Smoking is the main preventable risk factor for noncommunicable diseases.

In Italy in 2023 the number of smokers was approximately fourteen million, with a minimal reduction in the total number in the last decade (20.9% in 2013 versus 19.3% in 2023).

Addiction and habituation to cigarette smoking

They develop because the nicotine in smoke and the gestures put in by smokers, have a "reinforcing" action.

Nicotine is not the primary cause of smoking-related diseases

Smoking-related diseases such as Chronic Obstructive Pulmonary Disease (COPD) are, instead, mainly a consequence of the combustion of toxic components produced by cigarette and tobacco smoke.

smoke & nicotine

LET'S GET THIS STRAIGHT

Nicotine IS NOT a carcinogen

Nicotine, unlike alcohol, is not a carcinogen and does not in itself cause cancer. It is a priority to adopt strategies aimed at reducing the risk associated with smoking.

Prevention of smoking initiation and promotion of cessation remain priority strategies

When it is not possible to completely eliminate cigarette consumption, it is essential to intervene with measures that reduce the risk associated with exposure to toxic substances produced by combustion.

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Epidemiological summary

Smoking is the main preventable risk factor for noncommunicable diseases (NCDs) [1]

According to Eurostat data (2019), the EU average of daily smokers over 15 is 18.4% [2]. In Italy (ISTAT, Italian National Institute of Statistics 2023 & ISS, 2024) [3,4], the number of smokers ranges from about ten to fourteen million, depending on the two main databases available: a number that is still too high, which requires concrete actions and responses, also because in the last decade the reduction in the prevalence curve of smokers has been almost flat.

In fact, smokers over 14 were 20.9% in 2013 and 19.3% in 2023 (figure 1).

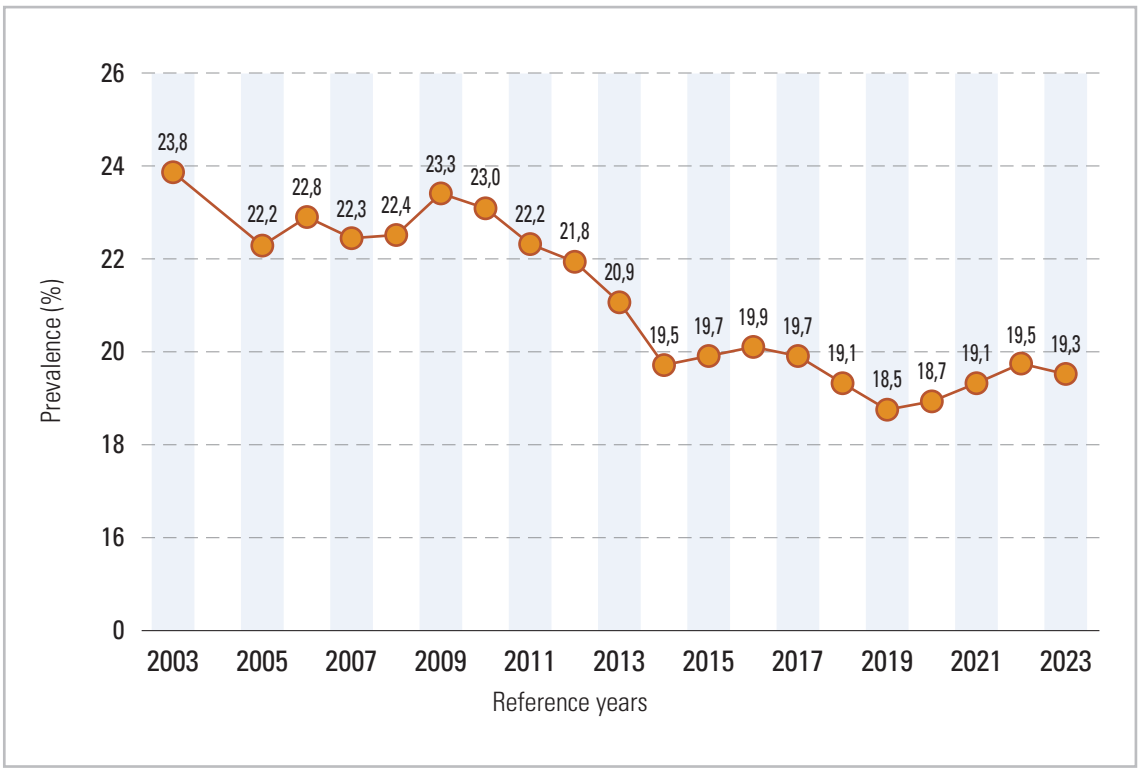


Fig. 1
ISTAT, Italian National Institute of Statistics. Prevalence of smokers in the 14+ population (2003-2023)

