·8% were former users and 10·6% were current users, including 5·3% occasional and 5·2% regular users (Table 1).
Patterns of exclusive and combined CC, EC and HTP use are detailed in Figure 1 and Supplementary Table 2. Out of 7,293 current smokers of CC 60·2% were exclusive smokers of CC, of 2.760 current EC users 17·9% were exclusive users of EC and of 2,369 current HTP users 12·1% were exclusive users of HTP.

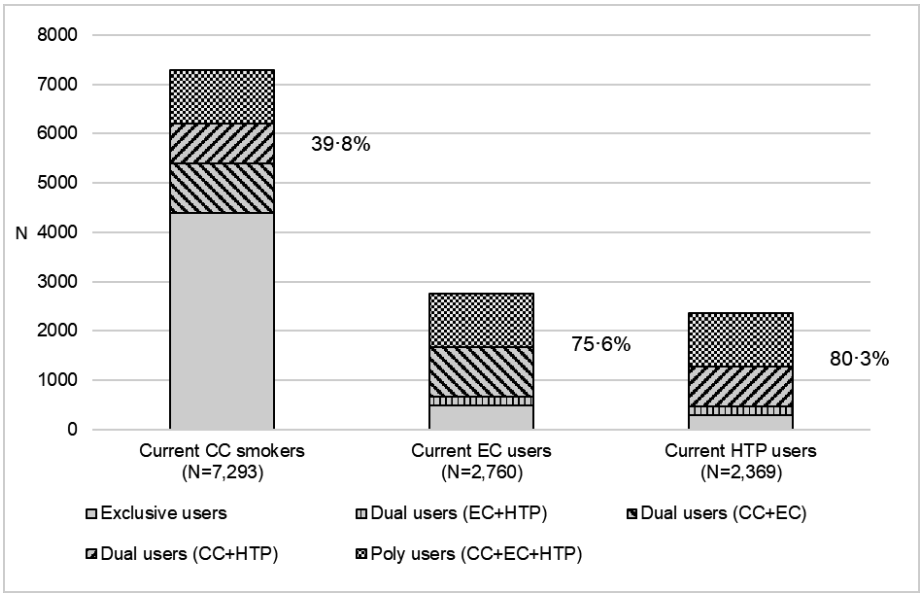
Overall, 82·1% of EC users and 87·9% of HTP users, were dual or poly users. In particular, 75·6% and 80·3% of EC and HTP users, respectively, reported also using CC. Among CC smokers, the average number of CC smoked per day was 10·7 and did not significantly differ between exclusive, dual and poly users.

Table 1. Tobacco and nicotine product use among 22,428 adults included in the study. Italy, 2023-2024.

	N (%)
Tobacco and nicotine product use[a]	
Smoking status	
Never	9,581 (42·7)
Former	5,554 (24·8)
Current	7,293 (32·5)
Electronic cigarette use	
Never	17,635 (78·6)
Past	2,033 (9·1)
Current	2,760 (12·3)
Occasional	1,616 (7·2)
Regular	1,144 (5·1)
HTP use	
Never	18,313 (81·7)
Past	1,746 (7·8)
Current	2,369 (10·6)
Occasional	1,195 (5·3)
Regular	1,174 (5·2)

HTP: heated tobacco product. [a]The full set of questions used to define and categorise tobacco and nicotine product use is reported in Supplementary Box 1.

Figure 1. Pattern of exclusive, dual, and poly use among conventional cigarette smokers, electronic cigarette users and heated tobacco product users. Italy, 2023-2024.



CC: Conventional cigarettes; EC: electronic cigarettes; HTP: heated tobacco products. Percentages indicate the proportion of users who consume CC plus EC and/or HTP. N: number of participants.

Participants reported a range of adverse events experienced during or after using each tobacco or nicotine product. The mean number of different adverse events reported was 1·41 for CC consumption, 0·78 for EC use and 0·74 for HTP use. Among CC smokers, 31·8% reported no adverse events, 29·0% reported one type of event, 19·8% two, 19·4% reported three or more types of adverse events. Among EC and HTP users 55·3% and 55·5% experienced no adverse effects, respectively, and 8·2% and 6·8%, respectively, reported three or more adverse events. Dry cough was the most frequently reported event for CC smoking (40·0%), followed by sore throat (20·9%), mouth dryness (20·2%) and vertigo (11·9%). For ECs, the most common events were mouth dryness (15·8%), dry cough (15·5%), sore throat (8·9%) and nausea (7·4%). Similarly, HTP users most commonly reported mouth dryness (15·9%), dry cough (15·2%), sore throat (8·2%) and mouth irritation (7·0%; Supplementary Figure 1, Table 2).

Table 2. Number and type of adverse events experienced during or after the use of conventional cigarettes, electronic cigarettes and heated tobacco products among 22,428 adults included in the study. Italy, 2023-2024.

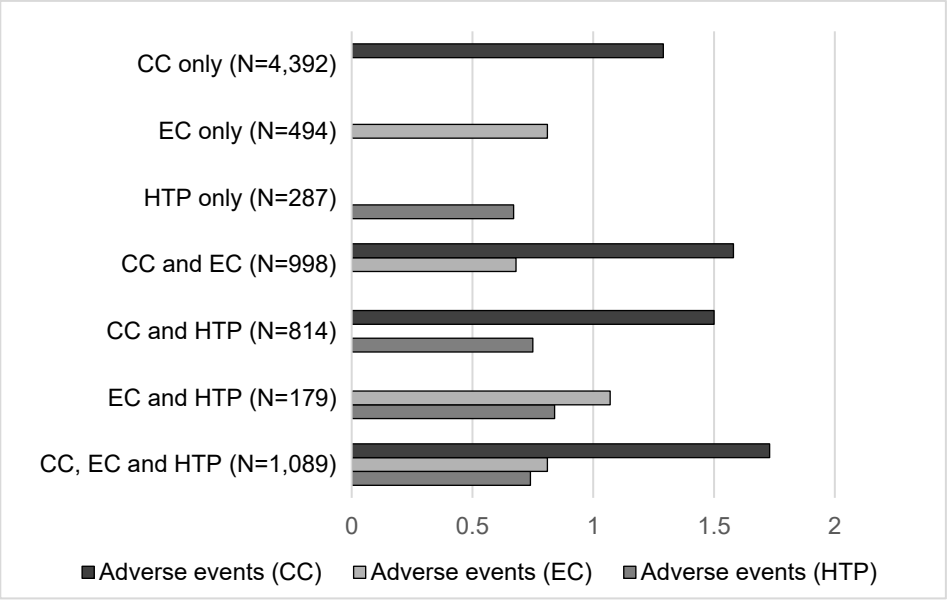
	CC use	EC use	HTP use
Average number of different adverse events reported, mean (SD)			
	1·41 (1·46)	0·78 (1·17)	0·74 (1·15)
Number of different adverse events reported, N (%)			
None	2,318 (31·8)	1,527 (55·3)	1,315 (55·5)
1	2,115 (29·0)	706 (25·6)	642 (27·1)
2	1,446 (19·8)	302 (10·9)	252 (10·6)
3	830 (11·4)	140 (5·1)	97 (4·1)
4+	584 (8·0)	85 (3·1)	63 (2·7)
Adverse event, N (%)			
Dry cough	2,919 (40·0)	429 (15·5)	360 (15·2)
Sore throat	1,521 (20·9)	247 (8·9)	194 (8·2)
Dryness at the mouth	1,475 (20·2)	435 (15·8)	376 (15·9)
Vertigo	867 (11·9)	149 (5·4)	126 (5·3)
Headache	837 (11·5)	196 (7·1)	142 (6·0)
Constriction of the respiratory tract	764 (10·5)	96 (3·5)	77 (3·3)
Mouth irritation	720 (9·9)	195 (7·1)	166 (7·0)
Nausea	507 (7·0)	203 (7·4)	147 (6·2)
Dizziness	277 (3·8)	64 (2·3)	52 (2·2)
Burn to the lips	235 (3·2)	76 (2·8)	66 (2·8)
Mouth ulcer	129 (1·8)	38 (1·4)	41 (1·7)
Other	68 (0·9)	23 (0·8)	15 (0·6)

CC: conventional cigarettes; EC: electronic cigarettes; HTP: heated tobacco products; SD: standard deviation.

Among CC smokers, mean number of different adverse events for CC smoking increased from 1·29 (SD= 1·36) for exclusive CC smokers to 1·65 (SD= 1·61; $p<0·001$ compared with exclusive CC smokers) for those also using EC, 1·63

(SD= 1·61; p<0·001) for those also using HTP and 1·73 (SD= 1·69; p<0·001) for those using EC and HTP (Figure 2, Supplementary Figure 2). In multivariable models adjusted for age, sex and smoking intensity, CC smokers also using EC (aOR: 1·32, 95% CI: 1·17-1·50), also using HTP (aOR: 1·14, 95% CI: 1·01-1·30) and also using both EC and HTP (aOR: 1·50, 95% CI: 1·29-1·75) had a higher likelihood of experiencing at least one adverse event compared to exclusive CC smokers (Supplementary Table 3).

Figure 2. Average number of different adverse events experienced during or after the use of conventional cigarettes, electronic cigarettes or heated tobacco products, by pattern of product consumption among 22,428 adults included in the study. Italy, 2023-2024.



CC: Conventional cigarettes; EC: electronic cigarettes; HTP: heated tobacco products.

5.5 Discussion

In this study, we analyzed baseline data from a large sample of Italian adults to investigate patterns of use of tobacco and nicotine-containing products, as well as adverse events associated with their use. To our knowledge, this is among the first population-based studies comparing the burden of self-reported short-term adverse symptoms across exclusive, dual and poly users of cigarettes, ECs and HTPs. Our findings revealed that exclusive use of ECs and HTPs is uncommon, with most users opting for dual or poly use, combining these products with CCs. Dual users of CCs and novel tobacco and nicotine products reported a higher number of different adverse events during or after cigarette smoking compared

with CC-only smokers, highlighting the increasing harm of combining conventional and novel products.

Among current EC users, only fewer than one in five were exclusive users, while the majority combined their use with other tobacco products. Similarly, among current HTP users, only one in eight were exclusive users, while the rest were dual or poly users. Dual use with CCs was particularly prevalent, with three quarters of EC users and four fifths of HTP users also smoking CCs. These findings confirm that large majority of users of novel products combine them with existing or acquired smoking behavior, rather than using them as an alternative. This pattern of dual or poly use underlines the limited role of these devices in promoting complete cessation of conventional smoking. Instead, it may reflect a common behavior of using novel devices alongside CCs to obtain nicotine in places where cigarette use is prohibited. Our results are in broad agreement with previous findings. A recent systematic review based on representative samples found that about two-thirds of HTP users were dual users, combining HTP use with conventional cigarettes.[5] In addition, independent research shows that smokers who use novel products are less likely to quit than exclusive smokers.[7, 11, 12] The low prevalence of exclusive use of novel products observed in our sample supports this interpretation and highlights the ineffectiveness of novel tobacco products in promoting effective smoking cessation.

A substantial proportion of CC smokers enrolled in our study reported symptoms such as dry cough, sore throat, and mouth dryness. These results reinforce the extensive body of literature linking smoking to both immediate and long-term health consequences.[1, 2] Interestingly, our data also show that ECs and HTPs are far from free of adverse effects. Users of these devices reported a variety of symptoms, some of which overlap with those experienced by CC users (e.g., dry cough, mouth dryness), and others potentially more specific to these products, such as nausea. These findings are consistent with evidence from the literature and with WHO guidelines, which warn that novel tobacco products emit harmful chemicals that can cause adverse effects.[1, 13-16] While novel products are often marketed as safer alternatives to smoking, our findings highlight their potential to cause immediate discomfort and adverse health effects, raising concerns about their public health impact.

By investigating the relationship between patterns of use and adverse events, we found that with the same intensity of CC smoking, dual users of CCs and novel tobacco products reported a significantly higher number of different adverse events, than exclusive CC smokers. This finding supports a growing hypothesis in the literature that dual use may have worse health consequences than smoking alone. The most recent meta-analysis on the topic found that current dual use of CC and EC was associated with 20 to 40% higher odds of disease, than CC-only smoking.[16] A recent case-control study in the United States of nearly 5,000 lung cancer cases and more than 27,000 controls showed that dual users of CC and

EC had a fourfold increased risk of lung cancer compared with exclusive CC smokers.[17] This substantial increase in risk among dual users is thought to be due to combined effects of exposure to harmful chemicals in both conventional smoke and aerosol emissions from e-cigarettes [19, 20]. Our findings support this hypothesis by showing that dual users of CC plus EC and/or HTP experience more frequent adverse events, even in the short term. It is plausible that the combined use of multiple products increases exposure to different toxicants, exacerbates inflammation and may contribute to carcinogenesis and respiratory damage [17, 21]. Further research is needed to confirm these mechanisms and to better understand the long-term effects of dual use, particularly in relation to cancer risk and other chronic diseases.

As our sample was recruited using a convenience sampling approach, it is not representative of the general population, limiting the generalizability of the results. However, the distribution of the sample in terms of age, sex and geographical area is comparable to that of the Italian population. In addition, the large sample size allowed us to examine a wide range of patterns of tobacco and nicotine product use with sufficient statistical power to detect meaningful differences. This large sample also allowed detailed analyses of adverse events associated with individual products and their combinations of use, providing insights into the risks of dual and poly use. Another potential limitation is the cross-sectional nature of this baseline analysis, which prevents us from inferring causal relationships between patterns of use and the occurrence of adverse events, as well as determining the temporal sequence of product initiation among dual and poly-users. Therefore, while our findings suggest associations between combined product use and higher likelihood of adverse events, they should not be interpreted as causal. Longitudinal follow-up of the cohort, already planned for the coming years, will address this limitation and allow prospective assessment of adverse events and long-term health effects of these products, which are currently under-researched. Moreover, a potential limitation of this study is that all data were collected through self-reported questionnaires. This approach is inherently subject to potential recall bias, reporting bias, and misclassification in both exposure (product use and intensity) and outcomes (adverse events). Furthermore, residual confounding cannot be ruled out, since we were unable to take into account all the potential covariates (e.g., years of exposure to tobacco/nicotine products and lifestyle factors) that could affect the occurrence of adverse events. Future studies should aim to replicate and expand upon our findings using smaller, more controlled samples with validated measurement tools. Finally, our study focused exclusively on adults, and the small proportion of young adults (18-24 years) in our sample -one in forty- did not allow meaningful stratified analyses. Since adolescents and young adults may show distinct patterns of product use and increased vulnerability to adverse effects, future research should specifically address these age groups. The adverse event

questionnaire was based on a previously published instrument originally developed for e-cigarette users. Although the symptoms included are common acute manifestations potentially experienced after the use of different nicotine-containing products, the questionnaire was not designed to identify product-specific adverse effects. Therefore, our findings should be interpreted as describing differences in the burden of self-reported symptoms across patterns of nicotine product use rather than establishing causal effects attributable to individual products.

Conclusions

In conclusion, our findings indicate that exclusive use of EC and HTP is rare, suggesting that these devices are not being adopted as alternatives to CC, but that most users combine them with conventional smoking through dual or poly use. These dual users of CCs and novel tobacco and nicotine products have an increased likelihood of experiencing adverse events compared with CC-only smokers. Also, the mean number of different adverse events experienced during or after CC smoking is significantly higher in dual or poly users. To this number we must add the number of adverse events due to EC or HTP use, which is far from negligible. Therefore, our findings are consistent with the growing evidence of a higher health risk for dual users compared to CC-only smokers, suggesting that EC and HTP may undermine rather than support tobacco control efforts. Additional longitudinal and comparative studies are needed to improve our understanding of the health impacts of exclusive and combined use of novel nicotine and tobacco containing products.

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Supplementary Materials available online at:
https://www.tobaccopreventioncessation.com/Adverse-events-associated-with-dual-and-poly-use-of-conventional-cigarettes-electronic,210416,0,2.html

Chapter 6

The role of novel nicotine-containing products on SARS-CoV-2 infection and COVID-19 progression: a systematic review and meta-analysis

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(as Letter to the Editor)

6.1 Abstract

Background: Some researchers speculated that novel nicotine-containing products could lower the risk of SARS-CoV-2 infection. We aim to investigate the role of such products on SARS-CoV-2 infection and COVID-19 progression.

Methods: We conducted a systematic literature review and meta-analysis (updated to February 2023) on all the studies providing data on the link between electronic cigarette (e-cig) and heated tobacco product (HTP) use, and SARS-CoV-2 infection and COVID-19 progression, using PubMed/MEDLINE and Web of Science. PROSPERO: CRD42020207003.

Results: Starting from 553 non-duplicate publications, we found 18 original articles. The pooled odds ratio (OR) of SARS-CoV-2 infection for e-cig users vs. e-cig never/non-users, based on 13 studies (4 cohort and 9 cross-sectional studies), was 1.31 (95% confidence interval, CI: 1.09-1.58). Six studies (4 cohort and 2 cross-sectional studies) provided estimates of COVID-19 progression according to novel product use: none of them found a significant decreased risk of COVID-19 progression among novel product users, while significant increased risks were found regarding hospitalization, severity outcomes and long COVID symptoms. Three cross-sectional studies investigated the association between HTP use and SARS-CoV-2 infection, showing either no association or an increased risk among HTP users.

Discussion: No evidence was found on the alleged protective role of e-cig use on SARS-CoV-2 infection. On the contrary, e-cigarette use is significantly associated with a 30% increased risk of infection. Novel product use might also increase the risk of COVID-19 progression.

6.2 Introduction

The WHO, supported by several scientific studies, have highlighted the health risks of using electronic cigarettes (e-cigs), particularly related to respiratory disorders [1-3]. Heated tobacco products (HTPs) produce selected toxicants and carcinogens in lower concentrations than conventional cigarettes, but they emit others not generated by conventional cigarettes, having uncertain impact on health but for sure being not risk-free [4]. To date, there is no scientific literature on the medium- and long-term health effects of e-cigs and HTPs. In addition to safety issues, there is substantial concern about the public health consequences of e-cigs and HTPs, such as the renormalization of cigarette smoking and the use of these products among young adults and ex-smokers as a gateway to conventional smoking initiation and relapse, respectively [1, 5]. A recent longitudinal study by Gallus et al. showed that novel products do not seem to be an effective tool for tobacco control. In fact, both e-cig and HTP use predicted starting smoking conventional cigarettes among never smokers and relapse among ex-smokers, and appeared to reduce smoking cessation among smokers [6]. For these reasons the WHO recommends to consider HTPs as conventional tobacco products and discourage the use of e-cigs also as a smoking cessation tool for smokers [1].

A relatively low smoking prevalence among COVID-19 patients was observed [7]. Some researchers, whose link to the tobacco industry cannot be ruled out in some cases [8], speculated that nicotine could have a protective effect against SARS-CoV-2, and consequently that e-cigs could reduce the risk of SARS-CoV-2 infection [9-11].Also a systematic review of the literature suggested that nicotine containing products might be used to support smokers to stop as part of public health efforts during the COVID-19 pandemic [7].

Several systematic reviews and meta-analyses have investigated the role of conventional cigarette smoking on COVID-19 severity and mortality, suggesting a direct association between cigarette smoking and risk of progression of COVID-19 [7, 12, 13]. However, there is lack of summary evidence regarding the role of e-cigs and HTPs on SARS-CoV-2 infection and COVID-19 progression.

This systematic review and meta-analysis was conducted to investigate the role of novel nicotine-containing products on SARS-CoV-2 infection and COVID-19 progression.

6.3 Methods

We conducted a systematic literature review on all the studies providing data on the link between e-cig and HTP use, and SARS-CoV-2 infection or COVID-19 progression (hospitalization, severity or mortality). Moreover, a meta-analysis was conducted to quantify the association between e-cig use and SARS-CoV-2 infection. The study followed the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) reporting guideline. The protocol of this study was published on PROSPERO (CRD42020207003).

The literature search was conducted in two main scientific databases (i.e., PubMed/MEDLINE and Web of Science; WoS), and the search strings used are provided in Supplementary Table 1.

We included in the systematic review observational studies with e-cig use and/or HTP use as exposure variables and SARS-CoV-2 infection and/or COVID-19 progression as outcomes. Publications written in a language other than English or not published in peer-review journals indexed in PubMed/MEDLINE or WoS (e.g., articles posted in pre-print archives only) were excluded from the review. No restriction on study participants (e.g., age group, sex) or setting were applied. Studies eligible for the meta-analysis provided relative risks (RR) or hazard ratios (HR) or prevalence ratios (PR), or odds ratios (OR) of SARS-CoV-2 infection for e-cig users compared with non-users.

Using our search strategy on 7 February 2023, we identified 437 publications in Pubmed/MEDLINE and 442 publications in WoS. After deleting duplicates, a total of 551 articles were obtained (Figure 1). An EndNote library (version: EndNote X7) was created to include all the publications identified by our search strings. Titles and abstracts of all the 551 peer-reviewed original publications identified in the traditional review were screened to identify publications that met the inclusion criteria of the present review (first screening). The full texts of all the potentially eligible publications were retrieved and independently assessed for eligibility (second screening), resulting in 18 eligible articles, including two additional articles from other sources not found in the literature search (Supplementary Table 2). Of them, 14 provided data on the risk of SARS-CoV-2 infection (13 eligible for meta-analyses, comparing e-cig users with non-users) and 6 provided data on the risk of COVID-19 progression (Figure 1).

