Tobacco and nicotine use

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Abstract | Tobacco smoking is a major determinant of preventable morbidity and mortality worldwide. More than a billion people smoke, and without major increases in cessation, at least half will die prematurely from tobacco-related complications. In addition, people who smoke have a significant reduction in their quality of life. Neurobiological findings have identified the mechanisms by which nicotine in tobacco affects the brain reward system and causes addiction. These brain changes contribute to the maintenance of nicotine or tobacco use despite knowledge of its negative consequences, a hallmark of addiction. Effective approaches to screen, prevent and treat tobacco use can be widely implemented to limit tobacco's effect on individuals and society. The effectiveness of psychosocial and pharmacological interventions in helping people quit smoking has been demonstrated. As the majority of people who smoke ultimately relapse, it is important to enhance the reach of available interventions and to continue to develop novel interventions. These efforts associated with innovative policy regulations (aimed at reducing nicotine content or eliminating tobacco products) have the potential to reduce the prevalence of tobacco and nicotine use and their enormous adverse impact on population health.

Tobacco is the second most commonly used psychoactive substance worldwide, with more than one billion smokers globally[1]. Although smoking prevalence has reduced in many high-income countries (HICs), tobacco use is still very prevalent in low-income and middle-income countries (LMICs). The majority of smokers are addicted to nicotine delivered by cigarettes (defined as tobacco dependence in the International Classification of Diseases, Tenth Revision (ICD-10) or tobacco use disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)). As a result of the neuro-adaptations and psychological mechanisms caused by repeated exposure to nicotine delivered rapidly by cigarettes, cessation can also lead to a well-characterized withdrawal syndrome, typically manifesting as irritability, anxiety, low mood, difficulty concentrating, increased appetite, insomnia and restlessness, that contributes to the difficulty in quitting tobacco use[2–4].

Historically, tobacco was used in some cultures as part of traditional ceremonies, but its use was infrequent and not widely disseminated in the population. However, since the early twentieth century, the use of commercial cigarettes has increased dramatically[5] because of automated manufacturing practices that enable large-scale production of inexpensive products that are heavily promoted by media and advertising. Tobacco use became highly prevalent in the past century and was followed by substantial increases in the prevalence of tobacco-induced diseases decades later[5]. It took decades to establish the relationship between tobacco use and associated health effects[6,7] and to discover the addictive role of nicotine in maintaining tobacco smoking[8,9], and also to educate people about these effects. It should be noted that the tobacco industry disputed this evidence to allow continuing tobacco sales[10]. The expansion of public health campaigns to reduce smoking has gradually decreased the use of tobacco in HICs, with marked increases in adult cessation, but less progress has been achieved in LMICs[1].

Nicotine is the addictive compound in tobacco and is responsible for continued use of tobacco despite harms and a desire to quit, but nicotine is not directly responsible for the harmful effects of using tobacco products (BOX 1). Other components in tobacco may modulate the addictive potential of tobacco (for example, flavours and non-nicotine compounds)[11]. The major harms related to tobacco use, which are well covered elsewhere[5], are linked to a multitude of compounds present in tobacco smoke (such as carcinogens, toxicants, particulate matter and carbon monoxide). In adults, adverse health outcomes of tobacco use include cancer in virtually all peripheral organs exposed to tobacco smoke and chronic diseases such as eye disease, periodontal disease, cardiovascular diseases, chronic obstructive pulmonary disease, stroke, diabetes mellitus, rheumatoid arthritis and disorders affecting immune function[5]. Moreover, smoking during pregnancy can increase the risk of adverse reproductive effects, such as ectopic pregnancy, low birthweight and preterm birth[5]. Exposure to

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https://doi.org/10.1038/s41572-022-00346-w

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secondhand cigarette smoke in children has been linked to sudden infant death syndrome, impaired lung function and respiratory illnesses, in addition to cognitive and behavioural impairments[5]. The long-term developmental effects of nicotine are probably due to structural and functional changes in the brain during this early developmental period[12,13].

Nicotine administered alone in various nicotine replacement formulations (such as patches, gum and lozenges) is safe and effective as an evidence-based smoking cessation aid. Novel forms of nicotine delivery systems have also emerged (called electronic nicotine delivery systems (ENDS) or e-cigarettes), which can potentially reduce the harmful effects of tobacco smoking for those who switch completely from combustible to e-cigarettes[14,15].