The fight against smoking therefore represents an important health policy challenge in Europe, as also highlighted by the Europe's Beating Cancer Plan (launched in 2021 by the European Union), which aims to achieve by 2040 a prevalence of smokers of less than 5%[5], preceded, in 2025, by a 30% reduction in the number of smokers compared to 2010 data, equal, in the Italian case, to an overall prevalence of 16%.[6]

To date, many countries base their policies to combat smoking exclusively on the principles of prevention and cessation. It is clear that both of these guidelines must also be pursued through effective policies of universal prevention, correct communication, the training of healthcare personnel in anti-smoking centres, capable of acting with a multidisciplinary approach in a homogeneous way across the territory.

Preventing smoking initiation and promoting cessation remain the priority strategies to reduce smoking-related risks. Yet, millions of smokers decide to continue smoking and this requires additional effort from the medical-scientific community and decision makers. It is necessary to strengthen current strategies and, where it is not possible to eliminate the use of cigarette smoking, try to limit the dangers arising from exposure to toxic substances, which, as is known, are present in significant quantities in tobacco products that involve the combustion process (cigarettes, cigars, rolling tobacco, etc.). In these circumstances, it is necessary to evaluate what the possible relative benefits may be in switching to the use of non-combustion products, with a significantly lower exposure profile to toxic or potentially toxic substances compared to cigarette smoke and how this perspective can be considered.

Harmful and potentially harmful substances in cigarette smoke

The burning of a cigarette generates smoke and ash

Cigarette smoke contains more than 7,000 harmful and potentially harmful constituents (HPHCs) (Figure 2). [7,8] There are several lists of HPHCs, drawn up by the main international public health agencies (e.g. WHO, IARC, FDA), which include the substances considered most toxic to health (from 9 to 93). [8-13]

HPHCs = Harmful and Potentially Harmful Constituents

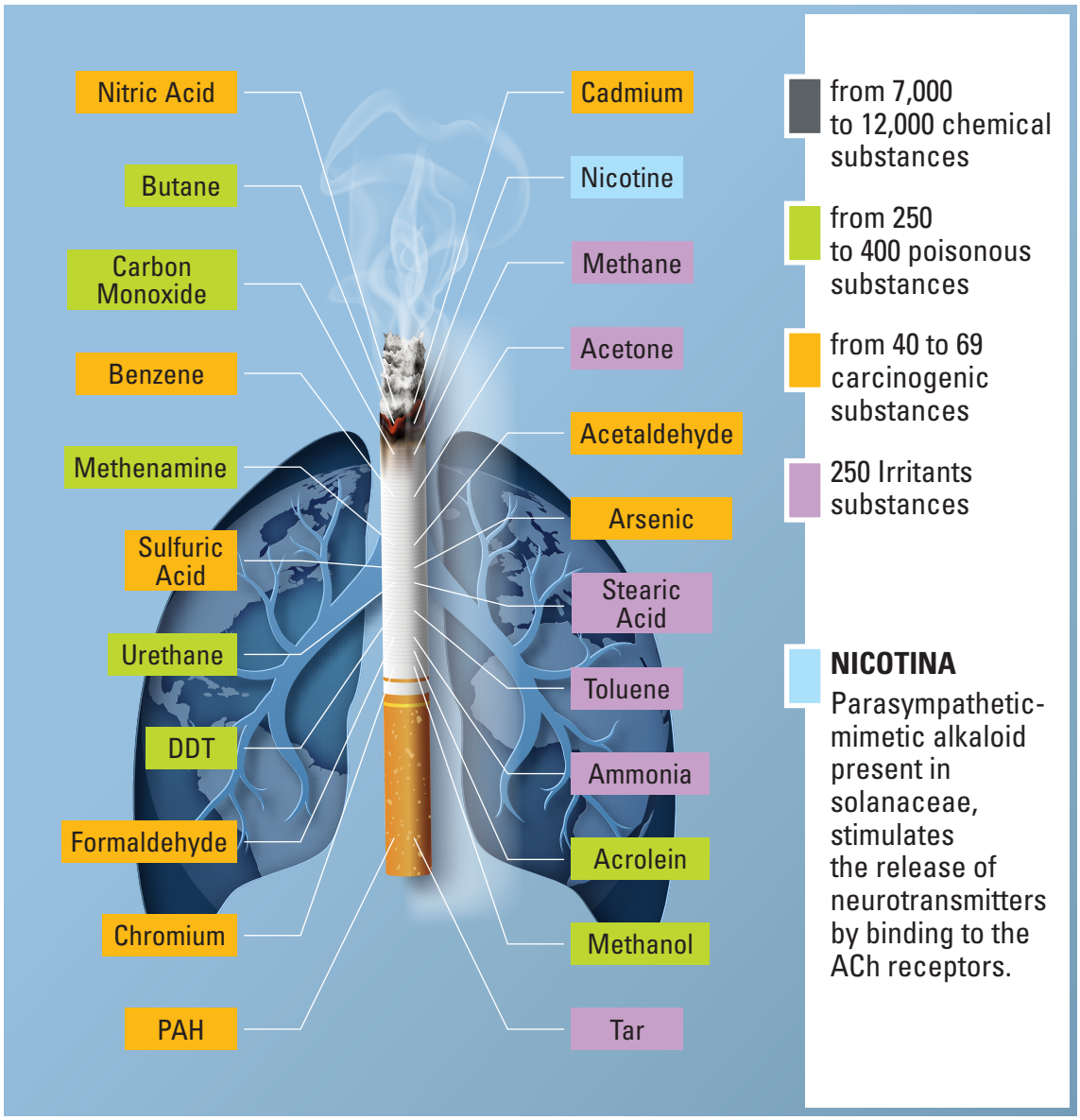
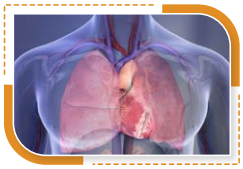