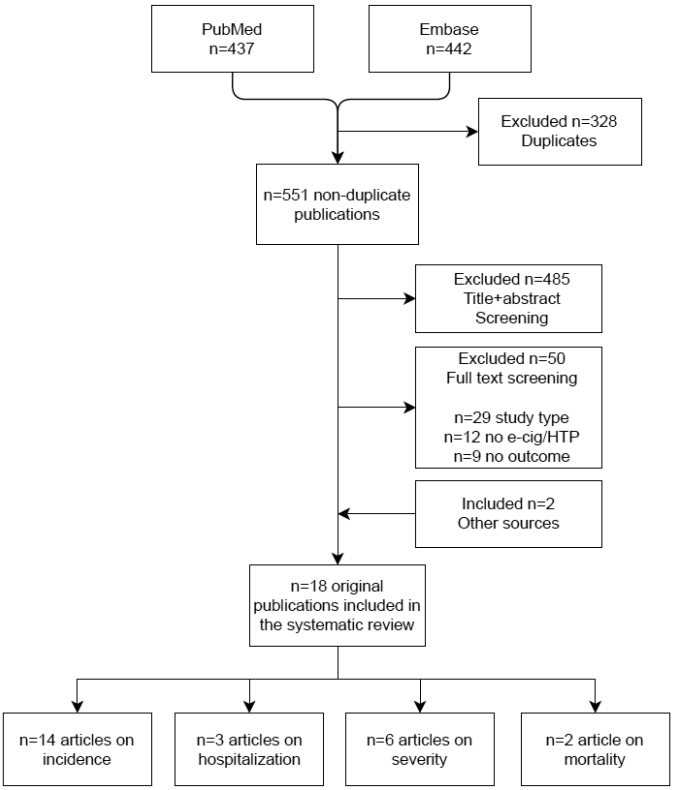
A standardized form in Microsoft Excel was used to extract data. For each publication, the following relevant information was extracted: first author, year of publication, journal, source of identification, study design, country, study name, type of population, the number of individuals, the device used, RR or HR or PR, or OR, the corresponding 95% confidence interval (CI), and the model used to derive it (with the list of covariates).

The use of e-cigs (or HTPs) was reported in different forms across the included studied. When more than one exposure was provided, we prioritized them in the following order: 1) e-cig users (including dual e-cig and cigarette users) vs e-cig non-users (including cigarette smokers); 2) e-cig users (including dual e-cig and cigarette users) vs non-users (neither e-cig nor cigarette); 3) dual users vs non-users (neither e-cig nor cigarette); and 4) exclusive e-cig users vs non-users (neither e-cig nor cigarette).

Most of the studies provided results as ORs. For the few studies providing HRs, RRs or PRs, the measures were assumed as proxies of ORs. We used random-

effects meta-analytic approaches to derive summary estimates of the OR of SARS-CoV-2 infection for e-cig users versus e-cig non-users. When necessary and possible, we computed estimates of OR by pooling the ORs for various categories (e.g., dual and exclusive users or daily and occasionally users), using the Hamling method [14]. We used the I^2 statistic to assess heterogeneity among studies [15].All statistical analyses were performed using the software SAS (Version 9.4) and R (Version 4.2.1).

Figure 1. Flow-chart of the systematic review.



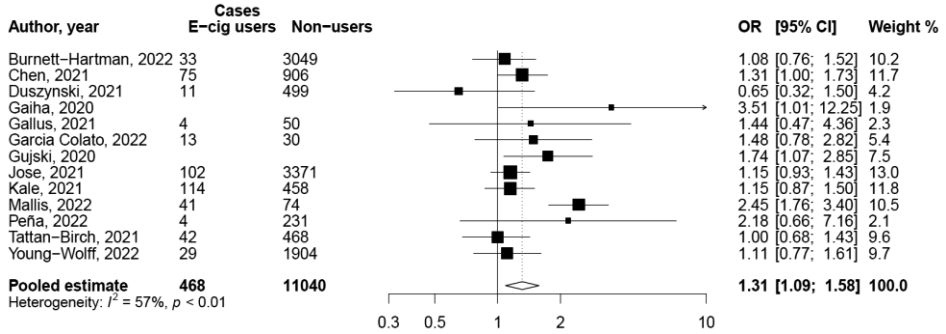
6.4 Results

Study characteristics of the 18 included publications on the association between e-cig and HTP use and SARS-CoV-2 infection and COVID-19 progression are provided in Supplementary Table 2. The age range was heterogenous among the included studies, with four of them focusing on adolescents or young adults. All studies but one provided adjusted OR estimates.

Out of 14 eligible publications on SARS-CoV-2 infection, 13 studies provided data on the risk of SARS-CoV-2 infection for e-cig users compared with non-users, based on a total sample of more than 300,000 individuals and more than 12,000

COVID-19 cases, while the remaining study focused only on HTP users. A pooled OR of 1.31 (95% CI: 1.09-1.58; Figure 2) of SARS-CoV-2 infection was found for e-cig users compared with non-users. Three studies provided estimates on the association between HTP use and SARS-CoV-2 infection (Supplementary Table 3). One of them found a significant increased risk of SARS-CoV-2 infection for both HTP exclusive users, the OR being 1.65 (95% CI: 1.26-2.15), and HTP dual users (i.e., HTPs and conventional cigarettes), the OR being 4.66 (95% CI: 3.89-5.58).

Figure 2. Forest plot of pooled odds ratio for SARS-CoV-2 infection for e-cig users versus non-users.



CI: confidence interval; OR: odds ratio.

Six studies provided estimates on the association between novel nicotine-containing product use and COVID-19 progression (Table 1): four focused on e-cig use, one on HTP use and one on both e-cig and HTP use. Several outcomes were considered in these studies, including hospitalization, oxygen administration, admission to intensive care unit (ICU), death, long COVID (i.e., presence of symptoms after 12 weeks since COVID-19 diagnosis), and other COVID-19-related symptoms. Regarding e-cig use, the study by McFadden et al. found a significant increased risk of experiencing eight COVID-19 symptoms for e-cig users compared with non-smokers (neither e-cig nor conventional cigarette users), while the study by Whitaker et al. found a significant increased risk of symptoms at 12 weeks for e-cig users compared with non-users (OR=1.11; 95% CI: 1.01-1.21). The study by Nishimura et al. found a significant increased risk of COVID-19 hospitalization (OR=2.35; 95% CI: 1.76-3.16), and mortality (OR=2.78; 95% CI: 1.97-3.92) for HTP users compared with HTP non-users.

Table 1. Results from six original publications providing adjusted estimates -odds ratios (OR) or hazard ratios (HR)- on the association between electronic cigarette (e-cig) or heated tobacco product (HTP) use and COVID-19 progression (i.e., hospitalization, severity or mortality).

First Author, year [reference]	**Device**	**Outcome**	**OR (95% CI)**
Burnett-Hartman, 2022 [16]	E-cig	Hospitalization or death	1.02 (0.22-4.74)
Gao, 2022* [17]	E-cig	Hospitalization	1.06 (0.88-1.28)
	E-cig	ICU admission	1.04 (0.57-1.89)
	E-cig	Mortality	1.12 (0.81-1.55)
McFadden, 2022 [18]	E-cig	COVID-19 ED visit	1.15 (0.60-2.22)
	E-cig	Congestion	1.24 (0.97-0.57)
	E-cig	Cough	1.18 (0.89-0.57)
	E-cig	Headache	**1.35 (1.03-1.75)**
	E-cig	Myalgia	**1.40 (1.11-1.76)**
	E-cig	Anosmia/dysgeusia	**1.39 (1.08-1.78)**
	E-cig	Sore throat	0.99 (0.77-1.26)
	E-cig	Fever	0.97 (0.74-1.26)
	E-cig	Chills	**1.45 (1.07-1.97)**
	E-cig	Dyspnea	1.41 (0.99-1.99)
	E-cig	Lightheaded	**1.76 (1.28-2.42)**
	E-cig	Chest pain	**1.68 (1.17-2.40)**
	E-cig	Nausea/vomiting	**1.74 (1.21-2.50)**
	E-cig	Diarrhea	**1.74 (1.18-2.56)**
	E-cig	Fatigue	1.24 (0.73-2.13)
Whitaker, 2022 [19]	E-cig	Symptoms at 12 weeks	**1.11 (1.01-1.21)**
Gallus, 2023 [20]	E-cig	Composite outcome	1.60 (0.96-2.67)
	E-cig	Mortality	1.24 (0.56-2.72)
	HTP	Composite outcome	1.21 (0.47-3.12)
	HTP	Mortality	1.16 (0.35-3.89)
Nishimura, 2023 [21]	HTP	Hospitalization	**2.35 (1.76-3.16)**
	HTP	Oxygen administration	**2.78 (1.97-3.92)**

CI: confidence interval; ED: emergency department; ICU: intensive care unit. *Results were reported in the form of HR. Estimates in bold are statistically significant at 0.05 level.

6.5 Discussion

In this systematic review, no evidence was found on the alleged protective role of e-cig use on SARS-CoV-2 infection. On the contrary, within the first systematic review and meta-analysis on the topic, we found that e-cig users had 31% higher risk of infection compared with non-users. Only three studies provided estimates on the association between HTP use and SARS-CoV-2 infection, finding either no association or an increased risk among HTP users.

In a previous meta-analysis, Simons and colleagues found a reduced risk and an equivalent risk of testing positive for SARS-CoV-2 among current and former conventional cigarette smokers compared with never smokers, respectively [7]. In that systematic review, authors identified studies on the use of alternative nicotine products in current and/or former smokers, but did not provide a pooled estimate of the association between their use and COVID-19 outcomes. However, they emphasized the role of alternative nicotine products as a tool to support smokers to stop smoking as part of public health efforts during COVID-19 pandemic, in contrast with the results of the present systematic review.

In our systematic review we found no evidence on the protective role of nicotine-containing product use on COVID-19 progression. In fact, none of the included studies found a significant decreased risk of COVID-19 progression among novel product users. Instead, significant increased risks were found for e-cig or HTP users regarding long COVID symptoms, hospitalization, oxygen administration and several other COVID-19-related symptoms.

In a large meta-analysis on the role of smoking in COVID-19 progression, Gallus and colleagues found a 30–50% excess risk of COVID-19 progression for current and former conventional cigarette smokers compared with never smokers [13]. Within the present systematic review, we were not able to provide a pooled estimate of the role of novel nicotine-containing products on COVID-19 progression, due to the limited and heterogeneous studies on the issue, but growing evidence from the literature shows that e-cig and HTP use might increase the risk of various severity outcomes among COVID-19 positive individuals.

The main challenge and limitation of this systematic review is the high heterogeneity among population characteristics and definitions of e-cig and HTP use and COVID-19-related outcomes in the included studies. Regarding population characteristics, some studies focused on students or young adults, while the majority were based on adult populations. Regarding the definition of use of novel nicotine-containing products, e-cig (or HTP) use was reported in different forms (e.g., exclusive or dual use), thus, when possible, we prioritized selected exposures or combined them to reduce heterogeneity. Regarding outcomes, we were not able to provide a pooled estimate of the risk of COVID-19 progression according to e-cig/HTP use because of the high heterogeneity of the endpoints considered. A further limitation of the meta-analysis is that most of

the included studies were cross-sectional, and only a few were prospective cohort studies, thus limiting the ability to provide evidence on the causal association between the use of e-cigs and HTPs and COVID-19 outcomes. We decided not to assess quality of eligible studies. In fact, the recommended tool to evaluate the quality of observational studies is the Newcastle-Ottawa Quality Assessment Scale (NOS) [22], available only for case-control and cohort studies (and not for cross-sectional studies). Such scale more likely detects the quality of the report rather than the quality of the study. Moreover, the scoring of most of its items is somewhat subjective.

For future research on novel nicotine-containing products, standardized definitions of use, including dual or poly-use, need to be established. The market of these products is growing rapidly and new products are constantly emerging, it is therefore important to retrieve detailed information on the devices used. When addressing COVID-19 outcomes, and more in general the health effects of novel products, future studies should also provide estimates of intensity and duration of use in order to evaluate dose-risk relationships. All the studies should provide results from multivariate analyses, with relative risks estimated, at least, after adjustment for age, sex and smoking status.

In conclusion, our systematic review is compatible with a 30% excess risk of SARS-CoV-2 infection for e-cig users versus e-cig non-users. We also ruled out a possible protective role of novel nicotine-containing product use on COVID-19 progression. Given the current widespread use of novel nicotine-containing products, our findings provide an additional reason to avoid their use.

6.6 References

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Supplementary Materials

Supplementary Table 1. Search string used in various sources for the conduction of the systematic review.

Source	Date	String	N articles
Pubmed/MEDLINE	07/02/2023	(IQOS OR "heated tobacco" OR heat-not* OR glo[tiab] OR juuls OR vape* OR vaping OR e-cigarette OR "electronic cigarette" OR e-cigarettes OR "electronic cigarettes" or "electronic nicotine" OR (ENDS AND (nicotine OR tobacco))) (covid OR covid-19 OR SARS-CoV-2)	437
Web of Science	07/02/2023	(IQOS OR "heated tobacco" OR heat-not* OR glo[tiab] OR juuls OR vape* OR vaping OR e-cigarette OR "electronic cigarette" OR e-cigarettes OR "electronic cigarettes" or "electronic nicotine" OR (ENDS AND (nicotine OR tobacco))) (covid OR covid-19 OR SARS-CoV-2)	442
Duplicates			-328
Total (non-duplicates)			551
Other sources			+2
Total			553

Supplementary Table 2. Characteristics of 18 original publications on the association between electronic cigarette (e-cig) and heated tobacco product (HTP) use and SARS-CoV-2 infection and COVID-19 progression included in the systematic review, with corresponding outcomes analysed (i.e., incidence, hospitalization, severity and mortality) and measure of association reported.

First Author, year [reference]	Country	Study design	Sample size	Age range	Outcome	Measure of association	Adjustments
Burnett-Hartman, 2022 [1]	USA	Cohort	126,475	≥18	I, S	aOR for e-cig users vs. e-cig non-users	Age, sex, BMI, smok, com, others
Chen, 2021 [2]	UK	Cohort	13,077	20-63	I	aOR for exclusive e-cig users vs. non-smokers aOR for dual e-cig and cigarette users vs. non-smokers	Age, sex, SES, com
Duszynski, 2021 [3]	USA	Cross-sectional	8214	12-60+	I	aOR for e-cig users vs. e-cig non-users	Age, sex, others
Gaiha, 2020 [4]	USA	Cross-sectional	4048	13-24	I	aOR for exclusive e-cig users vs. non-smokers aOR for dual e-cig and cigarette users vs. non-smokers	Age, sex, BMI, others

Gallus, 2021 [5]	Italy	Cross-sectional	499	18-50+	I	aOR for e-cig users vs. e-cig non-users aOR for HTP users vs. HTP non-users	Age, sex, BMI, smok, alc
Gallus, 2023 [6]	Italy	Cohort	1820	18-80+	S, M	aOR for ever e-cig users vs. e-cig never users aOR for ever HTP users vs. HTP never users	Age, sex, edu, smok, others
Gao, 2022 [7]	UK	Cohort	7,869,534	18-80+	H, S, M	aHR for e-cig users vs. e-cig non-users	Age, sex, SES, smok, others
Garcia Colato, 2022 [8]	USA	Cohort	764	≥18 (mean=20)	I	aRR for exclusive e-cig users vs. non-smokers aRR for dual e-cig and cigarette users vs. non-smokers	Age, sex, com, others
Gujski, 2020 [9]	Poland	Cross-sectional	5082	20-60+	I	aOR for daily e-cig users vs. e-cig non-users aOR for occasional e-cig users vs. e-cig non-users aOR for daily HTP users vs. HTP non-users aOR for occasional HTP users vs. HTP non-users	Age, sex, com, smok, others
Jose, 2021 [10]	USA	Cross-sectional	69,264	12-80+	I	aOR for exclusive e-cig users vs. non-smokers aOR for dual e-cig and cigarette users vs. non-smokers aOR for e-cig users vs. e-cig non-users	Age, sex, smok, others
Kale, 2021 [11]	UK	Cross-sectional	2791	18-65+	I	aOR for e-cig users vs. e-cig non-users	Age, sex, SES, smok, com, others
Mallis, 2022 [12]	USA	Cross-sectional	679	18-26+	I	PR for e-cig users vs. e-cig non-users	-
McFadden, 2022 [13]	USA	Cross-sectional	1734	18-80+	H, S	aOR for exclusive e-cig users vs. non-smokers aOR for dual e-cig and cigarette users vs. non-smokers aOR for e-cig users vs. non-smokers	Age, sex, others
Nishimura, 2023 [14]	Japan	Cross-sectional	30,130	16-81	I, H, S	aOR for exclusive HTP users vs. non-smokers aOR for dual HTP and cigarette users vs. non-smokers	Age, sex, edu, SES, smok, alc, com, others
Peña, 2022 [15]	Finland	Cross-sectional	27,098	20-75+	I	aRR for e-cig users vs. e-cig non-users	Age, sex, edu, BMI, others
Tattan-Birch, 2021 [16]	UK	Cross-sectional	3179	≥18 (mean=52.4)	I	aOR for e-cig users vs. e-cig non-users	Age, sex, SES, smok, others
Whitaker, 2022 [17]	UK	Retrospective cohort	76,155	18-74+	S	aOR for e-cig users vs. e-cig non-users	Age, sex, SES, BMI, smok, others
Young-Wolff, 2022 [18]	USA	Retrospective cohort	74,853	18-35	I	aHR for e-cig users vs. e-cig non-users	Age, sex, BMI, com, others

aHR: adjusted hazard ratio; alc: alcohol; aOR: adjusted odds ratio; aRR: adjusted relative risk; BMI: body mass index; com: comorbidities; edu: education; H: hospitalization; I: incidence; M: mortality; PR: prevalence ratio; S: severity; SES: socio-economic status; smok: smoking. The term 'others' in Adjustments column stands for all the adjusting variables other than age, sex, body mass index, alcohol, smoking, socio-economic status, education and comorbidities.

Supplementary Table 3. Results from three original publications providing adjusted estimates -odds ratios (OR)- on the association between heated tobacco product (HTP) use and SARS-CoV-2 infection.

First Author, year [reference]	**Measure of exposure**	**OR (95% CI)**
Gallus, 2021 [5]	HTP users vs. HTP non-users	1.57 (0.62-3.97)
Gujski, 2020 [9]	Daily HTP users vs. HTP non-users	0.73 (0.26-2.05)
	Occasional HTP users vs. HTP non-users	1.87 (0.91-3.84)
	HTP users vs. HTP non-users*	1.26 (0.51-3.13)
Nishimura, 2023 [14]	Exclusive HTP users vs. non-smokers	**1.65 (1.26-2.15)**
	Dual HTP and cigarette users vs. non-smokers	**4.66 (3.89-5.58)**
	HTP users vs. HTP non-users*	**3.03 (2.58-3.55)**

CI: confidence interval. *Results estimated with the Hamling method. Estimates in bold are statistically significant at 0.05 level.

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Chapter 7

Attitudes towards tobacco and nicotine control policies in Italy: insights from a 2024 national survey

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7.1 Abstract

Introduction: This study assesses the Italian population's support for innovative tobacco control policies, which aims at reducing use of nicotine-containing products and exposure to secondhand smoke and aerosol.

Methods: A cross-sectional study was conducted in 2024 among a representative sample of 3,125 Italian adults. We assessed support on banning tobacco sales to people born after a certain year (Smoke-Free Generation, SFG), raising the minimum age for purchasing tobacco to 21 years (Tobacco 21, T21), substantially increasing tobacco taxation, banning electronic cigarettes (e-cigarette) and heated tobacco products (HTP) in indoor public places and workplaces, and prohibiting tobacco and e-cigs advertising.

Results: Support for tobacco control policies was 67.0% for the SFG policy, 72.9% for the T21 policy, 61.5% for a tax increase, 80.8% for a ban on indoor e-cigarette and HTP use in public places and 81.7% in workplaces respectively, and 78.2% for an advertising ban for all nicotine products. Support for all policies increased with age (p-values for trend ranging from <0.001 to 0.037) and was significantly lower among current smokers (support ranging from 17.9% to 59.7%). E-cigarette users showed lower support for a SFG (32.4%) and advertising bans (41.4%), while HTP users were less supportive of all policies except the T21 policy (support ranging from 13.2% to 43.9%).

Conclusion: In Italy, strong public support exists for new tobacco control laws, especially among never smokers and non-users of novel products. However, also a considerable proportion of current smokers, e-cigarette and HTP users support these policies. Policymakers can confidently advance these strategies, while public campaigns should target less supportive groups.

7.2 Introduction

Cigarette smoking is a leading cause of preventable mortality and morbidity worldwide, responsible for about 8 million deaths annually, including 1 million due to secondhand smoke (SHS) [1, 2]. In Italy, tobacco use is responsible for more than 70,000 deaths per year, representing 15% of all deaths [3]. The economic burden of smoking is also significant, with smoking-related hospital admissions costing more than €1.5 billion annually [4].

Italy was a pioneer in the fight against tobacco and SHS exposure, becoming the first large country to introduce comprehensive smoke-free legislation in 2003 banning smoking in indoor public places such as restaurants, bars and workplaces [5]. Since then, however, no relevant national tobacco control policy has been introduced. The Tobacco Control Scale (TCS), which quantifies the implementation of tobacco control policies based on World Bank and World Health Organization (WHO) recommendations, testifies the stagnation of Italian tobacco control policies [6]. In the latest TCS ranking, Italy placed 18th among 37 European countries, with a score of 52 out of 100, a drop of three places compared to the previous edition. Notably, Italy scored particularly low on cigarette pricing (13 points out of 30), as cigarette prices in Italy remain relatively low, around six euros per pack, compared to countries like France and the United Kingdom, where they can cost up to twice as much [7]. In addition, although current regulations in Italy explicitly prohibit the sale of tobacco and nicotine products to minors, enforcement appears inconsistent, and underage access remains a critical issue. Despite the legal framework designed to protect youth, evidence suggests that minors still manage to obtain and use these products, highlighting the urgent need for more effective enforcement strategies [8].

Legislative proposals such as banning the sale of tobacco to people born after a certain year (Smoke-Free Generation policy, SFG), raising the minimum age for purchasing tobacco to 21 years (Tobacco 21 policy, T21), and increasing taxes on conventional cigarettes are gaining international attention and have been demonstrated to be effective in reducing tobacco initiation and consumption other developed countries [9-11]. Despite the potential benefits of these policies, their implementation, compliance and success depend heavily on public support [5, 12, 13]. Laws that restrict access to tobacco, particularly the SFG, may be perceived by the public as an infringement of personal freedom. However, recent research suggests that support for policies aimed at reducing tobacco consumption and SHS exposure is relatively high in the Italian and European populations [14, 15].