This Primer focuses on the determinants of nicotine and tobacco use, and reviews the neurobiology of nicotine effects on the brain reward circuitry and the functioning of brain networks in ways that contribute to the difficulty in stopping smoking. This Primer also discusses how to prevent tobacco use, screen for smoking, and offer people who smoke tobacco psychosocial and pharmacological interventions to assist in quitting.

Box 1 | **Tobacco products**

Conventional tobacco products include combustible products that produce inhaled smoke (most commonly cigarettes, bidis (small domestically manufactured cigarettes used in South Asia) or cigars) and those that deliver nicotine without using combustion (chewing or dipping tobacco and snuff). Newer alternative products that do not involve combustion include nicotine-containing e-cigarettes and heat-not-burn tobacco devices. Although non-combustion and alternative products may constitute a lesser risk than burned ones[14,15,194], no form of tobacco is entirely risk-free.

Moreover, this Primer presents emerging pharmacological and novel brain interventions that could improve rates of successful smoking cessation, in addition to public health approaches that could be beneficial.

Epidemiology

Prevalence and burden of disease. The Global Burden of Disease Project (GBDP) estimated that around 1.14 billion people smoked in 2019, worldwide, increasing from just under a billion in 1990 (REF.[1]). Of note, the prevalence of smoking decreased significantly between 1990 and 2019, but increases in the adult population meant that the total number of global smokers increased. One smoking-associated death occurs for approximately every 0.8–1.1 million cigarettes smoked[16], suggesting that the estimated worldwide consumption of about 7.4 trillion cigarettes in 2019 has led to around 7 million deaths[1].

In most populations, smoking prevalence is much higher among groups with lower levels of education or income[17] and among those with mental health disorders and other co-addictions[18,19]. Smoking is also more frequent among men than women (FIGS 1–3). Sexual and/or gender minority individuals have disproportionately high rates of smoking and other addictions[17,20]. In addition, the prevalence of smoking varies substantially between regions and ethnicities; smoking rates are high in some regions of Asia, such as China and India, but are lower in North America and Australia. Of note, the prevalence of mental health disorders and other co-addictions is higher in individuals who smoke compared with non-smokers[18,19,21]. For example, the odds of smoking in people with any substance use disorder is more than five times higher than the odds in people without a substance use disorder[19]. Similarly, the odds of smoking in people with any psychiatric disorder is more than three times higher than the odds of smoking in those without a psychiatric diagnosis[22]. In a study in the USA, compared with a population of smokers with no psychiatric diagnosis, subjects with anxiety, depression and phobia showed an approximately twofold higher prevalence of smoking, and subjects with agoraphobia, mania or hypomania, psychosis and antisocial personality or conduct disorders showed at least a threefold higher prevalence of smoking[22]. Comorbid disorders are also associated with higher rates of smoking[22,23].

Age at onset. Most smokers start smoking during adolescence, with almost 90% of smokers beginning between 15 and 25 years of age[24]. The prevalence of tobacco smoking among youths substantially declined in multiple HICs between 1990 and 2019 (REF.[25]). More recently, the widespread uptake of ENDS in some regions such as Canada and the USA has raised concerns about the long-term effects of prolonged nicotine use among adolescents, including the possible notion that ENDS will increase the use of combustible smoking products[25,26] (although some studies have not found much aggregate effect at the population level)[27].

Mortality. Smoking that commences in early adolescence or young adulthood and persists throughout life has a more severe effect on health than smoking that