Fig. 2
Main harmful and potentially harmful constituents (HPHCs) in cigarette smoke

Among the most dangerous substances we should mention acetaldehyde, acrolein, benzene, pyrene and benzopyrene, butadiene, fluoranthene, carbon monoxide (CO), formaldehyde, nitrosamines, nitrogen oxides (NOx), ammonia, acrylamide, aromatic amines, just to name a few most implicated in the determinism of cardiovascular and respiratory damage.

But there are also arsenic, sulfuric acid, methanol and heavy metals (such as cadmium and lead, which are very harmful to reproductive health), as well as several substances that the IARC (International Agency for Research on Cancer) has classified in Group 1 (with high carcinogenic potential). [13]

Pathophysiology of smoking-related cardiovascular and pulmonary damage



Connection between smoking and risk of developing diseases and neoplasms

The connection between smoking and the risk of developing cardiovascular diseases (myocardial infarction, angina, acute coronary syndrome, peripheral arterial disease, stroke, etc.), respiratory diseases (Chronic Obstructive Pulmonary Disease - COPD, Emphysema, lung cancer, etc.) and neoplasms in sites other than the lung (e.g. tumours of the oral cavity, bladder, etc.) is now clear. The pathophysiological mechanisms underlying this relationship are complex, however, and the different substances present in cigarette smoke play different roles in increasing the risk of developing smoking-related diseases. Figure 3 shows schematically what are the main pathophysiological mechanisms and the different substances involved in these processes with regard to the cardiovascular system and in particular for the development of atherothrombotic phenomena. (14)

The harmful cardiovascular effects caused by smoking are mainly due to the toxic substances released by the combustion of tobacco, while nicotine, the substance responsible for addiction, although it has a sympathomimetic activity that can induce vasoconstriction and transiently reduce oxygen supply and increase tissue demand, plays a marginal role compared to carbon monoxide, oxidizing gaseous components and other toxic chemical substances.