The growing popularity of electronic cigarettes (e-cigarettes) and heated tobacco products (HTP) has raised concerns about the renormalization of tobacco use and dual use [16]. These products are widely used by young people, potentially leading to nicotine addiction and long-term health consequences [17]. These products are marketed as potentially less harmful alternatives, however

independent research is cautious about this “harm reduction” claim [18]. The lack of a complete ban on these products in indoor public places and workplaces means that people are exposed to potentially harmful substances of the secondhand aerosol (SHA). In addition, this regulatory gap has led to widespread dual use, where people smoke conventional cigarettes outdoors and use e-cigarette and HTP indoors or in settings where conventional smoking is prohibited [19]. Recent evidence suggests that this pattern of consumption may be particularly harmful [18, 20]. In response to these concerns, policies banning their use in indoor public places and workplaces, as well as prohibiting tobacco and e-cigarette advertising, have been proposed to prevent further normalization of tobacco consumption and reduce SHA exposure [21].

Despite some recent research [14, 15], there is an important gap in the existing research on support for new policies conducted on representative samples of the Italian population. Furthermore, the current literature lacks studies that thoroughly examine the determinants of support for specific tobacco control policies. This gap limits the understanding of the socio-demographic dynamics that influence public opinion on such regulations. A better understanding of these factors is crucial for promoting effective policies and gaining the public support needed to implement new tobacco control measures in Italy.

Recognizing the importance of public opinion, this study aims to assess the levels of support for potential tobacco control legislation in Italy using a representative sample of the Italian population. Particularly, this analysis will focus on the SFG policy initiative, the T21 policy, the tax increase on conventional cigarettes, the ban on e-cigarette and HTP use in indoor public places and workplaces respectively, and the ban on tobacco and e-cigarette advertising. Furthermore, we intend to investigate socio-demographic determinants that influence individuals' support to specific tobacco control measures.

7.3 Methods

The data used in this study come from a cross-sectional survey conducted between March and September 2024 by the Istituto di Ricerche Farmacologiche Mario Negri (IRFMN), with fieldwork performed by DOXA. The sample comprised of 3125 participants (1515 men and 1610 women) representative of the Italian population aged 15 and over in terms of sex, age, geographical area and socio-economic characteristics. The Ethics Committee of Istituto Neurologico Carlo Besta–Milano acknowledged the collection of anonymous data in face-to-face population-based, observational, cross-sectional studies (File number 37, 2017). For participants aged 15 to 17 years, informed verbal consent was explicitly obtained from a parent or legal guardian prior to the interview, along with presentation and signature of the written information sheet, which was retained by the survey team.

Participants were selected using a multi-stage sampling technique to ensure representativeness. First, municipalities in all 20 Italian regions were selected on the basis of the size of the region and the municipality. Next, a random selection of electoral districts within each municipality was made. Individuals were then randomly selected from the electoral lists to ensure stratification by sex and age. For young people aged 15-17 who were not on the electoral rolls, a quota sampling approach was used, focusing on both sex and exact age. If a selected participant was unavailable or declined to participate, he or she was replaced with an individual who matched the sex, age group, and area of residence (same municipality and same district). This substitution process was designed to preserve the representativeness of the final sample.

Interviews were conducted by trained interviewers using a structured questionnaire administered via computer-assisted face-to-face interviews in participants' homes (CAPI mode). The questionnaire collected general socio-demographic information, smoking status, and use of novel nicotine containing product (e-cigarette and HTP). Participants' level of education was classified as low for those who completed middle school or less, intermediate for high school graduates, and high for university graduates or beyond. Never smokers were defined as individuals who reported having smoked fewer than 100 cigarettes in their lifetime. Former smokers were those who had smoked 100 or more cigarettes in their lifetime but had quit smoking from at least one year. Current smokers were defined as those who reported having smoked 100 or more cigarettes in their lifetime and who were currently smoking cigarettes or had quit within the past year. In addition to smoking status, the questionnaire also collected information on the use of e-cigarette and HTP use. Individuals were categorised as e-cigarette users if they reported current use (daily or occasional) of any type of e-cigarettes, including disposable, cartridge-based or rechargeable e-cigarettes containing nicotine salts. Individuals who reported not using any type of e-cigarette are hereafter referred to as “non-users of e-cigarettes”. For HTP use, individuals were categorised as users if they reported current use (daily or occasional) of any type of HTP, such as IQOS or Glo. Individuals who reported not using any type of HTP are hereafter referred to as “non-users of HTPs”.

A specific section of the questionnaire was dedicated to collect information regarding attitudes towards proposed tobacco control policies, including: i) Smoke-Free Generation Initiative policy (SFG): prohibiting tobacco and nicotine products sales to individuals born after a certain date (e.g., a lifetime ban on the sale of tobacco and nicotine products to people born after 1 January 2010), thereby restricting access to tobacco and nicotine throughout their lifetime; ii) Tobacco 21 policy (T21): raising the legal age of sale of tobacco and nicotine products from 18 to 21 years; iii) Increase tobacco taxation: increasing excise duties/taxes on conventional cigarettes, raising the cost of a cigarette pack from around €6 to €10, and use the revenue to support smoking cessation (e.g., free

access to smoking cessation services or free pharmacological therapies) or fund research; iv) Indoor ban of new products: banning the use of e-cigs and HTPs in indoor public places (e.g., public transport, clubs, bars, restaurants); v) Workplace indoor ban of new products: banning the use of e-cigarettes and HTPs in indoor workplaces; and vi) Advertising ban: banning advertisements for tobacco products and e-cigs, including on social networks. For each proposed regulation, participants were asked to express their level of support or opposition using the following response options: strongly in favour, in favour, against, strongly against, or does not know /does not state (Supplementary Box 1).

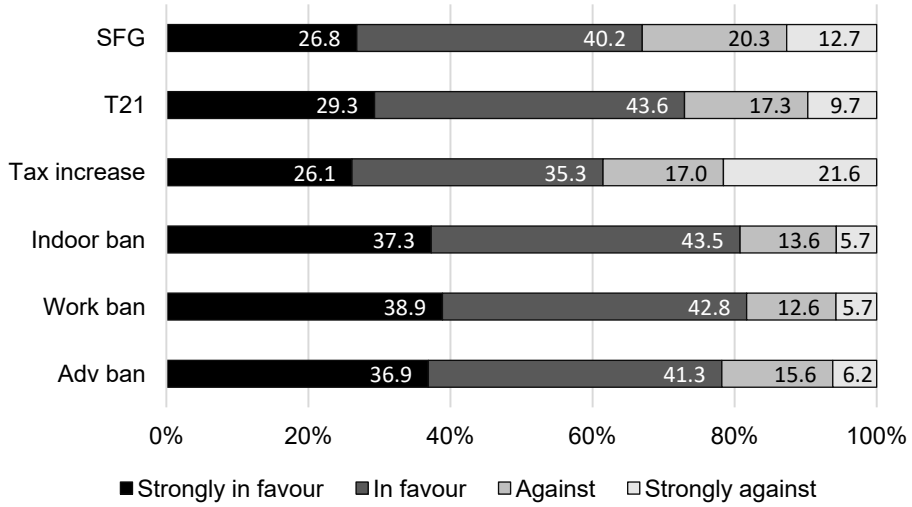
Data Analysis

Data processing included the generation of statistical weights to ensure the representativeness of the Italian population aged 15 years and over. Descriptive statistics were used to summarise the main findings. We estimated adjusted odds ratios (aOR) and corresponding 95% confidence intervals (CI) for support (in favour or strongly in favour) of the six proposed tobacco control policies based on sociodemographic and behavioural factors. aORs were estimated using unconditional multiple logistic regression models, adjusted for sex, age, educational level and geographical area. All the variables included in the analyses were complete, with no missing values. Therefore, no imputation or specific handling of missing data was required.
All statistical analyses were performed using the SAS statistical package, version 9.4 (SAS Institute) [22].

7.4 Results

Figure 1 shows the percentages of respondents according to their support to each of the six tobacco control policies. The overall percentage of favourable responses (“in favour” or “strongly in favour”) was 67.0% for the SFG policy, 72.9% for the T21 policy, 61.5% for the tax increase measure, 80.8% for the indoor ban on e-cigs and HTPs, 81.7% for the workplace ban on these products, and 78.2% for the advertising ban of all tobacco products and e-cigs.

Figure 1. Percent (%) distribution of support for selected inadequately adopted tobacco control policies in a representative cross-sectional sample of 3125 Italian adults. Italy, 2024.



SFG: smoke-free generation; T21: Tobacco 21; Tax increase: Increase excise duties/taxes on conventional cigarettes, raising the cost of a pack from about €6 to €10; Indoor ban: Ban the use of e-cigarettes and heated tobacco in indoor public places; Work ban: Ban the use of e-cigarettes and heated tobacco in indoor workplaces; Adv ban: Ban advertisements for tobacco products and electronic cigarettes, including on social networks. Full questions available in Supplementary Box 1. Percentages are calculated excluding responses "Does not know/does not state".

Regarding the SFG policy, people aged 25-44 years (aOR=1.75, 95% CI: 1.31-2.34), 45-64 years (aOR=1.92, 95% CI: 1.45-2.53), and ≥65 years (aOR=1.74, 95% CI: 1.30-2.33) were significantly more likely to support the policy than younger participants aged <25 years (p for trend =0.001; Table 1). Current smokers (aOR=0.19, 95% CI: 0.16-0.23), former smokers (aOR=0.72, 95% CI: 0.55-0.95) were less likely to support the SFG compared with never smokers. Both e-cigarette users (aOR=0.55, 95% CI: 0.32-0.96) and HTP users (aOR=0.57, 95% CI: 0.38-0.87) showed reduced support compared with non-users of e-cigarettes and non-users of HTPs. For the T21 policy, the support was higher in participants aged 25-44 years (aOR=2.49, 95% CI: 1.85-3.35), 45-64 years (aOR=3.14, 95% CI: 2.36-4.18), and ≥65 years (aOR=2.81, 95% CI: 2.08-3.79) compared to those aged <25 years (p for trend <0.001). Current smokers (aOR=0.18, 95% CI: 0.15-0.22) and former smokers (aOR=0.63, 95% CI: 0.47-0.85) were significantly less likely to support this measure compared with never smokers. For the tax increase policy, an increasing support was observed with increasing age of participants (p for trend=0.037).

Table 1. Support for tobacco control policies (smoke-free generation, SFG; Tobacco 21, T21; and Tax increase) in a representative sample of 3125 Italian adults, overall and according to socio-demographic and behavioural characteristics. Italy, 2024.

	N	SFG			T21			Tax increase[a]		
		In favour %[b]	aOR[c] (95% CI)	*p-value*	In favour %[b]	aOR[c] (95% CI)	*p-value*	In favour %[b]	aOR[c] (95% CI)	*p-value*
Total	3125	67.0	-	-	72.9	-	-	61.5	-	-
Sex										
Men	1515	66.7	Ref		70.0	Ref		58.0	Ref	
Women	1610	67.2	0.86 (0.73-1.01)	*0.069*	75.7	1.12 (0.94-1.33)	*0.212*	64.7	1.01 (0.84-1.20)	*0.959*
Age (years)										
<25	353	59.3	Ref		58.0	Ref		62.2	Ref	
25-44	808	65.4	**1.75 (1.31-2.34)**	***<0.001***	71.2	**2.49 (1.85-3.35)**	***<0.001***	56.7	1.14 (0.83-1.58)	*0.426*
45-64	1104	67.5	**1.92 (1.45-2.53)**	***<0.001***	75.0	**3.14 (2.36-4.18)**	***<0.001***	60.0	1.34 (0.98-1.83)	*0.064*
≥65	860	70.9	**1.74 (1.30-2.33)**	***<0.001***	78.0	**2.81 (2.08-3.79)**	***<0.001***	67.6	1.35 (0.98-1.86)	*0.069*
p for trend			***0.001***			***<0.001***			***0.037***	
Education[d]										
Low	973	72.0	Ref		77.1	Ref		66.5	Ref	
Intermediate	1676	64.5	0.87 (0.71-1.07)	*0.176*	70.1	0.87 (0.70-1.08)	*0.207*	59.4	0.99 (0.79-1.23)	*0.892*
High	476	65.5	0.83 (0.63-1.10)	*0.187*	74.8	1.03 (0.77-1.38)	*0.851*	58.6	0.91 (0.68-1.22)	*0.523*
p for trend			*0.153*			*0.933*			*0.554*	
Smoking status										
Never	1928	76.7	Ref		82.4	Ref		79.6	Ref	
Current	830	41.1	**0.19 (0.16-0.23)**	***<0.001***	48.8	**0.18 (0.15-0.22)**	***<0.001***	17.9	**0.06 (0.04-0.07)**	***<0.001***
Former	366	74.2	**0.72 (0.55-0.95)**	***0.022***	78.7	**0.63 (0.47-0.85)**	***0.003***	68.1	**0.50 (0.39-0.66)**	***<0.001***
E-cigarette use[e]										
Non-user	3054	67.8	Ref		73.7	Ref		62.4	Ref	
User	71	32.4	**0.55 (0.32-0.96)**	***0.036***	43.0	0.67 (0.40-1.11)	*0.124*	23.6	0.96 (0.50-1.83)	*0.896*
HTP use[f]										
Non-user	2985	68.6	Ref		74.5	Ref		63.8	Ref	
User	139	31.2	**0.57 (0.38-0.87)**	***0.008***	40.5	0.69 (0.47-1.01)	*0.057*	13.2	**0.48 (0.27-0.84)**	***0.010***

[a]Increase excise duties/taxes on conventional cigarettes, raising the cost of a pack from about €6 to €10, full question available in Supplementary Box 1; [b]Respondents answering to be "in favour" or "strongly in favour". Percentages are calculated excluding responses "Does not know/does not

state" (which ranged from 1.6% to 5.1%); [c]aORs are estimated with unconditional logistic regression models adjusted for sex, age, education, geographical area and smoking status; [d] Level of education was classified as low for those who completed middle school or less, intermediate for high school graduates, and high for university graduates or beyond; [e] Individuals who reported not using any type of e-cigarette are referred to as non-users; [f] Individuals who reported not using any type of HTP are referred to as non-users; CI: confidence interval; HTP: heated tobacco product. Statistically significant estimates at 0.05 level are in bold.

Current smokers (aOR=0.06, 95% CI: 0.04-0.07) and former smokers (aOR=0.50, 95% CI: 0.39-0.66) were significantly less supportive towards increasing tobacco taxation, as were HTP users (aOR=0.48, 95% CI: 0.27-0.84). No statistically significant differences were observed in support of these measures according to participants' sex and level of education. Support for a ban on e-cigarette and HTPs use in indoor public places was significantly higher among older participants (Table 2). Older people were more likely to support the indoor ban compared to participants aged <25 years (p for trend <0.001). Current smokers and HTP users were significantly less supportive of the indoor ban (aOR=0.18, 95% CI: 0.15-0.23, and aOR=0.42, 95% CI: 0.29-0.61, respectively). Participants aged 25-44 years (aOR=1.41, 95% CI: 1.00-1.98), 45-64 years (aOR=1.58, 95% CI: 1.14-2.19) and ≥65 years (aOR=1.60, 95% CI: 1.13-2.26) showed higher support for banning e-cigarette and HTP use in indoor workplaces compared to those aged <25 years (p for trend =0.012). Current smokers (aOR=0.16, 95% CI: 0.13-0.20) and HTP users (aOR=0.42, 95% CI: 0.29-0.62) were significantly less supportive of this policy. Participants aged 45-64 years (aOR=1.95, 95% CI: 1.43-2.65) and those aged ≥65 years (aOR=2.03, 95% CI: 1.46-2.83) were more in favour of the advertising ban than those aged <25 years (p for trend <0.001). Individuals with higher level of education were more likely to support the measure (aOR=1.41, 95% CI: 1.03-1.93) than those with lower level education. Current smokers (aOR=0.21, 95% CI: 0.17-0.26) and former smokers (aOR=0.64, 95% CI: 0.47-0.89) were less likely to support the advertising ban, and both e-cigarette users (aOR=0.45, 95% CI: 0.27-0.76) and HTP users (aOR=0.48, 95% CI: 0.33-0.71) were also significantly less supportive. No statistically significant differences in support of the three policies were observed according to sex.

Table 2. Support for tobacco control policies (indoor ban of electronic cigarettes, e-cigarette, and heated tobacco products; ban of e-cigs and HTPs in workplaces; and advertising ban of e-cigarettes and HTPs) in a representative sample of 3125 Italian adults, overall and according to socio-demographic and behavioural characteristics. Italy, 2024.

	N	Indoor ban			Work ban			Adv ban		
		In favour %[a]	aOR[b] (95% CI)	*p-value*	In favour %[a]	aOR[b] (95% CI)	*p-value*	In favour %[a]	aOR[b] (95% CI)	*p-value*
Total	3125	80.8	-	-	81.7	-	-	78.2	-	-
Sex										
Men	1515	78.9	Ref		79.7	Ref		76.2	Ref	
Women	1610	82.5	1.04 (0.86-1.26)	*0.709*	83.5	1.07 (0.87-1.30)	*0.534*	80.1	1.03 (0.85-1.24)	*0.783*
Age (years)										
<25	353	76.6	Ref		78.3	Ref		72.8	Ref	
25-44	808	78.3	**1.40 (1.00-1.94)**	***0.047***	79.6	**1.41 (1.00-1.98)**	***0.048***	72.5	1.20 (0.88-1.64)	*0.260*
45-64	1104	80.5	**1.62 (1.19-2.23)**	***0.003***	81.6	**1.58 (1.14-2.19)**	***0.006***	80.1	**1.95 (1.43-2.65)**	***<0.001***
≥65	860	85.1	**1.83 (1.30-2.57)**	***<0.001***	85.2	**1.60 (1.13-2.26)**	***0.009***	83.5	**2.03 (1.46-2.83)**	***<0.001***
p for trend			***<0.001***			***0.012***			***<0.001***	
Education[d]										
Low	973	82.9	Ref		83.5	Ref		80.6	Ref	
Intermediate	1676	79.2	1.04 (0.82-1.32)	*0.741*	80.7	1.06 (0.83-1.35)	*0.660*	76.2	1.01 (0.80-1.27)	*0.964*
High	476	82.1	1.26 (0.91-1.75)	*0.167*	81.4	1.11 (0.80-1.54)	*0.533*	80.5	**1.41 (1.03-1.93)**	***0.034***
p for trend			*0.198*			*0.526*			*0.055*	
Smoking status										
Never	1928	88.7	Ref		89.9	Ref		86.3	Ref	
Current	830	59.7	**0.18 (0.15-0.23)**	***<0.001***	59.5	**0.16 (0.13-0.20)**	***<0.001***	57.5	**0.21 (0.17-0.26)**	***<0.001***
Former	366	86.5	0.74 (0.53-1.04)	*0.086*	88.7	0.84 (0.58-1.21)	*0.345*	82.5	**0.64 (0.47-0.89)**	***0.007***
E-cigarette use[e]										
Non-user	3054	81.3	Ref		82.3	Ref		79.0	Ref	
User	71	58.9	0.85 (0.51-1.42)	*0.532*	57.5	0.77 (0.47-1.29)	*0.324*	41.4	**0.45 (0.27-0.76)**	***0.003***
HTP use[f]										
Non-user	2985	82.5	Ref		83.5	Ref		79.9	Ref	
User	139	43.0	**0.42 (0.29-0.61)**	***<0.001***	43.9	**0.42 (0.29-0.62)**	***<0.001***	41.8	**0.48 (0.33-0.71)**	***<0.001***

[a]Respondents answering to be “in favour” or “strongly in favour”. Percentages are calculated excluding responses “Does not know/does not state” (which ranged from 1.6% to 5.1%); [b]aORs are estimated with unconditional logistic regression models adjusted for sex, age, education, geographical area and smoking status; [d] Level of education was classified as low for those who completed middle school or less, intermediate for high school graduates, and high for university graduates or beyond; [e] Individuals who reported not using any type of e-cigarette are referred to as non-users; [f] Individuals who reported not using any type of HTP are referred to as non-users; CI: confidence interval; HTP: heated tobacco product. Statistically significant estimates at 0.05 level are in bold.

7.5 Discussion

In this study conducted on a nationally representative sample of Italian adults, we observed broad support (62% to 82%) for all the proposed tobacco control policies. Measures focused on discouraging the use of conventional cigarettes among young people with initiatives such as the SFG policy, T21 and tax increases were supported by 62% to 73% of respondents. Measures focusing on novel tobacco and nicotine products such as indoor and workplace bans of novel tobacco and nicotine products and bans on their advertising, were supported by 78% to 82% of respondents. Across all the proposed regulations support was higher among older adults and never smokers and lower, but still not negligible, among younger respondents and current smokers. These results indicate that there is a significant opportunity for the implementation of tobacco control measures in Italy, and policymakers can rely on the support of a broad base of the population, including those directly affected by these regulations.

The high level of support towards the SFG policy suggests that concerns about individual choice and generational equity are balanced by the willing to protect future generations from the harms of tobacco and nicotine addiction [23]. The support was particularly strong among older people and non-smokers, suggesting that these groups perceive such regulation as an essential measure to protect public health and future generations. The high support could be due to an increased awareness of the health risks of smoking, but also to the fact that this regulation would not directly affect the behaviour of adult respondents. Given the substantial support observed, the SFG initiative could be established as a long-term strategic objective. Meanwhile, the immediate reinforcement of existing age-related sales bans could serve as the first concrete policy action.

Similarly, as T21 directly restricts tobacco sales to people under 21, older adults are not directly subject to these restrictions and may therefore see the policy as a protective measure for younger people. This measure is particularly relevant, as most smokers start before the age of 21, and delaying smoking initiation can significantly reduce the likelihood of long-term addiction [24]. Even stricter enforcement of the existing ban on sales to minors under 18 would be beneficial, as many people take up smoking before reaching adulthood [25]. The findings on

SFG and T21 are consistent with a previous study conducted in a large convenience sample of Italian adults, which found slightly higher support for these measures (74% for SFG, 82% for T21) [15]. The lack of a representative sample in that study could explain the higher support observed. In the present study, we confirm the strong support for SFG and T21 in face-to-face interviews in a representative sample of the Italian population. This high level of support provides political momentum to advance T21 legislation in Italy. Implementation could be accompanied by targeted communication efforts aimed at young adults, with the aim of building understanding and compliance.