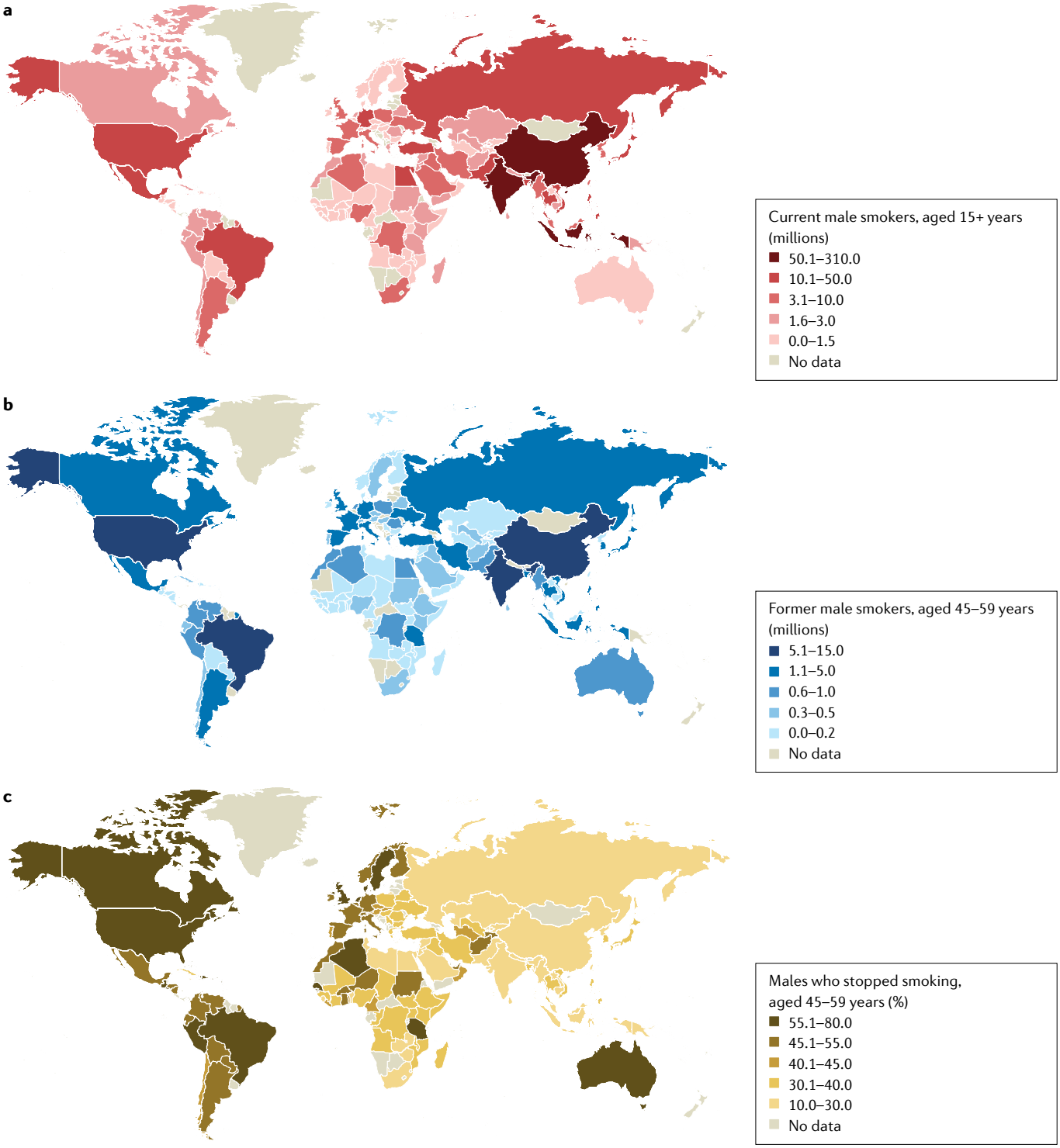

Fig. 1 | **Male smokers in the world. a** | Number of current male smokers aged 15 years or older per country expressed in millions. **b** | Former male smokers aged 45–59 years per country expressed in millions. **c** | Former male smokers aged 45–59 years per country expressed as the percentage of smokers who stopped. The data shown are for male smokers for the period 2015–2019 from countries with direct smoking surveys. The prevalence of smoking among males is less variable than among females. Data from REF.[1].

starts later in life and/or that is not persistent[16,28,29]. Over 640 million adults under 30 years of age smoke in 22 jurisdictions alone (including 27 countries in the European Union where central efforts to reduce tobacco dependence might be possible)[30]. In those younger than 30 years of age, at least 320 million smoking-related deaths will occur unless they quit smoking[31]. The actual number of smoking-related deaths might be greater than one in two, and perhaps as high as two in three, long-term smokers[5,16,29,32,33]. At least half of these deaths are