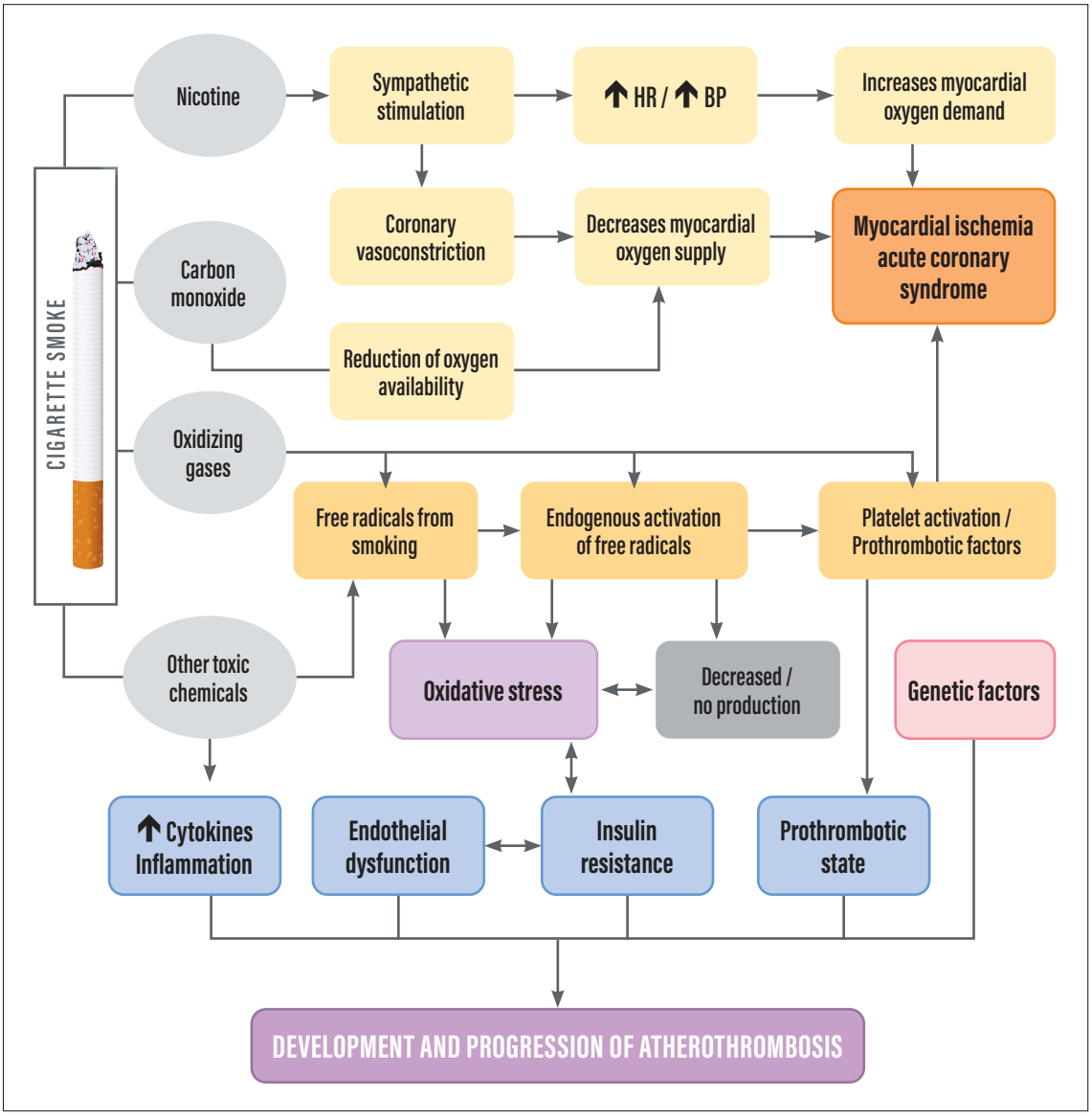


Fig. 3
Pathophysiological mechanisms of smoking-related cardiovascular diseases

In the case of smoking-related respiratory diseases, toxic substances produced as a result of the combustion process cause inflammation of the airways, leading to chronic bronchitis and increased mucus production. Free radicals and other chemicals damage the epithelial cells of the lungs, reducing their ability to regenerate and increasing the risk of infections (tissue damage). Chronic inflammation and tissue damage lead to reduced lung capacity and diseases such as Chronic Obstructive Pulmonary Disease (COPD) (reduced lung function). Prolonged exposure to carcinogens in smoke significantly increases the risk of developing lung cancer. [15]

Concerning the correlation between smoking-related pathologies and nicotine, it is worth remembering that the leading health authorities do not consider nicotine to be the main cause of smoking-related pathologies and that, even considering the levels of exposure to nicotine-containing products of adult and healthy consumers, the use of nicotine represents a limited risk to the health of the latter. [8, 15-17]

Addiction - habituation to smoking - nicotine

Addiction and habituation only occur if a substance or behaviour has a "reinforcing" action.

Chances that nicotine use will induce addiction depend on multiple factors:

- mode of use: release mechanism, release rate, quantity and pattern of release;
- environment surrounding the product: social factors and regulations;
- bio-psycho-social differences among users.