The proposal for a substantial increase in tobacco taxation, raising the cost of a pack from about €6 to €10 and allocating the revenue thus generated to smoking cessation support, was supported by an outstanding three out of five respondents, with lower support among current and former smokers, consistent with the notion that those who actively consume tobacco are more sensitive to price increases. Indeed, evidence from the literature shows that increasing the price of cigarettes is one of the most effective measure to reduce smoking prevalence and consumption [26]. Public support in this area could be used to advocate for fiscal policies aimed at reducing consumption while generating resources for cessation services and prevention campaigns. The high level of support overall may also be due to an understanding that price increases would lead to increased revenues that could then be reinvested in public health initiatives. In fact, it has been shown that an increase in prices would lead to higher revenue, which could be therefore reinvested in public health efforts [26]. Concerns have been raised about the disproportionate financial burden of price increases on lower-socioeconomic (SES) groups. However, an increase in prices does not necessarily imply that tax increases are also disproportionately burdensome on lower-SES populations. In fact, tobacco use among individuals of lower-SES is more responsive to changes in price, while higher-SES populations exhibit less sensitivity. As a result, a tax increase that raises tobacco prices will lead to the largest declines in smoking among lower-SES individuals, placing a greater burden on higher-SES consumers [27]. At the same time, the reduction in consumption in lower-SES groups would lead to a reduction in smoking-related diseases and the associated costs borne by individuals.

The literature has consistently shown that both T21 and price increases are effective in reducing smoking initiation and promoting smoking cessation. Indeed, studies indicate that raising the legal age for purchasing tobacco to 21 could significantly decrease the likelihood of young adults starting to smoke [28], while substantial increases in tobacco prices have been linked to lower consumption rates and higher cessation rates, especially among youth and lower-income groups [29]. Given the proven effectiveness and broad public support, these

policies could be considered strong candidates for implementation within a comprehensive tobacco control strategy in Italy.

The promotion of smoke and aerosol-free environments is essential to protect public health and reduce the harm caused by tobacco and nicotine products. Equalizing legislation for novel products with conventional cigarettes is crucial for public health protection [21]. In this context, around four out of five respondents were in favour of banning e-cigarettes and HTPs from indoor public places and indoor workplaces. This high level of support not only reflects concerns about public health due to exposure to HTP aerosol but also suggests a general discomfort, particularly among people who do not use e-cigarettes or HTPs, with being exposed to SHA [30, 31]. Support for both measures was significantly higher among older participants and non-smokers, who are usually less accustomed to these new products [32]. Older people may also recall more vividly the implementation of the comprehensive 2005 smoke-free legislation and recognise its effectiveness in reducing exposure to tobacco smoke and SHS [33], which may strengthen their support for extending similar restrictions to novel tobacco and nicotine products. HTP users were less likely to support these measures as they directly restrict the use of such products. However, still over 40% of HTP users and over half of e-cigarette users supported these measures, along with over 80% of other respondents, indicating potential for these laws to gain widespread support. These results provide a compelling rationale for revising current legislation to include novel products within existing indoor smoking bans. This would restore clarity to the regulations and address the growing public concern about exposure to SHA.

In Italy, tobacco products are currently banned from advertising in accordance with Directive 2003/33/EC of the European Parliament and of the Council of 26 May 2003 [34]. However, this regulation does not cover novel devices, allowing their promotion through various channels [35]. In addition, these products are theoretically proposed as cessation aids for long-term smokers, but their advertising strategies -through colours, flavours, and branding- attract younger populations of never smokers, thus increasing the number of nicotine dependent consumers [36]. In this context, the proposed ban on advertising of HTPs and e-cigarettes was supported by about four out of five respondents. This finding may reflect a shared belief in the negative impact of tobacco marketing on public health, as well as a consensus that reducing exposure to tobacco advertising can help reduce smoking consumption. Conversely, current smokers, former smokers and both e-cigarette and HTP users were less favourable towards the advertising ban, possibly because they are more accustomed to tobacco advertising. Results indicate that extending the advertising ban to all tobacco and nicotine products, would be supported and could limit the appeal of these products among youth.

Public health authorities should monitor compliance and adapt messaging to counter industry marketing narratives.

This study has some limitations. Although the sample size was sufficient to provide overall estimates with small standard errors, it was inadequate to provide precise estimates for smaller subpopulations. In particular, the results for e-cigarette and HTP user subgroups should be interpreted with caution due to the relatively small sample sizes of the subgroups, which may limit the power to detect statistically significant associations. The sampling method involved a substitution process whereby unavailable individuals were replaced with matched newly recruited participants. The unknown response and substitution rates represent a limitation; however, this substitution process was designed to ensure the final sample was still representative. The representativeness of the sample is a key strength, as it supports the generalisability of our findings to the general Italian population. The cross-sectional design of this study precludes any causal inference between the observed associations and, as with all survey-based studies, the reliance on self-reported demographic data may introduce reporting bias. Data on smoking status, e-cigarette use and HTP use are also self-reported and are therefore subject to potential misclassification bias. Despite limited information on non-respondents, the rigorous sampling strategy and the substitution method employed ensured the representativeness of the final sample. This, together with the multivariate analyses, strengthens the credibility of our results. The data on attitudes towards the investigated tobacco control policies may be affected by social desirability bias, whereby respondents tend to answer questions in a way that they perceive to be politically or socially correct. However, the level of support was high enough to justify the implementation of the policies in question, even when accounting for social desirability bias. Moreover, a larger survey conducted via Computer-Assisted Web Interviewing (i.e., not face-to-face and therefore unaffected by social desirability bias) found even higher levels of support for the SFG and T21 policies, confirming widespread support among the Italian population [15].

In Italy, a substantial majority of the population - including a non-negligible proportion of tobacco and nicotine product users - supports a wide range of tobacco control measures. The high level of support for the SFG and T21 initiatives suggests that fully enforcing the existing law banning sales to minors - possibly with the addition of penalties for adults who supply tobacco or nicotine to minors - could be a crucial step in protecting young people, especially given the current nicotine use emergency among youth. The win-win strategy of raising tobacco prices through increased taxation is proving to be a popular option, but its great potential remains actually unexploited. Public support in this area could be used to advocate for fiscal policies aimed at reducing consumption while generating resources for cessation services and prevention campaigns. Finally,

the support for extending existing tobacco policies to cover e-cigarettes and HTPs suggests that policymakers should feel confident about implementing these measures. Notably, equalizing the legislation of novel tobacco and nicotine products to conventional cigarettes could address regulatory gaps and respond to issues on their normalization. Importantly, implementing these regulations aligns with the objectives of Europe's Beating Cancer Plan, contributing to the creation of a Tobacco-Free Generation by 2040. To strengthen policy effectiveness, tailored actions should be directed at groups showing lower levels of support. Among tobacco and nicotine consumers, communication strategies should emphasise the personal and public health benefits of regulation (e.g., benefits of cessation, reduced addiction and health risks, cleaner indoor environments). Healthcare providers, peer-focused campaigns, and targeted digital media could play a pivotal role in enhancing acceptance among these groups. For younger individuals, school-based programmes, social media campaigns, and stricter enforcement around points of sale could help to improve understanding and adherence. These tailored strategies, alongside broader public awareness initiatives, can increase support among less favourable subgroups while enhancing the population-level impact of the proposed regulations.

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Chapter 8

Conflicts of interest in research on novel tobacco and nicotine products: Analysis of consecutive publications in PubMed/MEDLINE

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Submitted

8.1 Abstract

Background: Conflicts of interest (COI) are a major concern in research on novel tobacco and nicotine products (NTNPs). These products—such as heated tobacco products, electronic cigarettes, and nicotine pouches—are promoted under a “harm reduction” narrative. This study is the first to comprehensively assess the extent of industry-related conflicts of interest across research on NTNPs, including indirect links through industry-affiliated entities.

Methods: We systematically searched PubMed/MEDLINE for NTNP-related publications published from June to December 2024. Industry-related COI was identified through: authors’ affiliation, acknowledgements, funding, and COI statement. Two blinded reviewers classified abstracts as pro-, neutral, or against NTNPs.

Results: Of 867 eligible articles, 57 (6.6%) had COI, with over half not disclosing it in the COI statement. Pro-NTNP articles were 8.6% among publications without COI (70/810), and 64.9% among those with COI (37/57). Articles against NTNPs were 70.3% among publications without COI (569/810) and 12.3% among those with COI (7/57). Compared with articles without COI, the multivariable odds ratio of being pro-NTNP was 19.6 (95% confidence interval: 9.65-39.6) for publications with COI. Similar patterns were observed for both direct and indirect COIs.

Conclusions: Industry-linked research overwhelmingly promotes NTNPs, while independent studies largely oppose them. These findings underscore the need for more effective means to safeguard the integrity of tobacco and nicotine research, including stronger and better implemented journal COI policies and new systems of funding that protect against industry influence.

8.2 Introduction

Conflicts of interest (COI) are defined as “conditions in which professional judgment concerning a primary interest—such as patient welfare or research validity—may be unduly influenced by a secondary interest, such as financial gain”.[1] In recent years, biomedical journals have increasingly adopted COI disclosure policies, and the International Committee of Medical Journal Editors recommends that authors report all funding sources and financial ties to companies with a stake in their findings. It is important to distinguish COI from broader non-financial interests: while the latter reflect general perspectives or beliefs, COI arise when a secondary interest—typically financial—has the potential to distort professional judgment.[2]

While COI is a concern across biomedical research and the wider field of commercial determinants of health, given consistent evidence of efforts of commercial actors across industry sectors to shape science in their interests,[3] the tobacco industry’s long history of manipulating science is particularly well documented.[4] Tobacco companies have mis-used science both to deny the harms of their products and contest evidence supporting tobacco control measures.[5] This concern has grown with the emergence of novel tobacco and nicotine products (NTNPs), which include heated tobacco products (HTPs), electronic cigarettes (ECs), and nicotine pouches (NPs). HTPs use battery-powered devices to heat tobacco sticks[6, 7] and have seen rapid growth since the launch of IQOS by Philip Morris International (PMI) in 2014.[6, 7] ECs also use battery-powered devices but heat liquids or salts containing nicotine rather than tobacco leaf, while NPs are pre-filled pouches placed between the lip and gum that deliver nicotine in powdered form. Originating in Scandinavia, NPs are expanding rapidly to other markets.[8] Four major transnational tobacco companies dominate the global HTP and NP market, holding a significant share of the EC market. To our knowledge, no recent study has comprehensively assessed the impact of COI across the literature on all major NTNP types.

These products are marketed as tools for “harm reduction,” a narrative that has become central to industry-sponsored research. This strategy allows the industry to replace falling sales of conventional cigarettes[9] while portraying itself as part of the solution to the burden of tobacco-related disease.[10] Sales of NTNPs have surged since their introduction, enabling companies to withstand tighter regulation and reduced cigarette consumption while increasing overall profitability.

The industry has invested heavily in research on NTNPs, much of it appearing designed to promote these products [11]. Tactics to influence scientific evidence include funding third-party organisations that claim independence, such as the Foundation for a Smoke-Free World (FSFW), recently renamed Global Action to End Smoking (GAES), [12, 13] recruiting medical professionals; and financing covert research activities in Japan to create favourable conditions for products

like IQOS.[14] Despite assertions of independence, FSFW was established with a direct funding pledge from PMI, and tax records confirm it remained solely financed by PMI for years.[15]
The scale of industry funding for NTNP research means that potentially biased data already permeate the scientific literature. In line with historical evidence, recent systematic reviews consistently find a strong association between industry funding and conclusions favouring ECs and HTPs.[3, 10, 11, 16-18] Such interference makes it even harder to objectively assess the public health impact of NTNPs, as biased evidence can obscure real harms and exaggerate potential benefits—ultimately misleading policymakers, clinicians, and the public.
Given the rapid growth of ECs, HTPs, and NPs, and the increasing complexity of industry involvement—including indirect funding mechanisms, there is an urgent need to evaluate the most recent literature. Accordingly, this study aims to quantify the proportion of NTNP publications supported by the tobacco industry and assess whether such funding is associated with their conclusions.

8.3 Methods

Search strategy

We conducted a systematic literature search in PubMed/MEDLINE to identify all publications on NTNPs, including search terms related to ECs, HTPs, and NPs appearing in the title or abstract (Supplementary Table 1). Although not a systematic review per se, as one was not necessary to answer the research question, the search strategy mirrored that of a previous systematic review of patterns of use of these products, registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020137394).[19] Only articles with an English-language Abstract published from June to December 2024 were included. The search retrieved 947 publications. After removing two duplicates, 945 original articles were included in the evaluation process, all references were imported into an EndNote library, and full-text versions were retrieved.

Evaluation of the support towards NTNPs

For each eligible publication, the title and abstract were extracted and separately evaluated by two independent reviewers, blinded to article authorship and journal. The two reviewers assessed the authors' positions as pro- or anti-NTNPs. Articles with no abstract (e.g., commentaries, letters to the editor, or corrections) were excluded. A score from 1 to 5 was attributed to each article for each product (EC. HTP, NP) according to the following criteria: 1=strongly against NTNPs (i.e., expressing strong concerns on health effects among users, or passive exposure among non-users; strongly doubting the effectiveness of ECs, HTPs or NPs as a smoking cessation tool; strongly against harm reduction; strongly calling for

stricter regulation of ECs, HTPs or NPs); 2=against NTNPs (i.e., expressing the same concerns in point 1 in a softer way); 3=no propensity or neutral (i.e., the authors did not express a clear view in their conclusions); 4=in favour of NTNPs (i.e., supporting the use of ECs, HTPs or NPs for harm reduction among users and non-users, emphasizing toxicological emissions being less than those of conventional cigarettes; supporting ECs, HTPs or NPs as a smoking cessation tool; supporting harm reduction; ignoring or underestimating the importance of regulations on ECs, HTPs or NPs); 5=strongly in favour (i.e., expressing the same views as in point 4 in a stronger way). Articles offering no view on any NTNPs (non-inherent) were scored zero and did not contribute to the analysis. For each publication, the reviewers' scores were compared. Any discrepancies were discussed with a third reviewer while maintaining the authors' and reviewers' blinding, and were resolved by consensus. An overall NTNP score from 1 to 5 was assigned to each publication, based on the individual product scores within it. Articles scoring 1 or 2 were categorised as "Against NTNP", articles scored three as "neutral", and those scored 4 or 5 as "Pro NTNP". For articles addressing a single product, the overall NTNP score corresponded directly to the score assigned to that product. For articles covering multiple products, when product-specific scores differed, the overall NTNP score was derived by prioritising the non-neutral score (e.g., EC = 2 and HTP = 3 resulted in an overall score of 2).

Conflict of interest assessment

Any potential COI with nicotine or tobacco companies was evaluated by analysing various sections of the full text of eligible articles. Each publication was classified as "with a COI" or "without a COI". The presence of COI was detected if at least one of the following conditions was satisfied: i) authors' affiliation with the tobacco industry; ii) grant or funding of the study/project by the tobacco industry reported in the 'funding' section; iii) other acknowledgement of the tobacco industry, such as sponsorship or provision of materials, in the 'acknowledgments' section; or iv) declared COI in the 'conflict of interest' statement. Also, publications reporting a COI with entities affiliated with, or with proven financial links to, the nicotine or tobacco industry (e.g., FSFW, GAES, CoEHAR) were classified as linked to the tobacco industry and labelled as "Indirect COI" in secondary analyses.

Data extraction

Besides support for NTNPs (from the abstract only) and the presence of COI with the nicotine or tobacco industry, other relevant information regarding the publications was extracted using a standardised form designed in MS Excel. Data extracted were: i) year of publication; ii) journal and corresponding 2024 impact factor; and iii) country of the corresponding author.

Statistical analysis

We examined the distribution of pro NTNP publications according to publication and study characteristics, including the presence of a declared COI, the journal impact factor and the country of the corresponding author. For the latter, articles were aggregated to obtain countries or continents with at least 40 articles included in the analysis; the remainder aggregated into an "other" category. Multivariable logistic regression was conducted to obtain adjusted odds ratios (aOR) and corresponding 95% confidence intervals (CI) for an article to be evaluated as pro NTNP, after adjustments for journal impact factor, the country of the corresponding author, and having a COI.

8.4 Results

Of the 945 non-duplicate articles identified, 24 were not eligible, and 54 offered no view on NTNP (score=0) and were therefore excluded from the analysis (Supplementary Table 2). Of the remaining 867 articles, 772 dealt with EC (89.0%), 112 with HTP (12.9%), and 47 with NP (5.4%; Table 1); 55 dealt with multiple products (6.3%).

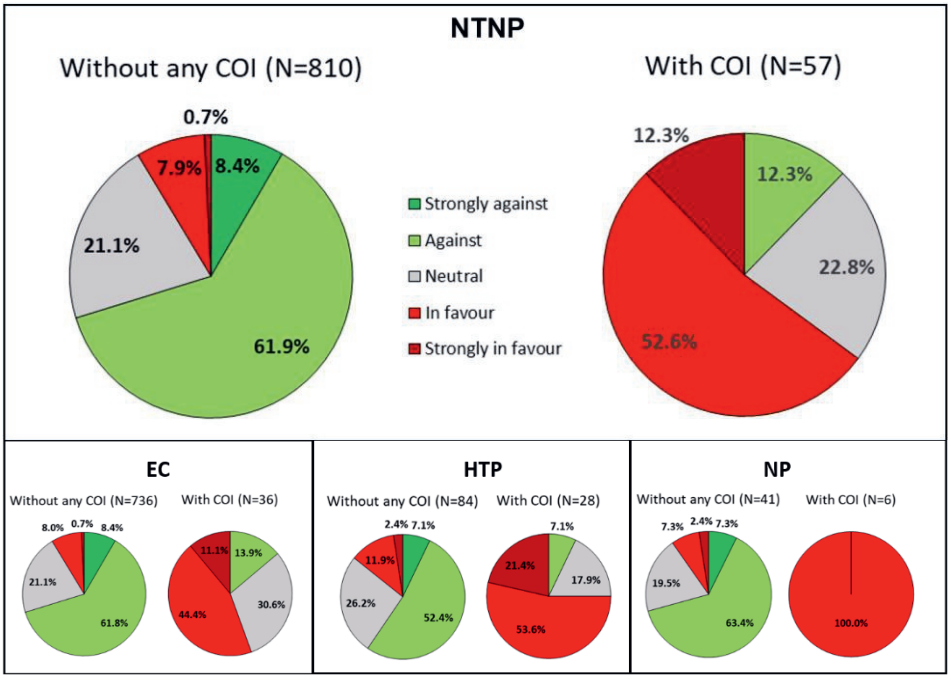
Table 1. Characteristics of 867 publications included in the systematic review, overall and by conflict of interest (COI) stratification.

	Total N	Publications without COI N (%)	Publications with any COI N (%)
Total	867	810 (93.4)	57 (6.6)
Nicotine product[a]			
EC	772	736 (95.3)	36 (4.7)
HTP	112	84 (75.0)	28 (25.0)
NP	47	41 (87.2)	6 (12.8)
Impact factor			
<2.5	301	291 (96.7)	10 (3.3)
2.5-3.6	325	301 (92.6)	24 (7.4)
>3.6	241	218 (90.5)	23 (9.5)
Country[b]			
USA	450	438 (97.3)	12 (2.7)
UK	56	50 (89.3)	6 (10.7)
Other European countries	113	95 (84.1)	18 (15.9)
China	47	31 (66.0)	16 (34.0)
Other Asian countries	105	100 (95.2)	5 (4.8)
Oceania	42	42 (100.0)	0 (0.0)
Other	54	54 (100.0)	0 (0.0)

[a] sums up to more than the total because some publications dealt with multiple products; [b] Countries or continents of the corresponding author with at least 40 publications; EC: electronic cigarettes; HTP: heated tobacco products; NP: nicotine pouches.

Overall, 810 (93.4%) had no COI and 57 (6.6%) had COI with tobacco companies (21 articles) or affiliated entities (36 articles). Notably, among the 57 publications with COIs, 29 did not declare them in their COI statements, despite revealing a COI in at least one of the other three evaluated sections (affiliations, acknowledgements, funding). Across all articles, 68 (7.8%) were evaluated as strongly against NTNP (score=1), 508 (58.6%) as against (score=2), 184 (21.2%) as neutral (score=3), 94 (10.8%) as in favour (score=4), and 13 (1.5%) as strongly in favour of HTP (score=5; Supplementary Table 3).
Among the 810 publications without COI, 569 (70.3%) were evaluated as against NTNP (i.e., against or strongly against NTNP), and 70 (8.6%) were evaluated as pro NTNP, whereas among the 57 publications with COI, 7 (12.3%) were against NTNP, and 37 (64.9%) were pro NTNP (Figure 1). Considering each product separately, 8.7% of EC publications without COI were pro NTNP vs 55.5% with COI; for HTP, the respective proportions were 14.3% vs 75.0%; and for NP, 9.7% vs 100.0% (detailed data in Supplementary Table 4).

Figure 1. Position towards novel tobacco and nicotine products (NTNP) in publications on NTNP published in 2024, with -or without- a conflict of interest (COI) with the tobacco and nicotine industry or their affiliated entities.



EC: electronic cigarettes; HTP: heated tobacco products; NP: nicotine pouches.

Among publications with a direct COI with the tobacco and nicotine industry, 66.7% were pro-NTNP. In contrast, among publications with a COI with entities affiliated with the tobacco and nicotine industry, 61.9% were pro NTNP.
Of the 716 articles focusing exclusively on EC, 9.4% were pro-NTNP. Articles focusing exclusively on HTP were more frequently supportive (30.5% of 59 studies; aOR: 2.51; 95% CI: 1.13-5.56), as were those investigating multiple products (27.4% of 62 studies; aOR: 2.84; 95% CI: 1.30-6.23; Table 2). According to the journal impact factor, articles published in journals with an impact factor between 2.5 and 3.6 were more often evaluated as pro NTNP than articles published in journals with an impact factor below 2.5 (15.4% vs 7.3%; aOR: 2.25; 95% CI: 1.25-4.05). Compared with articles with a corresponding author from the USA, those with a corresponding author from the UK were more frequently pro-NTNP (33.9% vs 9.6%; aOR: 4.57; 95% CI: 2.27-9.22). No other country or continent showed significantly different results.