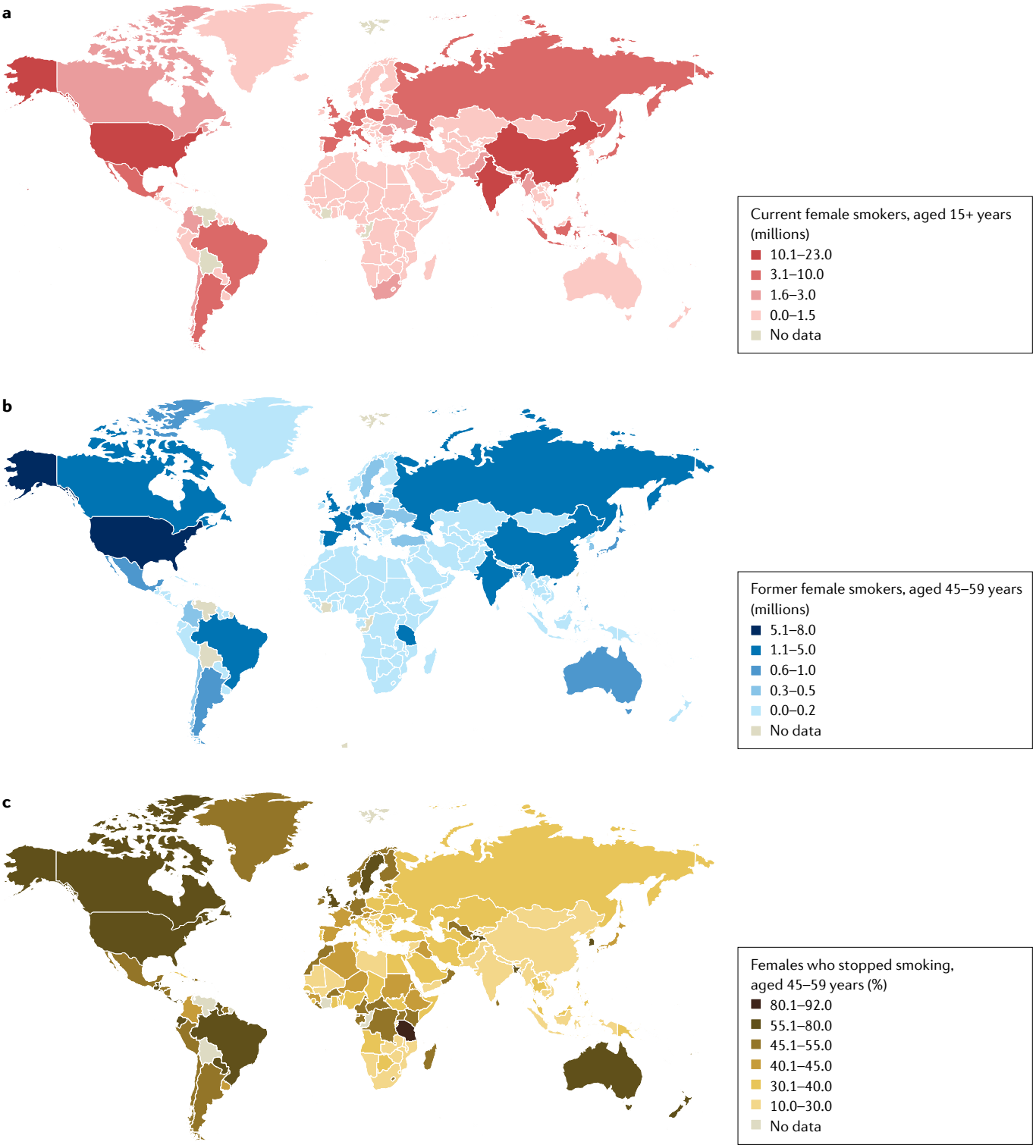

Fig. 2 | **Female smokers in the world. a** | Number of current female smokers aged 15 years or older per country expressed in millions. **b** | Former female smokers aged 45–59 years per country expressed in millions. **c** | Former female smokers aged 45–59 years per country expressed as the percentage of smokers who stopped. The data shown are for female smokers for the period 2015–2019 from countries with direct smoking surveys. The prevalence of smoking among females is much lower in East and South Asia than in Latin America or Eastern Europe. Data from REF.[1].

likely to occur in middle age (30–69 years)[16,29], leading to a loss of two or more decades of life. People who smoke can expect to lose an average of at least a decade of life versus otherwise similar non-smokers[16,28,29].