The potential of nicotine to induce addiction is based on three essential aspects:

1) in the initial phases of use, the need to use progressively higher quantities in order to produce the same effects in the smoker (a phenomenon called "tolerance");

2) "reinforcing" action (*reward*), which means that it is sufficiently gratifying to stimulate self-management;

3) sudden cessation can lead to a strong desire (craving) and a recognizable abstinence syndrome. [18]

In the case of cigarette smoking, the probability of developing an addiction and dependence comes from the combination of the "reinforcing" effects of the substance (nicotine) and the behaviours (ritual).

Cigarettes have a high potential for addiction, due to their rapid release through the lungs and the entire smoking ritual that surrounds their use. Nicotine alone, released relatively slowly in the case of so-called nicotine replacement therapy (NRT - used as a cessation aid and classified as a medicinal product), is used in cessation pathways, but these tools are nevertheless debated, as to their efficacy due to the pharmacokinetic profiles of the substance release and the different nature of use as to the behavioural profiles. [10,19-23]

Addiction to cigarette smoking extends beyond nicotine for several reasons:

- **behavioural:** smoking is often intertwined with daily habits and routines and can be associated with specific times, places, activities, reinforcing behaviours even in the absence of a craving for nicotine;
- **psychological bond:** smoking can be a defence mechanism against stress, anxiety, or boredom. Psychological comfort or routine can create an emotional bond;
- **social and cultural factors:** smoking can be influenced by the social environment and cultural norms; for some, it can be a means of connecting with others or integrating into social groups, adding a layer of social attachment;

- **sensory experience:** the sensory aspects of smoking, such as taste and smell, the feel of the cigarette, the act of lighting it, inhaling it. These sensory experiences go beyond the desire for nicotine;
- **other components of smoking:** the burning of tobacco releases MAO inhibitors (monoamine oxidase inhibitors) that prevent the inactivation of catecholamines within the neuron, causing more neurotransmitters and other chemicals to be released into the synaptic space that can impact the addictive potential of the product used.

Thus, although the nicotine in cigarette smoke has reinforcing properties that can lead to dependence/habituation, it is neither intoxicating nor functionally impairing (without psychotic effects) and does not meet many of the other criteria for drugs of abuse. [22]

In the case of cigarettes, taking into account the aforementioned behavioural aspects, it would perhaps be more appropriate to speak of addiction to smoking rather than exclusively to nicotine, also remembering that not all smokers (about 1 in 2) do not satisfy the DSM-5 criteria for addiction. [22,24]

The clinical impact of nicotine

- **Nicotine is addictive.**
- Nicotine **is not the primary cause of smoking-related diseases**, which are mainly a consequence of the toxic components produced by the combustion of cigarettes and tobacco. [25] This is why it is used in **nicotine replacement therapy** (NRT) as a cessation aid. [26]
- A misconception that absolutely needs to be dispelled: 61% of smokers and about 80% of American doctors think that nicotine causes cancer [27-29]. **Nicotine, unlike alcohol, is not a carcinogen and does not cause cancer in itself.** [25-26,30-31]
- Nicotine **does not directly cause cardiovascular disease**. Although it does not in itself cause cardiovascular disease, the relationship between nicotine and the cardiovascular system is complex. Nicotine **is not a cardiovascular toxicant but** has transient effects on the cardiovascular system and **its long-term use can induce adaptive vascular phenomena.** [8,26,32-37]
  The **sympathomimetic effects of nicotine** (such as increased heart rate and blood pressure, changes in cardiac contractility, vasoconstriction) occur acutely and are transient. [26 38-39]
- **Stimulants such as nicotine acutely increase arterial stiffness** (which is not indicative of disease risk), but chronic, long-term exposure may also lead to arterial stiffness compared to nonsmokers. These effects are generally less pronounced than those seen with cigarette smoking. [40-43]
- Even in the case of respiratory diseases, the **main cause of the onset of lung tumours and COPD** (Chronic Obstructive Pulmonary Disease) **are the substances produced as a result of the combustion process.** [44-45]
- As for the **effects of nicotine on the brain**, it is able to **induce so-called "adaptive"** changes (neuro-adaptation and neuroplasticity) **that are not permanent** and lead to a **return to the pre-exposure condition within a few weeks/months of quitting smoking**. Brain changes resulting from nicotine exposure (significant but reversible changes in neurotransmission activity) either underscore this neuroplasticity or are not indicative of brain damage or pathology. [26,46-47]

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