Table 2. Multivariate analysis of support for novel tobacco and nicotine products (NTNP) according to product, journal impact factor (2024), country and conflict of interest (COI), among 867 articles on NTNP published in 2024.

	N	Pro NTNP %	Overall aOR (95% CI)
Product			
Exclusively on EC	716	9.4	Ref.
Exclusively on HTP	59	30.5	**2.51 (1.13-5.56)**
Exclusively on NP	30	16.7	1.50 (0.46-4.89)
On multiple products	62	27.4	**2.84 (1.30-6.23)**
Impact factor			
<2.5	301	7.3	Ref.
2.5-3.6	325	15.4	**2.25 (1.25-4.05)**
>3.6	241	14.5	1.45 (0.77-2.76)
Country*			
USA	450	9.6	Ref.
UK	56	33.9	**4.57 (2.27-9.22)**
European countries (except UK)	113	19.5	1.40 (0.71-2.76)
China	47	21.3	0.59 (0.21-1.64)
Asian countries (except China)	105	9.5	0.94 (0.43-2.08)
Oceania	42	4.8	0.58 (0.13-2.50)
Other	54	1.9	0.21 (0.03-1.54)
COI			
None	810	8.6	Ref.
Any	57	64.9	**19.55 (9.65-39.61)**
Indirect[a]	21	61.9	**14.11 (5.27-37.81)**
Industry[b]	36	66.7	**24.88 (10.12-61.18)**

aOR: adjusted odds ratio for journal impact factor (2024), country and COI; CI: confidence interval. Statistically significant aORs in bold; * Countries or continents of the corresponding author with at least 40 publications; [a] Publications with a declared COI with an entity affiliated with the tobacco and nicotine industry; [b] Publications with a declared COI with the tobacco and nicotine industry; EC: electronic cigarettes; HTP: heated tobacco products; NP: nicotine pouches.

Publications assessed as having a COI with the tobacco and nicotine industry or affiliated entities were more likely to be pro NTNP than those without a COI (aOR: 19.55; 95% CI: 9.65-36.91). Both publications with direct COI with the industry (aOR: 24.88; 95% CI: 10.12-61.18) and those with indirect COI through an affiliated entity (aOR: 14.11; 95% CI: 5.27-37.81) were more likely to be pro-NTNP than publications without COI.

In the product-specific multivariate analyses, publications with COI were more likely to be pro NTNP compared to those without COI: EC (55.6% vs 8.7%; aOR: 11.03, 95% CI: 4.87-24.94), HTP (75.0% vs 14.3%; aOR: 15.73, 95% CI: 4.47-55.36), while for NP all six publications with COI were pro (100% vs 9.8%), making it impossible to estimate an aOR (Supplementary Table 5).

8.5 Discussion

Among independent articles - which represent the vast majority of the literature on NTNP - the majority were against these products, with fewer than 1 in 10 supporting them. By contrast, two out of three articles in which authors had a COI supported such products.

Our review reveals a striking imbalance in conclusions between papers with and without COI. This pattern mirrors findings from previous, less comprehensive reviews, which also reported that studies with industry involvement were far more likely to present favourable conclusions about ECs or HTPs.[10, 11, 16-18] This interpretation is supported by extensive evidence of the industry's long-standing practice of manipulating science to protect profits and delay regulation.[3, 5, 11, 14] Once the tobacco industry provides funding, directly or indirectly, it appears difficult for researchers to contradict the sponsor. Given the industry's financial dependence on NTNPs and its growing investment in these products, it has a clear vested interest in shaping the evidence base to support its commercial strategies.

The same imbalance was evident for both direct and indirect COIs. Articles openly funded by the tobacco industry were strongly supportive of NTNPs, but those linked to industry-affiliated entities showed a similar pattern; nearly two-thirds were pro-NTNP. As toxicological and in vitro studies have declined and population-based research has become more common, these indirectly funded publications account for most COI-related research on NTNPs. In a 2019 Lancet letter, the founder of the FSFW acknowledged that PMI funds the organisation, while asserting its independence.[20] Yet research disputes this claim of independence and suggests instead that FSFW should be seen as an "industry-

influenced scientific lobby group promoting tobacco industry interests".[12, 13] Although presented as independent, the conclusions of these entities have been shown to reflect and promote industry interests. They are increasingly visible in the scientific landscape and appear designed to contaminate independent literature by promoting pro-NTNP narratives under the guise of neutrality.

To capture all potential industry involvement, we examined multiple sections of each article—author affiliations, acknowledgements, funding statements, and COI statements. This approach revealed that most articles with clear links to the tobacco industry failed to disclose these ties in their COI statements. In blinded peer review, where author identities are concealed, such omissions mean reviewers cannot detect COI, increasing the risk that industry-funded studies are perceived as independent.

These findings underscore the need for stricter and more consistent COI policies in tobacco and nicotine research. Some leading journals have already acted: BMJ journals prohibit publication of research funded wholly or partly by the tobacco industry and extend this ban to authors with personal financial ties.[21] The European Journal of Public Health has adopted similar measures.[22] While ICMJE guidelines provide a standardised disclosure framework,[23] enforcement remains inconsistent. particularly when funding flows through industry-backed entities such as FSFW/GAES.[24] We argue that these policies should be universally adopted and rigorously enforced, with mechanisms to identify indirect funding and prevent industry-sponsored narratives from being presented as independent science. Reviewers, editors, and readers should critically assess all indicators of industry links when interpreting NTNP research.

Differences emerged when considering the various products. Most of the literature on EC is independent, with 736 publications without COI compared to only 36 with COI. Fewer than 1 in 10 articles focusing exclusively on EC products were supportive of them. In contrast, HTP showed much greater industry involvement, with 84 publications without COI and 28 with COI, reflecting the substantial investments by the tobacco industry in this sector, including nearly one billion US dollars allocated by PMI to the FSFW.[24] This pattern aligns with the industry's strategy to promote HTPs under the "harm reduction" narrative, and largely fits with the industry's interests and market share by continuing to market products that deliver tobacco and nicotine. Finally, NPs, particularly the most recent NTNP, warrant attention: although only a few publications with COI are available, all are pro-NTNP, underscoring the potential for early and substantial industry influence in shaping the evidence base on these emerging products. In a context where sales of conventional cigarettes have been declining for decades, the industry is using NTNPs to target younger generations, fostering early nicotine addiction and thus securing future customers.

Country-specific differences were also evident, with the United Kingdom standing out for its higher proportion of pro-NTNP publications. This finding reflects policies

in England that actively promote ECs as cessation tools. Consequently, many studies conducted in the UK, including those without COI, have focused on this potential role, while giving less emphasis to concerns more prominent in other countries, such as nicotine dependence and youth and adolescent uptake. Although clinical trials in controlled settings suggest that ECs can support quitting cigarette smoking, this is not seen in real-world evidence, with evidence that they increase smoking initiation among young people.[25, 26] Moreover, the EC market is evolving rapidly, with the widespread adoption of new products, such as disposable devices, that differ substantially from those tested in clinical trials. In the real world, ECs are being viewed less as a smoking cessation tool and more as a mainstream product used by young people, adolescents, and dual users, all of whom represent high-risk groups.[19, 27]

This study has some limitations. Although only about 1 in 15 publications had a declared COI, the effect size was large, providing adequate statistical power for our analyses. Specifically, the adjusted odds ratio for being pro-NTNP in COI-related publications was nearly 20, with narrow confidence intervals, indicating a strong association despite the relatively small COI group. This is consistent with power calculations showing that large effect sizes can compensate for low prevalence in logistic regression models. Moreover, this was the most extensive study on this specific issue.[10, 16, 17] Another limitation is that our assessment of each study's stance relied solely on the abstract. Some interpretations may appear only in the full text and may therefore not have been captured. However, given the very large number of publications included, a full-text review would have been impractical and methodologically disproportionate. Importantly, our findings suggest that abstracts generally provide a sufficiently clear and representative summary of the authors' overall position, supporting the validity of this approach. Another limitation is that we relied solely on the statements in the publications, which may have underestimated the true extent of industry involvement. Previous research indicates that undisclosed or indirect ties are common, particularly when funding is routed through affiliated entities or front groups.[11] Future studies should consider methods to verify COI beyond self-reporting, such as cross-referencing author affiliations and funding sources with external databases (e.g., the WHO Tobacco Industry Interference database) or applying investigative approaches, such as network analysis of institutional and financial links. These strategies would enable a more comprehensive assessment of industry influence and strengthen transparency in tobacco and nicotine research. In addition, we did not categorise publications by study type, meaning that original studies, reviews, and opinion pieces were analysed together. This may have resulted in some degree of overlap in the underlying evidence base, potentially leading to double counting of the same data. Furthermore, opinion pieces could also contribute to bias in either direction. While this approach allowed us to capture the overall narrative of the literature, it may have affected the magnitude of the

observed associations. Although we did not examine study design features in detail, extensive historical evidence on corporate influence in science suggests that bias may also arise through the framing and design of research questions and comparisons. Future studies should therefore explore in greater depth how industry involvement may shape methodological choices in NTNP research, beyond the interpretation of results.

This study also has important strengths. We reviewed all consecutive articles on NTNPs published within a recent time window, examining the broader field rather than focusing on a single product or topic. This approach provides the most up-to-date and comprehensive overview of the current literature. We also included publications with indirect COI, which may appear independent to non-expert readers but, as our findings show, are as biased as those directly funded by the industry. Finally, the large number of articles included ensures robustness and generalizability of our results.

When considering only independent research, NTNPs are largely opposed, with most publications highlighting concerns rather than benefits. In contrast, the “harm reduction” narrative promoted by the tobacco and nicotine industry relies on a limited number of publications that largely support its financial interests by disproportionately supporting its products. To safeguard research integrity, journals should adopt stricter policies to prevent articles produced under indirect COI arrangements from being published as independent, following recommendations already proposed in the literature.[11] There is also an urgent need for alternative funding mechanisms that protect research from industry influence. Alternative models have been proposed in which independent research on tobacco and nicotine products would be funded through earmarked taxes or levies on the industry itself. This would help to ensure that the evidence used to inform public health policies is free from COI.[28]

In conclusion, publications with COI, often not disclosed in the COI statement tend to promote NTNPs. Independent research, by contrast, generally opposes NTNPs. The tobacco industry invests substantial resources to support its products, particularly HTPs, and has recently shown growing interest in NPs. Indirect funding through entities that appear independent represents the latest strategy to advance this narrative. To counterbalance this influence, there is an urgent need for independent research on these products and stricter restrictions on the publication and dissemination of industry-sponsored studies.

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Supplementary Materials will be available online after publication.

Chapter 9

General discussion

9.1 Main findings

9.1.1 What's new: brief summary of the most relevant findings

This PhD research program resulted in seven scientific articles, presented in Chapters 2–8 of this dissertation. These studies address complementary aspects of novel tobacco and nicotine products (NTNPs), including patterns of use, health effects, attitudes towards tobacco control policies, and the role of industry influence on scientific research.

Chapter 2 presents a systematic review on patterns of use of heated tobacco products (HTPs) [1]. Evidence from this comprehensive review indicates that HTP use is strongly associated with current or former smoking, with more than two thirds of HTP users being dual users of HTPs and conventional cigarettes. Prospective data further suggest that HTP use may increase the likelihood of cigarette smoking initiation and reduce the probability of smoking cessation.

Findings from a nationally representative survey of the Italian adult population (Chapter 3) [2] indicate that 2.3% of Italian adults use electronic cigarettes (e-cigarettes) and 4.5% use HTPs, with prevalence decreasing with age. Dual use with conventional cigarettes is extremely common, involving 87.8% of e-cigarette users and 92.5% of HTP users. Finally, HTP use showed an increasing trend between 2022 and 2024.

On the other hand, NTNP use is substantially more widespread among adolescents (Chapter 4) [3]. Overall, 27.7% of students included in this study reported use of at least one nicotine product in the last month, with 21.9% using e-cigarettes, 18.0% smoking conventional cigarettes, and 15.8% using HTPs. Dual use was reported by 15.8% of participants. Alcohol consumption was associated with the use of all nicotine products, and cigarette smoking was strongly associated with concurrent use of other nicotine products. These findings highlight a concerning pattern of early nicotine exposure and poly-product use among minors.

The analysis of short-term adverse events associated with the use of conventional cigarettes, e-cigarettes and HTPs (Chapter 5) [4] Further shows that dual and poly-users experience a higher frequency of symptoms compared with exclusive cigarette smokers, suggesting increased short-term harm associated with combined product use.

The systematic review and meta-analysis on the association between NTNP use and SARS-CoV-2 infection and COVID-19 progression (Chapter 6) [5] found no evidence of a reduced risk of COVID-19 progression among NTNP users. On the contrary, e-cigarette use was associated with an increased risk of SARS-CoV-2 infection, and available evidence suggests a potential increase in the risk of severe COVID-19 outcomes.

From a policy perspective, the study on public attitudes (Chapter 7) [6] provides updated evidence on a high level of public support for a wide range of tobacco

control interventions, including those targeting NTNPs, in Italy. This widespread support may indicate favourable conditions for the implementation of more comprehensive regulations in Italy.
Finally, Chapter 8 investigates conflicts of interest in scientific research on NTNPs [7]. The results of the review highlight a substantial distortion in the evidence base, with publications linked to the tobacco industry being far more likely to report favourable conclusions towards NTNPs compared with independent research.
Taken together, these studies consistently show that NTNP use is characterised by high levels of dual use, increasing uptake among younger populations, and limited evidence of smoking cessation in real-world settings. In addition, emerging evidence points to potential health risks and highlights the influence of the tobacco and nicotine industry on the scientific evidence base.

9.1.2 Methodological considerations of the studies used

The research conducted within this PhD programme is based on complementary methodological approaches, including nationally representative cross-sectional surveys, the baseline analysis of a large prospective cohort study with planned follow-up assessments, and several systematic reviews of the scientific literature. These complementary methodological approaches enable the investigation of multiple dimensions of NTNPs, such as patterns of use, health effects, public attitudes towards tobacco control policies and the influence of the tobacco industry on scientific research.
This dissertation includes several studies that relied on data from cross-sectional DOXA surveys on smoking conducted in Italy. These surveys are characterised by nationally representative samples of the adult population, obtained through multistage sampling procedures and standardised data collection methods [2]. A major strength of these surveys is the representativeness of the sample, as well as the use of a standardised questionnaire that has been applied consistently over time. This allows for a reliable assessment of the prevalence, patterns and trends in cigarette, e-cigarette and HTP use. Data from these surveys were also used to analyse support for new tobacco control policies within the Italian population.
Another cross-sectional study included in this dissertation was conducted among Italian secondary school students in collaboration with the Italian League Against Cancer (LILT Monza Brianza) and IRFMN, providing valuable insight into NTNP use among minors—a population often underrepresented in national surveillance systems. [3]. The large sample size and multi-regional coverage strengthen the relevance of these findings for understanding youth nicotine use.
Although cross-sectional studies are a valuable tool for describing prevalence and exposure patterns at a population level, they have inherent methodological

limitations. Notably, due to their design, exposure and outcome information is collected at the same point in time. This makes it impossible to establish temporal relationships and derive causal inferences. Consequently, the mechanisms through which specific determinants and outcomes interact cannot be fully clarified. For this reason, findings from cross-sectional analyses should be interpreted with caution and ideally confirmed through longitudinal research.

To address this limitation, a large prospective cohort study was conducted in collaboration with DOXA and IRFMN to evaluate the medium- and long-term health effects associated with NTNP use. This cohort, involving over 20,000 participants at baseline, will allow longitudinal assessment of trajectories of NTNP use and associated health outcomes [4]. Baseline data have already been analysed using a cross-sectional approach to assess the association between cigarette, e-cigarette and HTP use and the occurrence of short-term adverse events. Starting from 2026, planned follow-up waves will enable the longitudinal evaluation of health outcomes associated with different patterns of nicotine product use. The availability of follow-up data represents a major strength, enabling future analyses on incidence and causal relationships that cannot be captured through cross-sectional designs.

In addition to original epidemiological studies, this PhD research included several literature reviews adopting different methodologies. A systematic review and meta-analysis was conducted to evaluate patterns of HTP use, as well as the relationship between HTP use and conventional cigarette smoking, including transitions between the two [1]. This study was conducted as part of the European Joint Action on Tobacco Control 2 (JATC-2) project, with IRFMN participating as a partner [8]. A second systematic review and meta-analysis investigated the role of NTNP use in relation to SARS-CoV-2 infection and progression of the disease [5]. These studies provide a broader perspective beyond the Italian context and strengthen the overall robustness of the findings by integrating data from multiple populations and study designs. Finally, a systematic search of the scientific literature was performed to assess the prevalence of industry-related conflicts of interest in NTNP research, and to examine their potential influence on study conclusions. Particular attention was given to indirect links through industry-affiliated entities [7].

Across the studies included in this dissertation, several methodological considerations related to potential sources of bias and uncertainty should be acknowledged. In the adult population surveys, the use of nationally representative samples reduces the risk of selection bias, although some degree of bias may still arise from non-response or substitution procedures. In contrast, the school-based survey among adolescents is not representative of the general youth population, and it also excludes individuals not attending school, who may have different patterns of tobacco and nicotine use.

Information bias is also a relevant concern, as most data were based on self-reported measures of smoking behaviour, NTNP use, and health outcomes. This may have led to misclassification due to recall bias or social desirability bias, particularly for behaviours subject to social norms or legal restrictions, such as underage nicotine use.
Residual confounding cannot be excluded in observational analyses. Although multivariable models adjusted for key sociodemographic and behavioural factors, unmeasured or imperfectly measured variables may have influenced the observed associations.
Finally, the external validity of the findings should be carefully interpreted. The Italian context provides a relevant case study, characterised by early introduction of HTPs and high uptake of NTNPs, particularly among young people. However, differences in regulatory environments, market dynamics, and cultural factors may limit the generalisability of the results to other countries. These differences do not limit the relevance of the findings, but rather highlight the importance of comparative research to better understand how contextual factors shape the impact of novel tobacco and nicotine products in different national settings.

9.2 Advance in knowledge

The studies included in this dissertation contribute to advancing knowledge on NTNPs across three main domains: their potential health effects, their role in shaping tobacco use patterns and tobacco control, and the influence of the tobacco and nicotine industry on the scientific evidence and policy debate.

9.2.1 Contribution of the research to the understanding of the role of novel tobacco and nicotine products on tobacco control

9.2.1.1 Prevalence and patterns of novel tobacco and nicotine product use among adults

Understanding the prevalence and patterns of use of NTNPs among adults is essential to evaluate their potential impact on tobacco control. The studies included in this dissertation advances current knowledge on the role of NTNPs in tobacco control by providing robust, population-based evidence that challenges the assumption that these products are primarily used as substitutes for conventional cigarettes.
The analysis of nationally representative data from Italy contributes updated and policy-relevant estimates on the diffusion of e-cigarettes and HTPs in a country where these products -particularly HTPs- have rapidly penetrated the market. The findings clarify that the prevalence of e-cigarette and HTP use in Italy remains relatively limited at the population level, but displays distinct patterns across population subgroups [2]. Both products are substantially more common among

younger adults, while their prevalence declines sharply with increasing age. These findings provide updated national estimates and confirm that NTNP uptake is primarily concentrated in younger segments of the adult population rather than among older smokers who might be expected to adopt such products as smoking cessation alternatives. This age gradient provides important insight into the population dynamics of NTNP adoption.

A key finding emerging from these analyses is the extremely high prevalence of dual use with conventional cigarettes. By showing that approximately nine out of ten e-cigarette and HTP users also report current cigarette smoking, the findings contribute to the growing body of literature indicating that these products are rarely used as substitutes for conventional smoking in real-world settings. Instead, they are predominantly used concurrently with cigarettes, suggesting that e-cigarettes and HTPs often function as complementary sources of nicotine rather than as alternatives to smoking in real-world conditions. This pattern is particularly relevant from a tobacco control perspective, as an increasing body of evidence indicates that dual users may experience greater health risks than exclusive cigarette smokers [9, 10].

The systematic review and meta-analysis conducted within this PhD programme further contextualises these findings at the international level. This comparative perspective confirms that the patterns observed—namely the strong link with smoking and the high prevalence of dual use—are consistent across multiple settings, while also identifying country-specific dynamics, such as the particularly rapid diffusion of HTPs in Italy and Japan [1]. Importantly, evidence from several prospective studies examining transitions between products does not support the hypothesis that HTPs function as effective smoking cessation tools. On the contrary, HTP users appear to be less likely to quit smoking and more likely to initiate or relapse into cigarette smoking. This finding is particularly relevant for tobacco control, as it shifts the interpretation of HTPs from potential cessation tools to products that may sustain or even expand nicotine use at the population level.

Taken together, these findings contribute to advancing current knowledge on NTNP use among adults by providing updated prevalence estimates, documenting the persistence of widespread dual use, and integrating national data with the broader international evidence. Overall, the results suggest that e-cigarettes and HTPs are primarily integrated into existing smoking behaviours rather than replacing conventional cigarette use, raising important considerations for tobacco control policies and public health surveillance.

9.2.1.2 Prevalence and patterns of novel tobacco and nicotine product use among minors

The spread of NTNPs among adolescents represents a key concern for tobacco control. This dissertation advances current knowledge on tobacco control by providing updated evidence that the diffusion of NTNPs is not confined to adult smokers, but is instead highly prevalent among adolescents, including those legally prohibited from accessing these products. The study conducted within this PhD programme among Italian middle and high school students provides updated evidence on the prevalence and patterns of nicotine product use among minors, highlighting the widespread diffusion of both conventional and novel products despite existing legal restrictions on their sale to individuals under 18 years of age [3].

More than one in four students reported having used at least one nicotine product in the previous month. Conventional cigarettes, e-cigarettes and HTPs were all widely used, and a substantial proportion of students reported dual or multiple product use. In addition, a non-negligible prevalence of nicotine pouch use was observed, suggesting that this emerging nicotine product has already begun to reach the adolescent population. These findings indicate that the use of nicotine products among minors is not limited to conventional smoking but increasingly involves a diversified set of products.