Direct epidemiological studies in several countries paired with model-based estimates have estimated that smoking tobacco accounted for 7.7 million deaths globally in 2020, of which 80% were in men

and 87% were current smokers[1]. In HICs, the major causes of tobacco deaths are lung cancer, emphysema, heart attack, stroke, cancer of the upper aerodigestive areas and bladder cancer[28,29]. In some lower income countries, tuberculosis is an additional important cause of tobacco-related death[29,34], which could be related to, for example, increased prevalence of infection, more severe tuberculosis/mortality and higher prevalence

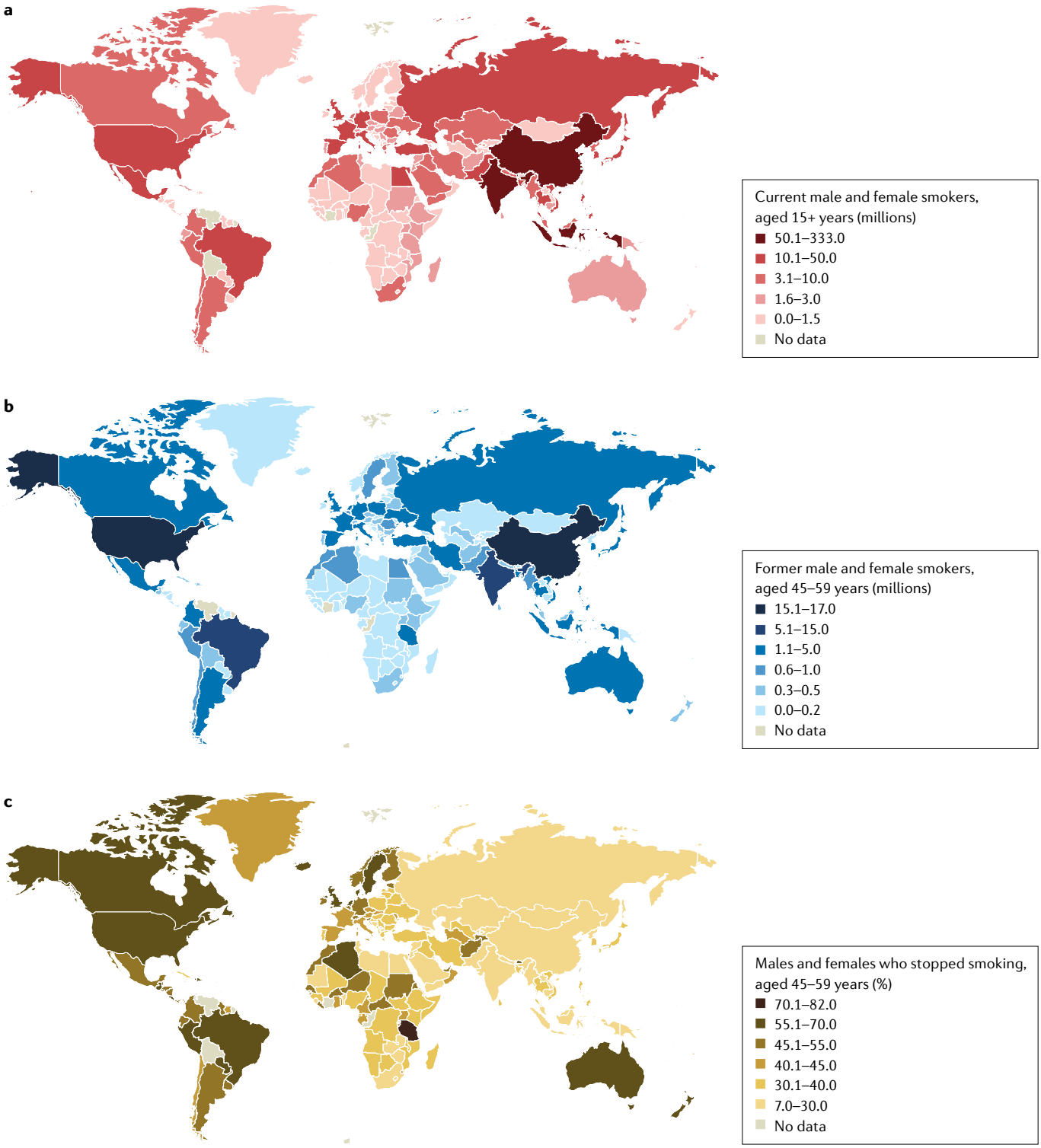

Fig. 3 | **Male and female smokers (combined) in the world. a** | Number of current male and female smokers aged 15 years or older per country expressed in millions. **b** | Former male and female smokers aged 45–59 years per country expressed in millions. **c** | Former male and female smokers aged 45–59 years per country expressed as the percentage of smokers who stopped. The data shown are for the period 2015–2019 from countries with direct smoking surveys. Cessation rates are higher in high-income countries, but also notably high in Brazil. Cessation is far less common in South and East Asia and Russia and other Eastern European countries, and also low in South Africa. Data from REF.[1].