While these products are often framed within a harm reduction perspective aimed at adult smokers, the findings show that the prevalence of NTNP use among high school students is even higher than that observed in the adult population. These results suggest that NTNPs are particularly prevalent among adolescents, a population that is legally prohibited from purchasing these products. This discrepancy provides critical evidence for the tobacco control debate, suggesting that NTNPs may play a role in facilitating early nicotine initiation rather than supporting cessation among established smokers.

These findings are consistent with other national data on youth nicotine use in Italy. Estimates from the Global Youth Tobacco Survey conducted among adolescents aged 13–15 years reported prevalence levels for cigarette smoking, e-cigarette use and HTP use that closely align with those observed in our study [11]. Similarly, recent national data indicate that around one third of Italian adolescents have used at least one nicotine product [12]. These results contribute to advancing the current understanding of youth nicotine use by providing updated evidence on the widespread diffusion of multiple nicotine products among minors and documenting the increasing diversification of nicotine consumption patterns in this population.

9.2.1.3 Benefits vs risks: evaluation of the overall impact of novel tobacco and nicotine products on public health

A central question in the debate surrounding NTNPs concerns their overall balance of risks and benefits for public health. These products have been promoted within a harm reduction framework, based on the assumption that

smokers who completely switch from conventional cigarettes to alternative nicotine delivery systems may experience a reduction in exposure to toxic substances [13, 14]. Under this theoretical scenario, the replacement of combustible cigarettes with less harmful nicotine products could potentially contribute to reducing the burden of smoking-related diseases.

However, the available evidence suggests that the magnitude of these potential benefits may be considerably more limited than initially proposed. While some randomized clinical trials (RCTs) indicate that e-cigarettes may show a modest efficacy for smoking cessation compared with nicotine replacement therapy (NRT) [15], a closer examination of the outcomes of these trials raises important concerns. Reanalysis of the data from RCTs included in the Cochrane review on e-cigarettes for smoking cessation shows that only a very small proportion of smokers randomized to e-cigarettes ultimately achieve complete cessation of both smoking and nicotine use [16]. Most participants either continue smoking conventional cigarettes or continue using e-cigarettes after quitting smoking, resulting in ongoing nicotine dependence. In particular, a substantial proportion of smokers who receive e-cigarettes as part of cessation interventions become dual users, continuing to smoke while also using e-cigarettes. Consequently, the intervention appears to lead more frequently to sustained nicotine use or even dual use rather than to tobacco and nicotine cessation.

Evidence from observational and real-world studies further challenges the effectiveness of NTNPs as smoking cessation tools. Prospective studies consistently indicate that users of e-cigarettes and HTPs are less likely to successfully quit conventional cigarette smoking than non-users, while cross-sectional analyses repeatedly document high levels of dual use among users of these products [1, 17]. Rather than replacing cigarette smoking, NTNPs therefore appear in many cases to be integrated into existing smoking behaviours, increasing the number of occasions for nicotine intake and potentially sustaining long-term dependence.

An additional concern relates to the population groups most likely to adopt these products. The prevalence of NTNP use is particularly high among adolescents and young adults, exceeding that observed among the adult population. The diffusion of these products among individuals who would otherwise be unlikely to initiate nicotine use represents a potential source of new nicotine dependence and may contribute to sustaining tobacco and nicotine consumption in younger generations.

Taken together, these considerations suggest that the overall balance between potential benefits and risks associated with NTNPs may be substantially less favourable than often claimed. While the theoretical harm reduction potential of these products relies on complete substitution of cigarette smoking, the available evidence indicates that this scenario is relatively uncommon in practice. Instead, widespread dual use, limited success in smoking cessation, and high uptake

among young populations collectively raise important concerns regarding the overall public health impact of these products.

9.2.1.4 Support towards new tobacco control policies in Italy

Beyond documenting the epidemiology of NTNP use, an additional contribution of the research presented in this dissertation concerns the assessment of public support for potential tobacco control policies in Italy. Understanding population attitudes toward regulatory measures is essential for evaluating the feasibility and potential effectiveness of future tobacco control interventions. Using data from a nationally representative sample of Italian adults, the study included in this dissertation provides updated evidence on the level of support for a range of tobacco control policies targeting both conventional cigarettes and NTNPs [6].
Policies aimed at reducing smoking initiation among young people received substantial support. In particular, measures such as the introduction of a Tobacco 21 (T21) policy—raising the legal age for purchasing tobacco and nicotine products to 21 years—and the implementation of a Smoke-Free Generation (SFG) strategy were supported by a large majority of respondents. Importantly, the high level of support observed in this representative sample confirms earlier findings obtained from a larger survey based on DOXA data, which also documented strong public support for SFG and T21 policies in Italy [18].
Significant support was also observed for fiscal policies, with respondents in favour of a substantial increase in the price of a packet of cigarettes.
Notably, strong support was observed for policies addressing NTNPs, such as extending indoor smoking bans to include e-cigarettes and HTPs in indoor public places and workplaces, and introducing a ban on the advertising of these products. These findings highlight a growing public awareness of the potential health risks associated with exposure to second-hand aerosol and of the role of marketing in promoting nicotine use, particularly among young people. Extending existing tobacco regulations to cover NTNPs could therefore address important regulatory gaps and prevent the normalisation of these products in public spaces.
These findings indicate that the implementation of stronger tobacco control measures in Italy could rely on a wide base of public support. In particular, extending existing regulations to NTNPs, strengthening policies aimed at preventing youth initiation, and implementing fiscal measures represent realistic and potentially effective strategies to advance tobacco control in the Italian context.

9.2.2 Contribution of the research to the existing knowledge on e-cigarette and HTP health effects

9.2.2.1 The role of e-cigarette and HTP on SARS-CoV-2 infection and COVID-19 progression

The studies included in this PhD dissertation also contribute to the growing body of evidence on the health effects of NTNPs. At the beginning of the COVID-19 pandemic, several hypotheses emerged regarding the potential relationship between nicotine use and SARS-CoV-2 infection, although the evidence supporting this hypothesis was limited and controversial [19, 20]. In a previous meta-analysis conducted by our research group, conventional cigarette smoking was found to be associated with a higher risk of COVID-19 progression and mortality, with smokers experiencing approximately a 30–50% increased risk of severe outcomes compared with never smokers. This evidence suggested that tobacco use represents an important risk factor for worse COVID-19 prognosis [21].

Building on this earlier work, the research included in this dissertation expanded the available evidence by conducting a systematic review and meta-analysis investigating the association between the use of NTNPs—specifically e-cigarettes and HTPs—and both SARS-CoV-2 infection and COVID-19 progression [5].

The results of the meta-analysis showed no evidence supporting the hypothesis that e-cigarette use may protect against SARS-CoV-2 infection. On the contrary, the pooled analysis indicated that e-cigarette users had higher risk of SARS-CoV-2 infection compared with non-users. Evidence on HTP use was more limited, as only a small number of studies provided relevant estimates.

Similarly, the review found no evidence supporting a protective role of nicotine-containing products in relation to COVID-19 progression. Conversely, several studies suggested an increased risk of adverse outcomes among NTNP users, including hospitalization, oxygen administration, long COVID symptoms, and other COVID-19-related clinical manifestations.

These findings contribute to the literature by providing a more consistent interpretation of a previously fragmented evidence base. More recent studies have increasingly aligned with the absence of any protective effect of vaping or HTP use. Emerging evidence on e-cigarettes suggests potential associations with increased susceptibility to respiratory infections and disease severity [22], while studies on HTPs indicate an increased risk of COVID-19-related outcomes [23]. In this context, our meta-analysis helps consolidate these findings by quantitatively and qualitatively synthesising the available data.

These findings provide important public health insights. First, they refute the hypothesis that nicotine-containing products may offer protection against SARS-CoV-2 infection or COVID-19 progression. Second, the observed association between e-cigarette use and increased infection risk suggests that these products may contribute to respiratory vulnerability, particularly during infectious disease outbreaks. Given the widespread and increasing use of NTNPs, particularly among younger populations, these findings reinforce concerns about their potential health impacts.

9.2.2.2 Short-term adverse events associated with e-cigarette, HTP and conventional cigarette use

Another contribution of the research conducted during this PhD concerns the investigation of short-term adverse health effects associated with the use of e-cigarettes and HTPs. While the health effects of conventional smoking are well established, evidence on the immediate symptoms associated with the use of NTNPs and their combined use with cigarettes remains limited. The study included in this dissertation contributes to filling this gap by analysing self-reported adverse events in relation to different patterns of tobacco and nicotine product use among Italian adults [4].

The study showed that the combined use of conventional cigarettes with e-cigarettes and/or HTPs was associated with a greater burden of short-term adverse events. Dual users reported a higher number of different symptoms experienced during or after cigarette smoking compared with exclusive cigarette smokers, even when smoking intensity was similar. These findings indicate that e-cigarettes and HTPs are far from free of adverse effects and may contribute to acute respiratory and systemic symptoms.

The observation that dual or poly users experienced a greater number of adverse events than cigarette-only smokers provides further support to the growing hypothesis that combined use of multiple nicotine products may have more harmful health consequences than smoking alone, adding novel evidence on short-term, self-reported symptomatology as an early indicator of harm [9, 10]. A plausible explanation is that the simultaneous exposure to toxicants emitted by both cigarette smoke and aerosols from novel devices may increase overall toxicant exposure and exacerbate inflammatory responses.

In addition to this work, during the course of this PhD I contributed to a study conducted within our research group investigating the short-term cardiovascular effects associated with the use of the HTP IQOS from Philip Morris International (PMI) [24]. The results showed that the use of IQOS produced acute increases in heart rate similar to those observed after cigarette smoking, and that cardiovascular parameters among IQOS users differed substantially from those of non-smokers. No significant differences in heart rate and blood pressure responses were observed between cigarette smokers and IQOS users, suggesting comparable short-term impairment of cardiovascular function following product use. These findings are consistent with independent experimental studies showing that exposure to emissions from heated tobacco products can induce acute cardiovascular effects [25].

These findings advance current knowledge of the short-term health effects of NTNPs. These products are certainly not harmless alternatives, and using them alongside conventional cigarettes may lead to an increased number of adverse symptoms. From a public health perspective, these results reinforce concerns that the increasing popularity of e-cigarettes and HTPs, particularly when used

alongside conventional cigarettes, may increase rather than reduce the burden of nicotine consumption on public health.

9.2.3 The role of the tobacco and nicotine industry

9.2.3.1 Reassessing the harm reduction claim

As discussed in the introductory chapters of this dissertation, harm reduction is one of the central arguments used to justify the introduction and promotion of NTNPs. According to this narrative, these products would represent substantially less harmful alternatives to conventional cigarettes and could therefore contribute to reducing the overall burden of smoking-related disease by promoting smoking cessation. However, a growing body of independent scientific evidence accumulated in recent years has challenged this assumption. The studies presented in this PhD dissertation contribute to this debate by providing evidence that calls into question the extent to which NTNPs can effectively reduce harm at the population level.

Firstly, the epidemiological analyses included in this work confirm that the majority of e-cigarette and HTP users do not replace conventional cigarettes with these products, but instead combine them through dual or poly use [1, 2]. Secondly, the studies included in this dissertation also contribute to the growing body of evidence on the health effects of NTNPs [4, 5]. Collectively, these findings further undermine the claim that these products serve as effective harm reduction tools.

The potential role of e-cigarettes as a smoking cessation tool remains a matter of ongoing scientific debate. Some clinical trials and cessation programs suggest that e-cigarettes may help certain smokers to quit under controlled conditions and with appropriate support [15]. However, outside clinical settings, real-world evidence is increasingly indicating that these products are more often used alongside cigarettes than as a replacement, thus nullifying their potential public health benefits [1, 2, 17].

Overall, the accumulating evidence from independent research suggests that the harm reduction narrative surrounding NTNPs may be overstated. Rather than representing a pathway toward reducing smoking-related harm, the widespread diffusion of these products risks reinforcing nicotine addiction and potentially delaying smoking cessation.

Despite this growing body of evidence, the concept of harm reduction continues to be strongly promoted by the tobacco and nicotine industry [7, 13]. The framing of NTNPs as “reduced-risk” or “smoke-free” alternatives remains a central component of industry communication strategies, shaping both public perception and policy debates.

9.2.3.2 The attempt by the industry to influence the scientific evidence

A further contribution of the research conducted during this PhD concerns the investigation of the influence of the tobacco and nicotine industry on the scientific literature related to NTNPs. The study included in this dissertation analysed a large body of recent publications on NTNPs to assess whether the presence of conflicts of interest (COI), either direct or indirect, was associated with the stance of the scientific articles toward these products [7].

The results revealed a clear and substantial imbalance between independent publications and those with industry links. Overall, nearly two out of three publications with COI presented favourable conclusions about these products, whereas fewer than one in ten independent articles did so.

Importantly, this pattern was observed not only for studies directly funded by the tobacco industry but also for those supported through entities that appear formally independent but are financially linked to industry actors. In recent years, tobacco companies have increasingly relied on such intermediary organisations to fund or promote research on NTNPs. Our analysis showed that publications associated with these organisations exhibited levels of support for NTNPs comparable to those observed in directly industry-funded studies, suggesting that indirect funding mechanisms may represent an important strategy to shape the scientific debate while maintaining the appearance of independence.

This study provides one of the most comprehensive assessments to date of the role of COI in the scientific literature on NTNPs. These findings not only confirm, but also extend, the extensive body of evidence documenting the long-standing strategies of the tobacco industry to influence scientific research and public health debates. Historically, the tobacco industry has systematically funded and promoted research aimed at creating uncertainty about the health effects of its products, delaying regulatory action, and shaping scientific consensus in ways that protect its commercial interests [26, 27]. The results of this dissertation show that similar strategies are now being applied to NTNPs, but in more complex and less transparent forms.

The influence of the tobacco industry on science and policy is also especially relevant in the Italian context. Evidence from the Global Tobacco Industry Interference Index, an international monitoring initiative assessing the level of industry influence on tobacco control policies, indicates that Italy ranks among the countries with the highest levels of tobacco industry interference in Europe [28]. During the course of my PhD, I contributed to the assessment of the Italian score together with my research group.

Overall, the findings presented in this dissertation highlight how the tobacco and nicotine industry continues to play an active role in shaping the scientific narrative surrounding its emerging products. While independent research increasingly questions the public health benefits of NTNPs, industry-linked publications remain disproportionately supportive of them. Ensuring transparency in COI, strengthening editorial policies, and promoting independent funding mechanisms

are therefore essential steps to protect the integrity of research and ensure that public health policies are based on unbiased scientific evidence.

9.2.4 Overall contribution to the knowledge on novel tobacco and nicotine products

Taken together, the studies included in this dissertation provide a coherent and integrated contribution to the understanding of NTNPs across epidemiology, health effects, and industry influence. First, the evidence on prevalence and patterns of use consistently shows that NTNPs are predominantly integrated into existing smoking behaviours, with widespread dual and poly use and substantial uptake among younger populations, rather than functioning as smoking cessation tools in real-world settings. Second, the findings on health effects indicate that these products are not harmless alternatives, contributing to short-term adverse outcomes and potentially increasing vulnerability to specific health conditions. Third, the analysis of conflicts of interest demonstrates that the scientific evidence base is systematically influenced by industry-linked research, which disproportionately supports NTNPs and promotes the harm reduction narrative.
By combining these three domains, this dissertation advances current knowledge by moving beyond isolated assessments of NTNPs and providing a comprehensive evaluation of their population-level impact. Overall, the findings challenge the assumptions underlying harm reduction and highlight the need to interpret the role of NTNPs within a broader framework that simultaneously considers patterns of use, health consequences, and the influence of the tobacco and nicotine industry.
This work also fits within a broader and ongoing line of research carried out by the Laboratory of Lifestyle Research at the Mario Negri Institute for Pharmacological Research. In this context, the present dissertation both builds upon previous studies conducted within the group and contributes to shaping future research activities, forming part of a continuous effort to generate independent evidence on NTNPs and to inform the scientific literature and public health debate on this rapidly evolving topic.

9.3 Conclusions, implications and key considerations

9.3.1 Key messages

Over the past few decades, Italy has experienced a decline in the prevalence of cigarette smoking, largely due to comprehensive tobacco control policies and increased public awareness of the associated health risks. However, recent evidence suggests that this downward trend has stalled, with smoking prevalence showing signs of stagnation in recent years. Meanwhile, the popularity of NTNPs, particularly e-cigarettes and HTPs, has led to a growing trend of nicotine and tobacco consumption in Italy [2].

The results presented in this dissertation contribute to the growing body of evidence suggesting that these products do not effectively promote smoking cessation among adult smokers in real-world settings. Instead, the most common pattern of use is dual or poly use, whereby smokers continue to use conventional cigarettes alongside e-cigarettes or HTPs rather than replacing them [1, 2]. Moreover, the diffusion of NTNPs in Italy is particularly pronounced among younger populations. Our findings show that these devices are widely used even by minors, despite legal restrictions on their sale, raising concerns about their role in fostering early nicotine addiction and sustaining future smoking epidemics [3].

The studies included in this dissertation contribute to the emerging literature showing that e-cigarettes and HTPs are associated with adverse health effects, including short-term symptoms and potential cardiovascular impairment, as well as increased susceptibility to respiratory infections such as SARS-CoV-2 [4, 5]. Although the long-term health consequences of these products are still being investigated, current evidence increasingly challenges the perception that they represent safe alternatives to conventional cigarettes.

These findings call into question the central premise of the harm reduction narrative that has accompanied the introduction of NTNPs. If these products are rarely used as complete substitutes for cigarettes, are increasingly adopted by young people and minors, and are associated with measurable health risks, their potential to reduce harm at the population level becomes negligible. Under these conditions, the theoretical framework of harm reduction appears compromised.

Despite the growing body of independent evidence raising concerns about NTNPs, the promotion of these products continues to be strongly driven by the tobacco and nicotine industry. As shown in the research presented in this dissertation, publications linked to industry funding are substantially more likely to present favourable conclusions about these products than independent studies [7]. Moreover, the industry increasingly relies on intermediary organisations and foundations presented as independent to support and disseminate research aligned with its commercial interests. These strategies contribute to shaping the scientific and public discourse around NTNPs and risk undermining evidence-based tobacco control policies.

9.3.2 Research gaps and recommendations for the scientific and public health community

Despite the rapidly growing body of literature on NTNPs, there are still several significant research gaps. It is essential to address these gaps to ensure that scientific evidence can effectively guide tobacco control policies and public health interventions in a rapidly evolving nicotine market.

The first area that requires further clarification is the role of e-cigarettes in smoking cessation. It is important for the scientific community to distinguish

clearly between two fundamentally different contexts. Firstly, e-cigarettes can be investigated as potential smoking cessation tools in controlled clinical settings under medical supervision, in a similar way to other pharmacological aids for quitting smoking. In this context, the debate regarding their effectiveness remains open. On the other hand, e-cigarettes are widely marketed and used as consumer products within the broader narrative of harm reduction. Real-world evidence increasingly suggests that these products are rarely used as complete substitutes for cigarettes, being more often associated with dual use and continued nicotine dependence [1, 2]. Mixing up these two contexts can lead to confusion in both scientific literature and policy discussions. Therefore, future research should carefully differentiate between clinical cessation interventions and the population-level use of e-cigarettes as consumer products.

In line with this, there is a need to shift the research focus towards large, prospective, population-based studies that capture real-world patterns of use. Such studies should prioritise the analysis of trajectories of nicotine use, including initiation, dual and poly use, and cessation, in order to provide a more accurate assessment of the public health impact of NTNPs.A second major research gap concerns the long-term health effects of these products. Prospective cohort studies are required to evaluate the long-term impact of exclusive and combined use of NTNPs on significant health outcomes, such as respiratory diseases, cardiovascular conditions and cancer. Additionally, studies should incorporate detailed information on the duration and intensity of use to better understand potential dose–response relationships. Generating robust, independent evidence in this area is particularly important given the existence of manipulated evidence from research that is supported, either directly or indirectly, by the tobacco and nicotine industries [7].

Another key priority is to continue monitoring the spread of NTNPs within the population. Surveillance systems should not only track the use of currently available products, but also monitor the emergence of new nicotine devices that could enter the market in the coming years. Particular attention should be paid to adolescents and minors, as they are especially vulnerable to nicotine addiction and have already demonstrated a high level of experimentation with NTNPs. The tobacco and nicotine industry has repeatedly demonstrated its ability to adapt to regulatory environments by introducing new products, reformulating existing ones or adjusting marketing strategies to circumvent restrictions. Therefore, continuous surveillance and independent research are necessary to identify these strategies and ensure that tobacco control policies remain effective in protecting public health.

9.3.3 Recommendations for policy makers

The findings of this dissertation also offer several insights for policymakers involved in tobacco control and public health. A central priority is preventing industry interference in the development of tobacco control policies. This issue is

particularly relevant in the Italian context, where the level of industry interference has been documented as relatively high compared to other European countries [28]. Representatives of organisations linked to the tobacco or nicotine industry have even been invited to contribute to parliamentary discussions on health-related issues, where they actively promote NTNPs and the associated harm reduction narrative [29].

In this context, policymakers should strictly adhere to the principles set out in Article 5.3 of the World Health Organization's Framework Convention on Tobacco Control (WHO FCTC). This article explicitly requires governments to protect public health policies from the influence of the tobacco industry [30]. As a signatory to the Convention, Italy has committed to implementing these principles. Decisions relating to tobacco and nicotine products must be based solely on independent scientific evidence, not information or research promoted by industry-linked actors.

At the same time, the evidence presented in this dissertation suggests that there may be an opportunity to reinforce tobacco control policies in Italy. Findings from our nationally representative survey indicate broad support among the Italian population for a range of potential regulatory measures. These include policies aimed at preventing young people from starting to smoke, such as raising the legal age for purchasing tobacco products to 21, as well as fiscal measures such as substantial increases in tobacco taxation. Other effective strategies that have already been implemented in several countries include the introduction of plain packaging and extending existing smoke-free regulations to NTNPs [31, 32]. These could further contribute to reducing tobacco use in Italy. Notably, the substantial public support for these measures indicates that policymakers could implement them with significant popular backing.

Particular attention should also be given to prevention and health education initiatives targeting younger generations. Adolescents and young adults are the age groups most exposed to the spread of NTNPs and are particularly vulnerable to nicotine addiction. It is therefore essential to implement evidence-based health education programmes that focus on the risks associated with both conventional cigarettes and NTNPs. Such programmes should be developed and delivered by independent public health institutions and scientific experts. The tobacco or nicotine industry should be strictly excluded from the design or implementation of such initiatives. These recommendations are consistent with the WHO FCTC Article 12, which mandates evidence-based education and public awareness programmes on tobacco control, as well as with WHO Europe school-based prevention toolkits, all of which emphasise the importance of protecting young people from exposure to tobacco and nicotine products and from industry influence [33, 34].

9.3.4 Evidence-based messages for the general public

The majority of smokers want to quit [35]. The tobacco and nicotine industry is increasingly exploiting this motivation by promoting NTNPs as alternatives that supposedly help smokers reduce harm or quit. However, these products are not usually used as effective smoking cessation tools. Instead, many smokers use them alongside conventional cigarettes, resulting in dual use rather than quitting completely [1, 2, 35]. These findings suggest that, at the population level, NTNPs may have limited effectiveness as smoking cessation tools in real-world settings. Therefore, smokers who wish to quit should prioritise strategies that aim to achieve complete nicotine dependence cessation. Evidence-based smoking cessation methods already exist, including behavioural support, counselling and approved pharmacological therapies [36, 37]. These approaches are supported by a large body of independent scientific evidence and remain the most reliable way to successfully quit smoking.

The diffusion of NTNPs among adolescents and young adults represents an additional area of concern. Parents, teachers and educators play a crucial role in preventing nicotine addiction among younger generations. NTNPs are often designed and marketed to appear modern, harmless or socially acceptable, which may contribute to their uptake among younger populations. However, these products deliver nicotine, a highly addictive substance, and expose users to a range of toxic compounds that pose risks to human health. The evidence discussed in this dissertation highlights the importance of clear and evidence-based communication on the risks associated with both conventional and novel nicotine products, particularly in educational and family settings, in order to prevent the development of nicotine dependence among young people.

Finally, the potential impact of e-cigarette and HTP use on bystanders should also be considered. The aerosol emitted by these products contains nicotine, toxic substances and heavy metals, and therefore cannot be considered harmless. In this context, the findings support the extension of precautionary approaches already applied to conventional smoking, particularly in enclosed or crowded environments, to minimise involuntary exposure and protect public health.

Overall, the evidence presented in this dissertation highlights the need to interpret the growing diffusion of NTNPs within a comprehensive public health framework. By integrating findings on patterns of use, health effects, and industry influence, this work underscores the complexity of their impact and the importance of addressing these products through coordinated research, policy, and prevention strategies. In this perspective, strengthening independent evidence, ensuring clear public communication, and maintaining robust tobacco control measures remain essential to effectively respond to the evolving nicotine landscape and to protect population health, particularly among younger generations.

9.4 References

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Summary

Introduction

Tobacco smoking remains one of the leading preventable causes of disease and premature mortality worldwide. Over the past decades, comprehensive tobacco control policies have contributed to a substantial decline in smoking prevalence in many high-income countries, including Italy. However, the tobacco and nicotine market has undergone profound changes in recent years with the introduction and rapid diffusion of novel tobacco and nicotine products (NTNPs), particularly electronic cigarettes (e-cigarettes) and heated tobacco products (HTPs).
These products are often promoted as less harmful alternatives to conventional cigarettes and as tools that may support smoking cessation under a “harm reduction” framework. The tobacco and nicotine industry has strongly embraced this narrative, presenting NTNPs as part of a transition toward a “smoke-free future”. However, the real-world impact of these products on smoking behaviour, population health, and tobacco control policies remains highly debated.
At the same time, concerns have emerged regarding their potential health effects, their uptake among adolescents and young people, and the role played by the tobacco industry in shaping the scientific and policy debate surrounding these products. Understanding how NTNPs are used in the population, their potential health consequences, and the broader context in which they are promoted is therefore essential to inform public health policies and tobacco control strategies.
These issues are introduced and framed within the broader scientific and policy context in Chapter 1 (Introduction), which outlines the rationale, background, and objectives of the dissertation.

Aims and Data

This PhD dissertation aimed to investigate the role of NTNPs in the context of tobacco control and public health. The research focused specifically on three main areas: the patterns of NTNP use in the population; the potential health effects associated with NTNP use; and the influence of the tobacco and nicotine industries on the scientific evidence surrounding these products.
The dissertation is based on seven scientific articles presented in Chapters 2–8. These studies employed various methodological approaches, including cross-sectional surveys, epidemiological analyses, and systematic reviews with meta-analyses. Several studies used data from nationally representative surveys conducted in Italy to assess the prevalence and patterns of cigarette, e-cigarette and HTP use among adults (Chapter 3) and adolescents (Chapter 4). A systematic review examined patterns of use of HTPs at the international level (Chapter 2). Other studies analysed adverse events associated with the use of different nicotine products (Chapter 5), and the potential relationship between NTNP use and SARS-CoV-2 infection and COVID-19 outcomes (Chapter 6). In addition, one study assessed public attitudes towards tobacco control policies in Italy (Chapter 7), while another investigated the presence of conflicts of interest

in the scientific literature on NTNPs and their association with the conclusions reported in published articles (Chapter 8).
Together, these studies provide a comprehensive overview of the evolving landscape of tobacco and nicotine products, contributing new evidence on their implications for public health.

The role of novel tobacco and nicotine products on tobacco control

Although these products are often presented as tools that may support smoking cessation and reduce harm, emerging evidence from population-based studies suggests a more complex picture.
In Italy, smoking prevalence had declined substantially in the last decades, largely due to robust tobacco control policies. However, in the last decade this downward trend has slowed, with smoking prevalence showing signs of stagnation in recent years. At the same time, the use of NTNPs, particularly e-cigarettes and HTPs, has increased among adults.
Evidence from nationally representative surveys analysed in this dissertation shows that NTNPs are often used alongside conventional cigarettes rather than as a replacement for them. The dual use of cigarettes and e-cigarettes or HTPs is common among adult smokers, suggesting that these products often complement rather than substitute traditional smoking. This pattern raises concerns about the effectiveness of NTNPs as smoking cessation tools in real-world settings.
Even more concerning is the widespread use of NTNPs among adolescents and underage students. Despite legal restrictions prohibiting the sale of nicotine products to minors, a significant proportion of underaged students reported using cigarettes, e-cigarettes or HTPs. Dual and poly-product use are also common among adolescents. The prevalence of NTNP use among high school students exceeds that observed in the adult population, highlighting the appeal of these products to younger generations.
These findings suggest that NTNPs may perpetuate nicotine addiction among existing smokers while simultaneously facilitating its initiation among young people. Consequently, their overall impact on tobacco control and population health may be far less favourable than claimed.

Health effects of e-cigarettes and HTPs

In addition to their implications for tobacco control, NTNPs raise important health and safety concerns. Although these products are sometimes perceived as a safer alternative to conventional cigarettes, there is growing evidence to suggest that they are not risk-free.
The research presented in this dissertation contributes to the understanding of the health effects associated with e-cigarette and HTP use. One study examined the association between NTNP use and SARS-CoV-2 infection and COVID-19

outcomes through a systematic review and meta-analysis of the available literature. The results suggested that the use of NTNPs may be associated with an increased risk of infection and adverse disease outcomes.
Another study analysed short-term adverse events associated with cigarettes, e-cigarettes and HTPs. The findings showed that NTNP users reported various symptoms, and that adverse events were particularly prevalent among dual or poly-product users. These results suggest that using multiple nicotine products may increase the burden of short-term health symptoms.
Overall, while the long-term health effects of NTNPs remain incompletely understood due to their recent market introduction, the available evidence indicates that these products expose users to toxic substances and pose risks to human health.

The role of the tobacco industry on scientific evidence

The tobacco industry has a well-documented history of attempting to influence scientific research and public debate to protect its commercial interests.
As part of this dissertation, a systematic review was conducted to examine the relationship between conflicts of interest (COI) and the conclusions reported in the scientific literature on NTNPs. The results revealed a strong association between industry involvement and favourable conclusions regarding these products. While the vast majority of independent studies expressed concerns about NTNPs, publications with declared COI were far more likely to support these products.
Industry influence was evident not only through direct funding, but also through indirect links, such as research funded by organisations with financial ties to the tobacco industry. Often, these connections are not clearly disclosed, which make it difficult for readers and peer reviewers to identify potential sources of bias.
These findings emphasise the tobacco and nicotine industry's ongoing efforts to influence the evidence base surrounding NTNPs and harm reduction. They also underline the importance of transparency and strict conflict-of-interest policies, as well as independent funding for research in this field.

Conclusions

This dissertation presents new evidence on the evolving role of NTNPs in tobacco control and public health. While these products are frequently promoted as safer alternatives to cigarettes and potential smoking cessation tools, their real-world use indicates a different picture.
In Italy, smoking prevalence has stopped declining, while the use of e-cigarettes and HTPs has increased. At the same time, NTNPs have become popular among adolescents and minors, raising concerns about early nicotine dependence.
The available evidence also suggests that NTNPs are associated with health risks through exposure to toxic substances. Further research is needed to

understand their long-term impact fully, but the idea that these products are harmless alternatives to smoking is not supported by current scientific evidence. Finally, the dissertation emphasises the ongoing influence of the tobacco and nicotine industry on the scientific and policy discourse surrounding NTNPs.

In Chapter 9 (General Discussion), the findings from all studies are integrated and critically discussed, highlighting their implications for tobacco control, research, and policy, as well as identifying key research gaps and providing recommendations for public health practice.

To protect public health, independent research on NTNPs must be strengthened, policies must be kept free from industry interference, evidence-based tobacco and nicotine control measures must be implemented, and clear and accurate communication about the risks associated with NTNPs must be promoted to the public.

Riassunto

Introduzione

Il fumo di tabacco rimane una delle principali cause prevenibili di malattia e mortalità prematura in tutto il mondo. Negli ultimi decenni, politiche globali di controllo del tabagismo hanno contribuito a una sostanziale diminuzione della prevalenza del fumo in molti paesi ad alto reddito, tra cui l'Italia. Tuttavia, il mercato del tabacco e della nicotina ha subito profondi cambiamenti negli ultimi anni con l'introduzione e la rapida diffusione di nuovi prodotti del tabacco e della nicotina (NTNP), in particolare sigarette elettroniche e prodotti del tabacco riscaldato (HTP).
Questi prodotti sono spesso promossi come alternative meno dannose alle sigarette convenzionali e come strumenti che possono aiutare a smettere di fumare in un contesto di “riduzione del danno”. L'industria del tabacco e della nicotina ha sostenuto con forza questa narrativa, presentando i NTNP come parte di una transizione verso un “futuro senza fumo”. Tuttavia, l'impatto reale di questi prodotti sulle abitudini dei fumatori, sulla salute della popolazione e sulle politiche di controllo del tabacco rimane molto dibattuto.
Allo stesso tempo, sono emerse preoccupazioni riguardo ai loro potenziali effetti sulla salute, al loro utilizzo tra gli adolescenti e i giovani e al ruolo svolto dall'industria del tabacco nel plasmare il dibattito scientifico e politico su questi prodotti. Comprendere come i NTNP vengono utilizzati dalla popolazione, le loro potenziali conseguenze sulla salute e il contesto più ampio in cui vengono promossi è quindi essenziale per informare le politiche di salute pubblica e le strategie di controllo del tabacco.
Questi temi vengono presentati e inquadrati nel più ampio contesto scientifico e politico nel Capitolo 1 (Introduzione), che illustra le premesse, il contesto e gli obiettivi della tesi.

Obiettivi e Dati

Questa tesi di dottorato mirava a indagare il ruolo dei NTNP nel contesto del controllo del tabagismo e della salute pubblica. La ricerca si è concentrata in particolare su tre aree principali: i pattern di utilizzo dei NTNP nella popolazione; i potenziali effetti sulla salute associati all'uso dei NTNP; e l'influenza dell’industria del tabacco e della nicotina sull’evidenza scientifica relativa a questi prodotti.
La tesi si basa su sette articoli scientifici presentati nei Capitoli 2-8. Questi studi hanno utilizzato vari approcci metodologici, tra cui indagini trasversali, analisi epidemiologiche e revisioni sistematiche con meta-analisi. Diversi studi hanno utilizzato i dati provenienti da indagini rappresentative a livello nazionale condotte in Italia per valutare la prevalenza e i pattern di consumo di sigarette, sigarette elettroniche e HTP tra adulti (Capitolo 3) e adolescenti (Capitolo 4). Una revisione sistematica ha esaminato le modalità di utilizzo di HTP a livello internazionale (Capitolo 2). Altri studi hanno analizzato gli eventi avversi associati all'uso di

diversi prodotti a base di nicotina (Capitolo 5) e la potenziale relazione tra l'uso di NTNP e l'infezione da SARS-CoV-2 e gli esiti della malattia da COVID-19 (Capitolo 6). Inoltre, uno studio ha valutato il parere dell'opinione pubblica sulle politiche di lotta al tabagismo in Italia (Capitolo 7), mentre un altro studio ha indagato la presenza di conflitti di interesse nella letteratura scientifica sugli NTNP e la loro associazione con le conclusioni riportate negli articoli (Capitolo 8).
Nel loro insieme, questi studi forniscono una panoramica completa del panorama in evoluzione dei prodotti del tabacco e della nicotina, contribuendo alla conoscenza sulle loro implicazioni per la salute pubblica.

Il ruolo dei nuovi prodotti del tabacco e nicotina nel controllo del tabagismo

Sebbene questi prodotti siano spesso presentati come strumenti che possono aiutare a smettere di fumare e ridurre i danni alla salute dei fumatori, le prove emergenti da studi condotti sulla popolazione suggeriscono un quadro più complesso.
In Italia, la prevalenza del fumo era diminuita notevolmente negli ultimi decenni, in gran parte grazie a solide politiche di controllo del tabagismo. Tuttavia, nell'ultimo decennio questa tendenza al ribasso ha subito un rallentamento, con la prevalenza del fumo che mostra segni di stagnazione negli ultimi anni. Allo stesso tempo, l'uso di NTNP, in particolare sigarette elettroniche e HTP, è aumentato tra gli adulti.
I dati provenienti da indagini rappresentative a livello nazionale analizzati in questa tesi mostrano che i NTNP, piuttosto che sostituire le sigarette convenzionali, sono spesso utilizzati congiuntamente. L'uso duale di sigarette e sigarette elettroniche o HTP è comune tra i fumatori adulti, il che suggerisce che questi prodotti spesso si aggiungono piuttosto che sostituire il fumo tradizionale. Questo modello solleva preoccupazioni circa l'efficacia dei NTNP come strumenti per smettere di fumare in contesti reali.
Ancora più preoccupante è l'uso diffuso dei NTNP tra adolescenti e studenti minorenni. Nonostante le restrizioni legali che vietano la vendita di prodotti a base di nicotina ai minori, una percentuale significativa di studenti minorenni ha dichiarato di fare uso di sigarette, sigarette elettroniche o HTP. Anche l'uso combinato di più prodotti è comune tra gli adolescenti. La prevalenza dell'uso di NTNP tra gli studenti delle scuole superiori supera quella osservata nella popolazione adulta, evidenziando l'attrattiva di questi prodotti sulle generazioni più giovani.
Questi risultati suggeriscono che i NTNP possono perpetuare la dipendenza dalla nicotina tra i fumatori esistenti e allo stesso tempo facilitarne l'inizio tra i giovani. Di conseguenza, il loro impatto complessivo sul controllo del tabagismo e sulla salute della popolazione potrebbe essere molto meno favorevole di quanto venga dichiarato.

Effetti sulla salute di sigarette elettroniche e HTP

Oltre alle loro implicazioni per il controllo del tabagismo, i NTNP sollevano importanti preoccupazioni in materia di salute e sicurezza. Sebbene questi prodotti siano talvolta percepiti come un'alternativa più sicura alle sigarette convenzionali, vi sono prove crescenti che suggeriscono che non sono privi di rischi.
La ricerca presentata in questa tesi contribuisce alla comprensione degli effetti sulla salute associati all'uso di sigarette elettroniche e HTP. Uno studio ha esaminato l'associazione tra l'uso di NTNP e l'infezione da SARS-CoV-2 e gli esiti del COVID-19 attraverso una revisione sistematica e una meta-analisi della letteratura disponibile. I risultati hanno suggerito che l'uso di NTNP può essere associato a un aumento del rischio di infezione e di esiti negativi della malattia.
Un altro studio ha analizzato gli eventi avversi a breve termine associati alle sigarette, alle sigarette elettroniche e agli HTP. I risultati hanno mostrato che gli utilizzatori di NTNP hanno riportato vari sintomi, e che gli eventi avversi erano particolarmente diffusi tra gli utilizzatori duali. Questi risultati suggeriscono che l'uso di più prodotti a base di nicotina può aumentare il carico dei sintomi di salute a breve termine.
Nel complesso, mentre gli effetti a lungo termine sulla salute dei NTNP rimangono incompleti a causa della loro recente introduzione sul mercato, le prove disponibili indicano che questi prodotti espongono gli utilizzatori a sostanze tossiche e comportano rischi per la salute umana.

Il ruolo dell'industria del tabacco sull'evidenza scientifica

L'industria del tabacco ha una storia ben documentata di tentativi di influenzare la ricerca scientifica e il dibattito pubblico per proteggere i propri interessi commerciali.
Nell'ambito di questa tesi, è stata condotta una revisione sistematica per esaminare la relazione tra i conflitti di interesse (COI) e le conclusioni riportate nella letteratura scientifica sui NTNP. I risultati hanno rivelato una forte associazione tra il coinvolgimento dell'industria e le conclusioni favorevoli relative a questi prodotti. Mentre la stragrande maggioranza degli studi indipendenti ha espresso preoccupazioni sui NTNP, le pubblicazioni con COI dichiarati erano molto più propense a sostenere questi prodotti.
L'influenza dell'industria era evidente non solo attraverso il finanziamento diretto, ma anche attraverso collegamenti indiretti, come la ricerca finanziata da organizzazioni con legami finanziari con l'industria del tabacco. Spesso questi collegamenti non vengono chiaramente dichiarati, il che rende difficile per i lettori e i revisori identificare potenziali fonti di parzialità.
Questi risultati sottolineano i continui sforzi dell'industria del tabacco e della nicotina per influenzare l'evidenza scientifica su NTNP e riduzione del danno. Sottolineano inoltre l'importanza della trasparenza e di politiche rigorose in

materia di conflitti di interesse, nonché di finanziamenti indipendenti per la ricerca in questo campo.

Conclusioni

Questa tesi presenta nuove evidenze sul ruolo dei NTNP nel controllo del tabagismo e nella salute pubblica. Sebbene questi prodotti siano spesso promossi come alternative più sicure alle sigarette e potenziali strumenti per smettere di fumare, il loro utilizzo nella realtà mostra un quadro diverso.
In Italia, la prevalenza del fumo ha smesso di diminuire, mentre l'uso di sigarette elettroniche e HTP è aumentato. Allo stesso tempo, i NTNP sono diventati popolari tra gli adolescenti e i minori, sollevando preoccupazioni circa lo sviluppo precoce di dipendenza dalla nicotina.
L'evidenza disponibile suggerisce che i NTNP sono associati a rischi per la salute dovuti all'esposizione a sostanze tossiche. Sono necessarie ulteriori ricerche per comprenderne appieno l'impatto a lungo termine, ma l'idea che questi prodotti siano alternative innocue al fumo non è supportata dalle attuali prove scientifiche. Infine, si evidenzia l'influenza continua dell'industria del tabacco e della nicotina sul dibattito scientifico e politico che circonda i NTNP.
Nel capitolo 9 (Discussione generale) vengono sintetizzati e analizzati criticamente i risultati di tutti gli studi, mettendo in evidenza le loro implicazioni per la lotta al tabagismo, la ricerca e le politiche e individuando le principali lacune nella ricerca, oltre a fornire raccomandazioni per la pratica della sanità pubblica. Per proteggere la salute pubblica, è necessario rafforzare la ricerca indipendente sui NTNP, mantenere la politica libera dall'interferenza dell'industria, attuare misure di controllo del tabacco e della nicotina basate sull'evidenza scientifica e promuovere una comunicazione chiara e accurata sui rischi associati ai NTNP al pubblico.

Samenvatting

Inleiding

Het roken van tabak blijft wereldwijd een van de belangrijkste vermijdbare oorzaken van ziekte en vroegtijdige sterfte. De afgelopen decennia hebben uitgebreide maatregelen ter bestrijding van tabaksgebruik bijgedragen aan een aanzienlijke daling van het aantal rokers in veel hoge-inkomenslanden, waaronder Italië. De tabaks- en nicotinemarkt is de afgelopen jaren echter ingrijpend veranderd door de introductie en snelle verspreiding van nieuwe tabaks- en nicotineproducten (NTNP's), met name elektronische sigaretten (e-sigaretten) en verhitte tabaksproducten (HTP's).
Deze producten worden vaak gepromoot als minder schadelijke alternatieven voor conventionele sigaretten en als hulpmiddelen die kunnen helpen bij het stoppen met roken binnen het kader van 'schadebeperking'. De tabaks- en nicotine-industrie heeft deze boodschap sterk omarmd en positioneert NTNPs als onderdeel van een overgang naar een 'rookvrije toekomst'. De daadwerkelijke impact van deze producten op rookgedrag, de volksgezondheid en het tabaksontmoedigingsbeleid blijft echter omstreden.
Tegelijkertijd zijn er zorgen gerezen over de mogelijke gezondheidseffecten van deze producten, het gebruik ervan onder adolescenten en jongeren, en de rol die de tabaksindustrie speelt bij het vormgeven van het wetenschappelijke en beleidsdebat rond deze producten. Inzicht in hoe NTNPs in de bevolking worden gebruikt, de mogelijke gevolgen voor de gezondheid en de bredere context waarin ze worden gepromoot, is daarom essentieel voor de onderbouwing van het volksgezondheidsbeleid en strategieën voor tabaksontmoediging.
Deze onderwerpen worden in hoofdstuk 1 (Inleiding) geïntroduceerd en in een bredere wetenschappelijke en beleidsmatige context geplaatst; daarin worden de rationale, de achtergrond en de doelstellingen van het proefschrift uiteengezet.