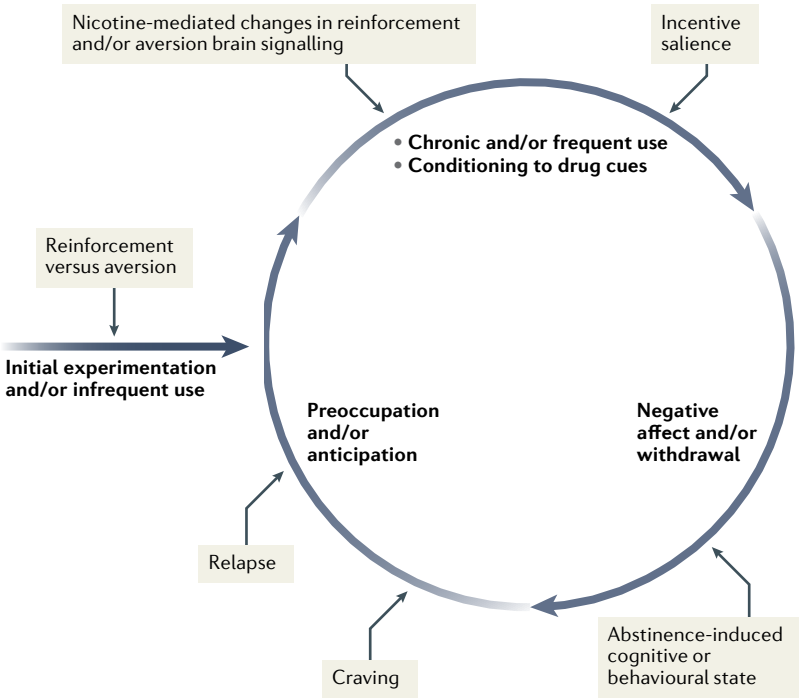

Fig. 4 | **Cycle of tobacco/nicotine use.** During initial use, nicotine exerts both reinforcing and aversive effects, which together determine the likelihood of continued use. As the individual transitions to more frequent patterns of chronic use, nicotine induces pharmacodynamic changes in brain circuits, which is thought to lead to a reduction in sensitivity to the aversive properties of the drug. Nicotine is also a powerful reinforcer that leads to the conditioning of secondary cues associated with the drug-taking experience (such as cigarette pack, sensory properties of cigarette smoke and feel of the cigarette in the hand or mouth), which serves to enhance the incentive salience of these environmental factors and drive further drug intake. When the individual enters into states of abstinence (such as daily during sleep at night or during quit attempts), withdrawal symptomology is experienced, which may include irritability, restlessness, learning or memory deficits, difficulty concentrating, anxiety and hunger. These negative affective and cognitive symptoms lead to an intensification of the individual's preoccupation to obtain and use the tobacco/nicotine product, and subsequently such intense craving can lead to relapse.

of treatment-resistant tuberculosis in smokers than in non-smokers in low-income countries[35,36].

Despite substantial reductions in the prevalence of smoking, there were 34 million smokers in the USA, 7 million in the UK and 5 million in Canada in 2017 (REF.[16]), and cigarette smoking remains the largest cause of premature death before 70 years of age in much of Europe and North America[1,16,28,29]. Smoking-associated diseases accounted for around 41 million deaths in the USA, UK and Canada from 1960 to 2020 (REF.[16]). Moreover, as smoking-associated diseases are more prevalent among groups with lower levels of education and income, smoking accounts for at least half of the difference in overall mortality between these social groups[37]. Any reduction in smoking prevalence reduces the absolute mortality gap between these groups[38].

Smoking cessation has become common in HICs with good tobacco control interventions. For example, in France, the number of ex-smokers is four times the number of current smokers among those aged 50 years or more[30]. By contrast, smoking cessation in LMICs remains uncommon before smokers develop tobacco-related diseases[39]. Smoking cessation greatly reduces the risks of smoking-related diseases. Indeed, smokers who quit smoking before 40 years of age avoid nearly all the increased mortality risks[31,33]. Moreover, individuals who quit smoking by 50 years of age reduce the risk of death from lung cancer by about two-thirds[40]. More modest hazards persist for deaths from lung cancer and emphysema[16,28]; however, the risks among former smokers are an order of magnitude lower than among those who continue to smoke[33].