Doelstellingen en gegevens

Dit proefschrift had tot doel de rol van NTNP's in de context van tabaksontmoediging en volksgezondheid te onderzoeken. Het onderzoek richtte zich specifiek op drie hoofdgebieden: de gebruikspatronen van NTNPs in de bevolking; de mogelijke gezondheidseffecten van NTNP-gebruik; en de invloed van de tabaks- en nicotine-industrie op het wetenschappelijk bewijs over deze producten.
Het proefschrift is gebaseerd op zeven wetenschappelijke artikelen die in hoofdstukken 2–8 worden gepresenteerd. Deze studies maakten gebruik van uiteenlopende methodologische benaderingen, waaronder transversale enquêtes, epidemiologische analyses en systematische reviews met meta-analyses. Een deel van de studies gebruikte gegevens uit nationaal representatieve enquêtes in Italië om de prevalentie en gebruikspatronen van sigaretten, e-sigaretten en HTP's onder volwassenen (hoofdstuk 3) en

adolescenten (hoofdstuk 4) te beoordelen. In een systematische review zijn de gebruikspatronen van HTP's op internationaal niveau onderzocht (hoofdstuk 2). Andere studies analyseerden bijwerkingen die samenhangen met het gebruik van verschillende nicotineproducten (hoofdstuk 5), evenals het mogelijke verband tussen NTNP-gebruik en SARS-CoV-2-infectie en COVID-19-uitkomsten (hoofdstuk 6). Daarnaast werd in één onderzoek de houding van het publiek ten opzichte van het tabaksontmoedigingsbeleid in Italië onderzocht (hoofdstuk 7), terwijl in een ander onderzoek werd gekeken naar het voorkomen van belangenconflicten in de wetenschappelijke literatuur over NTNP's en de relatie daarvan met de gerapporteerde conclusies (hoofdstuk 8).
Samen bieden deze studies een uitgebreid overzicht van het veranderende landschap van tabaks- en nicotineproducten en leveren ze nieuw bewijs over de implicaties voor de volksgezondheid.

De rol van nieuwe tabaks- en nicotineproducten bij tabaksontmoediging

Hoewel deze producten vaak worden voorgesteld als hulpmiddelen om te stoppen met roken en de schade te beperken, wijst recent bewijs uit bevolkingsonderzoek op een complexer beeld.
In Italië is de prevalentie van roken de afgelopen decennia aanzienlijk gedaald, grotendeels dankzij een krachtig tabaksontmoedigingsbeleid. In het afgelopen decennium is deze neerwaartse trend echter afgevlakt en vertoont de rookprevalentie de laatste jaren tekenen van stagnatie. Tegelijkertijd is het gebruik van NTNP's, met name e-sigaretten en HTP's, onder volwassenen toegenomen.
Op basis van gegevens van nationaal representatieve enquêtes die in dit proefschrift zijn geanalyseerd, blijkt dat NTNP's vaak naast conventionele sigaretten worden gebruikt, in plaats van als vervanging daarvoor. Dubbelgebruik van sigaretten en e-sigaretten of HTP's komt veel voor onder volwassen rokers, wat erop wijst dat deze producten traditioneel roken eerder aanvullen dan vervangen. Dit patroon roept vragen op over de effectiviteit van NTNPs als hulpmiddelen bij het stoppen met roken in de praktijk.
Nog zorgwekkender is het wijdverbreide gebruik van NTNPs onder adolescenten en minderjarigen. Ondanks wettelijke beperkingen die de verkoop van nicotineproducten aan minderjarigen verbieden, geeft een aanzienlijk deel van de minderjarige studenten aan sigaretten, e-sigaretten of HTP's te gebruiken. Ook het gelijktijdig gebruik van meerdere producten komt veel voor onder adolescenten. Het gebruik van NTNP's onder middelbare scholieren is hoger dan onder volwassenen, wat erop wijst dat deze producten vooral aantrekkelijk zijn voor jongere generaties.
Deze bevindingen wijzen erop dat NTNP's de nicotineverslaving bij bestaande rokers in stand kunnen houden en tegelijkertijd jongeren ertoe kunnen aanzetten om te beginnen met roken. Bijgevolg is het algehele effect op

tabaksontmoediging en volksgezondheid wellicht veel minder gunstig dan wordt beweerd.

Gezondheidseffecten van e-sigaretten en HTP's

Naast de gevolgen voor tabaksontmoediging roepen NTNP's belangrijke zorgen op over gezondheid en veiligheid. Hoewel deze producten soms worden beschouwd als een veiliger alternatief voor conventionele sigaretten, zijn er steeds meer aanwijzingen dat ze niet zonder risico zijn.
Het onderzoek dat in dit proefschrift wordt gepresenteerd draagt bij aan het inzicht in de gezondheidseffecten van e-sigaretten en HTP's. In één studie werd het verband tussen NTNPs en SARS-CoV-2-infectie en COVID-19-uitkomsten onderzocht aan de hand van een systematische review en meta-analyse van de beschikbare literatuur. De resultaten suggereren dat NTNP-gebruik mogelijk samenhangt met een verhoogd risico op infectie en ongunstige ziekte-uitkomsten.
Een andere studie analyseerde kortetermijnbijwerkingen die samenhangen met sigaretten, e-sigaretten en HTP's. Uit de bevindingen bleek dat gebruikers van NTNP's verschillende symptomen rapporteerden en dat bijwerkingen vooral voorkwamen bij gebruikers die meerdere producten tegelijk gebruikten. Deze resultaten suggereren dat het gebruik van meerdere nicotineproducten de last van gezondheidsklachten op korte termijn kan vergroten.
Hoewel langetermijngevolgen van NTNP's nog onvolledig bekend zijn vanwege hun recente introductie op de markt, wijst het beschikbare bewijs erop dat deze producten gebruikers blootstellen aan giftige stoffen en risico's voor de gezondheid met zich meebrengen.

De rol van de tabaksindustrie in het wetenschappelijke bewijs

De tabaksindustrie heeft een goed gedocumenteerde geschiedenis van pogingen om wetenschappelijk onderzoek en het publieke debat te beïnvloeden ter bescherming van haar commerciële belangen.
Als onderdeel van dit proefschrift is een systematische review uitgevoerd om de relatie te onderzoeken tussen belangenconflicten (COI) en de conclusies die in de wetenschappelijke literatuur over NTNP's worden gerapporteerd. De resultaten brachten een sterk verband aan het licht tussen betrokkenheid van de industrie en positieve conclusies over deze producten. Terwijl de overgrote meerderheid van de onafhankelijke studies bezorgdheid uitte over NTNP's, waren publicaties met een verklaard COI veel vaker geneigd deze producten te ondersteunen.
De invloed van de industrie manifesteerde zich niet alleen via directe financiering, maar ook via indirecte banden, zoals onderzoek dat werd gefinancierd door organisaties met financiële connecties met de tabaksindustrie. Deze verbanden

werden vaak niet expliciet vermeld, wat het voor lezers en peer reviewers moeilijk maakt om mogelijke bronnen van vertekening te identificeren.
Deze bevindingen benadrukken de voortdurende inspanningen van de tabaks- en nicotine-industrie om de wetenschappelijke onderbouwing rond NTNP's en schadebeperking te beïnvloeden. Ze onderstrepen tevens het belang van transparantie en stringent beleid inzake belangenconflicten, evenals onafhankelijke financiering van onderzoek op dit gebied.

Conclusies

Dit proefschrift presenteert nieuw bewijs over de veranderende rol van NTNP's in tabaksontmoediging en volksgezondheid. Hoewel deze producten vaak worden aangeprezen als veiliger alternatieven voor sigaretten en als mogelijke hulpmiddelen om te stoppen met roken, laat het gebruik ervan in de praktijk een ander beeld zien.
In Italië is de prevalentie van roken tot stilstand gekomen, terwijl het gebruik van e-sigaretten en HTP's is toegenomen. Tegelijkertijd zijn NTNP's populair geworden onder adolescenten en minderjarigen, wat zorgen oproept over vroegtijdige nicotineverslaving.
Het beschikbare bewijs suggereert bovendien dat NTNP's gezondheidsrisico's met zich meebrengen door blootstelling aan giftige stoffen. Verder onderzoek is nodig om de langetermijngevolgen volledig te begrijpen, maar het idee dat deze producten onschadelijke alternatieven voor roken zijn, wordt niet ondersteund door het huidige wetenschappelijke bewijs.
Ten slotte benadrukt het proefschrift de voortdurende invloed van de tabaks- en nicotine-industrie op het wetenschappelijke en beleidsdiscours rond NTNPs.
In hoofdstuk 9 (Algemene bespreking) worden de bevindingen van alle onderzoeken gebundeld en kritisch besproken, waarbij de implicaties voor tabaksontmoediging, onderzoek en beleid worden belicht, belangrijke lacunes in het onderzoek worden gesignaleerd en aanbevelingen worden gedaan voor de praktijk van de volksgezondheid.
Om de volksgezondheid te beschermen, moet onafhankelijk onderzoek naar NTNP's worden versterkt, moet beleid vrij blijven van inmenging door de industrie, moeten op bewijs gebaseerde maatregelen voor tabaks- en nicotinecontrole worden geïmplementeerd en moet duidelijke en accurate communicatie over de risico's van NTNP's richting het publiek worden bevorderd.

Impact Statement

In this chapter I describe how the main results of this thesis have been disseminated during the PhD trajectory and discuss their impact from a public health perspective. Moreover, I discuss how our findings might have an impact on the planning, implementation and evaluation of future research and public health practice.

Dissemination of results during the PhD trajectory

Peer-reviewed publications

The research conducted during this PhD has resulted in several peer-reviewed publications, contributing to the scientific literature on novel tobacco and nicotine products (NTNPs). Of the seven studies included in this dissertation, five have already been published in peer-reviewed journals, including four full research articles and one letter to the editor [1-5]. The manuscript reporting the review on conflicts of interest in the NTNP literature is currently under review in a peer-reviewed journal, while the manuscript based on the survey among Italian students conducted in collaboration with LILT has been submitted [6, 7].
These publications have already generated interest within the scientific community and have contributed to the growing body of independent evidence on NTNPs, particularly regarding their patterns of use, potential health effects, and implications for tobacco control. Together, these peer-reviewed contributions ensure that researchers, clinicians, policy-makers, and public health institutions can access, verify, and benefit from the thesis's findings.
Moreover, by being accessible through peer-reviewed channels, these studies can support evidence-informed decision-making, contributing to the development of guidelines, public health strategies, and future research priorities. In this sense, their impact lies not only in dissemination, but in their role in shaping how NTNPs are understood and addressed within the scientific and public health communities.

Other publications

During the PhD, I also authored several articles in Società Italiana di Tabaccologia's (SITAB) journal Tabaccologia, an Italian non–peer-reviewed journal dedicated to research and discussion on tobacco and nicotine control. These articles were aligned with the themes of my PhD programme and aimed at disseminating emerging evidence to a broader national audience of clinicians, researchers, and public health professionals.
Specifically, one article summarised the results of our study on the association between e-cigarette use and SARS-CoV-2 infection and COVID-19 outcomes. A second article presented data from a survey conducted in collaboration with the Italian League for the Fight against Cancer (Lega Italiana per la Lotta contro i

Tumori; LILT) on the use of tobacco and nicotine products among the population in the Lombardy region. Another contribution focused on the rapid rise of disposable e-cigarettes ("puff bars"), discussing their characteristics and potential public health implications. Finally, one article described the protocol for a forthcoming review on nicotine pouches, planned as a continuation of this research line.

Although these publications are not part of the peer-reviewed literature, they contribute to the timely dissemination of scientific findings and research perspectives within the Italian tobacco control community, helping to translate emerging evidence into discussion and awareness among professionals working in public health and clinical settings.

Furthermore, these publications have contributed to shaping the national discourse on tobacco control by providing independent, research-based perspectives in a space where industry narratives are also present. In this sense, their impact lies in facilitating knowledge transfer, supporting informed professional debate, and strengthening the capacity of the tobacco control community to respond to emerging challenges.

Oral presentations and awards

During the PhD programme, the results of this research were presented at several national and international scientific conferences, contributing to the dissemination and discussion of the findings within the tobacco control and public health community.

In 2022, preliminary results from the study on the association between e-cigarette use and SARS-CoV-2 infection were presented as a poster at the International Conference on E-Cigarettes in Paris. The same study was subsequently presented as an oral presentation at the European Conference on Tobacco or Health (ECToH) in Madrid in 2023.

Results from the study on short-term adverse events associated with the use of cigarettes, e-cigarettes, and heated tobacco products were presented as an e-poster at the World Conference on Tobacco Control (WCTC, Dublin 2025). Findings related to public support for tobacco taxation policies in Italy were presented at the European Network for Smoking and Tobacco Prevention (ENSP) Conference 2025 in Belgrade, which focused on the economic aspects of tobacco control.

Furthermore, the evaluation of public support for the Tobacco 21 policy and the Smoke-Free Generation initiative received the award for Best Scientific Research in Tobaccology at the 2024 national SITAB congress in Rimini.

Participation in these conferences provided valuable opportunities to discuss the results of this research with national and international experts in the field, receive feedback, establish professional connections, and further refine the interpretation

and dissemination of the findings within the broader scientific and public health community.

Podcast

Podcasts provided an additional avenue for dissemination, offering the opportunity to translate scientific concepts into formats that are accessible to a broader and more diverse audience.
During the PhD, I developed a three-episode podcast series entitled Tobacco-Free Talks, published on YouTube. The series was designed to communicate key issues related to tobacco and nicotine products through an engaging and conversational format [8-10]. It was developed during a research exchange at the ENSP in Brussels, conducted within the framework of the EUREST-RISE project funded by the European Commission [11]. This experience provided the opportunity to draw on ENSP's expertise in evidence-based communication and science dissemination.
The podcast episodes covered topics that extended beyond the specific scope of the PhD, including novel tobacco and nicotine products, second-hand smoke exposure, women's health, and the burden of tobacco-related diseases. These topics were presented within a broader narrative aimed at improving health literacy and addressing common misconceptions about tobacco and nicotine use. Importantly, the podcast episodes were also used in school settings as educational material, contributing to the dissemination of evidence-based information among adolescents. Reaching younger audiences is particularly relevant in the context of tobacco control, as this group is both highly exposed to NTNPs and especially vulnerable to nicotine addiction. The use of accessible and engaging formats facilitated discussion and critical reflection among students, supporting prevention efforts and reinforcing the role of early health education.
In addition, findings from this dissertation were further disseminated through participation in popular Italian YouTube podcasts featuring my daily supervisor, Silvano Gallus [12, 13]. These appearances reached audiences beyond the academic sphere, generating thousands of views and contributing to expanding the reach of independent scientific evidence on NTNPs to the general public.
Overall, these activities contributed to increasing the visibility and accessibility of the research, promoting more informed public discourse and supporting knowledge translation beyond traditional academic channels.

Teaching

During the PhD, I also had opportunities to contribute to teaching activities aimed at different audiences, where I presented and discussed findings from my research.

In 2024, I delivered a lecture to high school students during the Mario Negri Summer School project, focusing on the epidemiology of smoking in Italy. The lecture covered key trends in tobacco use and tobacco control policies, with particular attention to the emergence and diffusion of novel tobacco and nicotine products.

In the same year, I also contributed as a lecturer to the National School of Medical Tobaccology organised by SITAB. In this context, I presented an overview of novel tobacco and nicotine products, including e-cigarettes, heated tobacco products, and nicotine pouches, to an audience of physicians and healthcare professionals, discussing their characteristics, patterns of use, and potential public health implications, and presenting selected findings from my PhD research.

Additionally, I participated in an educational initiative on cancer prevention organised by the Italian Fondazione AIRC per la Ricerca sul Cancro, targeting fourth-year high school students. Within this programme, topics related to cancer prevention—including tobacco and nicotine use and the risks associated with NTNPs—were discussed. This initiative contributed to reinforcing prevention-oriented knowledge at an early stage and to promoting informed attitudes towards health behaviours among young people.

These teaching experiences provided an opportunity to translate scientific evidence into educational activities and to engage with students, clinicians, and healthcare professionals on current challenges in tobacco control.

Policy engagement and contribution to policy-making

During the PhD, the findings of this research also contributed to ongoing policy discussions on tobacco control in Italy. The Associazione Italiana di Oncologia Medica (AIOM) has promoted the “5 euro contro il fumo” initiative, a public petition advocating for a substantial increase in cigarette prices as a measure to reduce smoking prevalence and its associated health burden [14]. Within this context, selected results from this thesis—particularly those related to public support for tobacco control policies—were presented during a hearing at the Senato della Repubblica Italiana.

This contribution supported the integration of independent scientific evidence into policy discussions, particularly on the acceptability and potential effectiveness of fiscal and regulatory measures. By providing empirical data on population attitudes and behaviours, the research helped inform debates on the feasibility of strengthening tobacco control policies in Italy.

In addition, the findings were presented in a dedicated meeting with paediatricians, focusing on the prevention of nicotine use among younger populations. Engaging healthcare professionals working with children and adolescents is particularly relevant, as it can influence early prevention strategies and reinforce evidence-based communication with families.

Overall, these activities contributed to bridging research and policy by supporting evidence-informed decision-making and fostering dialogue between researchers, clinicians, and policy-makers on current challenges in tobacco control.

Overall impact of the research

Overall, the research conducted during this PhD has had a broad and multifaceted impact, contributing to scientific knowledge, professional dialogue, and public communication on novel tobacco and nicotine products.
Peer-reviewed publications represent the core scientific output of this work, ensuring that the findings are rigorously evaluated, permanently documented, and accessible to the international research and public health community. Presentations at national and international conferences further supported the dissemination of these results, providing opportunities to share evidence, receive feedback, and engage in scientific exchange with experts working in tobacco control.
Complementary dissemination activities, such as the podcast series, allowed the research to reach audiences beyond academic settings, translating complex scientific evidence into accessible formats for the wider public.
Taken together, these activities contributed to increasing the visibility and impact of the research, supporting evidence-informed discussion and strengthening awareness of the public health challenges associated with novel tobacco and nicotine products.

Future impact of the knowledge generated

The findings presented in this dissertation are expected to have important scientific and societal implications in the coming years. The evidence generated contributes to an evolving research field and addresses timely questions regarding the role of NTNPs in public health and tobacco control.
Part of the work included in this dissertation is still in the process of publication. Two manuscripts remain under review or under evaluation, including the systematic review on conflicts of interest in the scientific literature on NTNPs. This study highlights the strong association between industry-linked funding and favourable conclusions toward these products, showing that publications with conflicts of interest are far more likely to support NTNPs compared with independent research. By documenting how industry involvement may shape the scientific narrative surrounding these products, the study has the potential to contribute to ongoing discussions on research transparency, conflict-of-interest disclosure policies, and the need for stronger safeguards to protect the integrity of public health science.
Some of the research projects presented in this thesis represent the initial phase of longer-term investigations. In particular, the cohort study from which the data on short-term adverse events were derived includes planned follow-up waves

that will allow the analysis of longitudinal trajectories of nicotine product use and associated health outcomes. These future analyses will provide valuable insights into the long-term patterns of exclusive, dual, and poly-use of cigarettes, e-cigarettes, and heated tobacco products, as well as their potential implications for respiratory, cardiovascular, and other health conditions including cancer.

In addition, the study assessing public support for new tobacco control policies in Italy has particular relevance in the current policy context. Evidence on public support for tobacco control measures is particularly timely in the Italian context, where initiatives such as In recent years, several initiatives from civil society and public health organisations have advocated for stronger tobacco control measures, including proposals to substantially increase cigarette prices. One example is the campaign “5 Euro contro il fumo” are advocating for stronger regulatory and fiscal interventions., which promotes raising the price of a pack of cigarettes to five euros as a strategy to reduce smoking prevalence [14]. Evidence on public attitudes toward such measures can provide valuable support for policymakers by demonstrating that stronger tobacco control policies are not only effective but also supported by a substantial proportion of the population.

More broadly, the research presented in this dissertation contributes to strengthening the independent evidence base on NTNPs at a time when the scientific and policy debate around these products is rapidly evolving. By documenting patterns of use, potential health risks, and the influence of the tobacco and nicotine industry on scientific evidence, this work provides a foundation for future studies and may help inform evidence-based policies aimed at protecting public health and preventing nicotine addiction in future generations.

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About the author

Marco Scala was born in Brescia, Italy, on May 7, 1995. He obtained his Bachelor's degree in Bachelor Degree in Statistics and Information Management from the University of Milano-Bicocca, before completing a Master's degree in Biostatistics at the same University, graduating with honours (110/110 cum laude).

Since 2022, he has been a researcher at the Laboratory of Lifestyle Research of the Istituto di Ricerche Farmacologiche Mario Negri IRCCS in Milan, where his research focuses on the epidemiology of tobacco and nicotine products, tobacco control, and public health. His work has primarily investigated the patterns of use, health effects, and public health implications of novel tobacco and nicotine products, including electronic cigarettes, heated tobacco products, and nicotine pouches. During the same period, he pursued his PhD at CAPHRI (Care and Public Health Research Institute, Maastricht University).

Throughout his doctoral training, he authored several peer-reviewed scientific publications and presented his research at major national and international conferences, including the European Conference on Tobacco or Health (ECToH), the World Conference on Tobacco Control (WCTC), the European Network for Smoking and Tobacco Prevention (ENSP) Conference, and the International Conference on E-Cigarette. In 2024, he received the Award for Best Scientific Research in Tobaccology from the Italian Society of Tobaccology (SITAB) for his work on public support for innovative tobacco control policies in Italy.

His research has also contributed to several national and European collaborative projects, including the European Joint Action on Tobacco Control (JATC-2), and the Joint Action on Smoke- and Aerosol-Free Environments (JA-SAFE). He participated in the European networking project EUREST-RISE, completing a secondment period at ENSP in Brussels. His scientific interests include tobacco control policies, epidemiological methods, evidence synthesis, conflicts of interest in scientific research, and the prevention of non-communicable diseases. His long-term research goal is to generate high-quality independent evidence capable of informing public health policies and protecting populations from the health burden caused by tobacco and nicotine products, particularly among younger generations.

He is author or co-author of 21 articles published in peer-reviewed journals (Scopus h-index: 9).

List of publications

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