Mechanisms/pathophysiology

Nicotine is the main psychoactive agent in tobacco and e-cigarettes. Nicotine acts as an agonist at nicotinic acetylcholine receptors (nAChRs), which are localized throughout the brain and peripheral nervous system[41]. nAChRs are pentameric ion channels that consist of varying combinations of α_2–α_7 and β_2–β_4 subunits, and for which acetylcholine (ACh) is the endogenous ligand[42–44]. When activated by nicotine binding, nAChR undergoes a conformational change that opens the internal pore, allowing an influx of sodium and calcium ions[45]. At postsynaptic membranes, nAChR activation can lead to action potential firing and downstream modulation of gene expression through calcium-mediated second messenger systems[46]. nAChRs are also localized to presynaptic membranes, where they modulate neurotransmitter release[47]. nAChRs become desensitized after activation, during which ligand binding will not open the channel[45].

nAChRs with varying combinations of α-subunits and β-subunits have differences in nicotine binding affinity, efficacy and desensitization rate, and have differential expression depending on the brain region and cell type[48–50]. For instance, at nicotine concentrations found in human smokers, β_2-containing nAChRs desensitize relatively quickly after activation, whereas α_7-containing nAChRs have a slower desensitization profile[48]. Chronic nicotine exposure in experimental animal models or in humans induces an increase in cortical expression of $\alpha_4\beta_2$-containing nAChRs[51–55], but also increases the expression of β_3 and β_4 nAChR subunits in the medial habenula (MHb)–interpeduncular nucleus (IPN) pathway[56,57]. It is clear that both the brain localization and the type of nAChR are critical elements in mediating the various effects of nicotine, but other factors such as rate of nicotine delivery may also modulate addictive effects of nicotine[58].

Neurocircuitry of nicotine addiction. Nicotine has both rewarding effects (such as a 'buzz' or 'high') and aversive effects (such as nausea and dizziness), with the net outcome dependent on dose and others factors such as interindividual sensitivity and presence of tolerance[59]. Thus, the addictive properties of nicotine involve integration of contrasting signals from multiple brain regions that process reward and aversion (FIG. 4).

The rewarding actions of nicotine have largely been attributed to the mesolimbic pathway, which consists of dopaminergic neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens and prefrontal cortex[60–62] (FIG. 5). VTA integrating circuits

and projection regions express several nAChR subtypes on dopaminergic, GABAergic, and glutamatergic neurons[63,64]. Ultimately, administration of nicotine increases dopamine levels through increased dopaminergic neuron firing in striatal and extrastriatal areas (such as the ventral pallidum)[65] (FIG. 6). This effect is involved in reward and is believed to be primarily mediated by the action of nicotine on α_4-containing and β_2-containing nAChRs in the VTA[66,67].

The aversive properties of nicotine are mediated by neurons in the MHb, which project to the IPN. Studies in rodents using genetic knockdown and knockout strategies demonstrated that the α_5-containing, α_3-containing and β_4-containing nAChRs in the MHb–IPN pathway mediate the aversive properties of nicotine that limit drug intake, especially when animals are given the opportunity to consume higher nicotine doses[68–72]. In addition to nAChRs, other signalling factors acting on the MHb terminals in the IPN also regulate the actions of nicotine. For instance, under conditions of chronic nicotine exposure or with optogenetic activation of IPN neurons, a subtype of IPN neurons co-expressing *Chrna5* (encoding the α_5 nAChR subunit) and *Amigo1* (encoding adhesion molecule with immunoglobulin-like domain 1) release nitric oxide from the cell body that retrogradely inhibits MHb axon terminals[70]. In addition, nicotine activates α_5-containing nAChR-expressing neurons that project from the nucleus tractus solitarius to the IPN, leading to release of glucagon-like peptide-1 that binds to GLP receptors on habenular axon terminals, which subsequently increases IPN neuron activation and decreases nicotine self-administration[73]. Taken together, these findings suggest a dynamic signalling process at MHb axonal terminals in the IPN, which regulates the addictive properties of nicotine and determines the amount of nicotine that is self-administered.

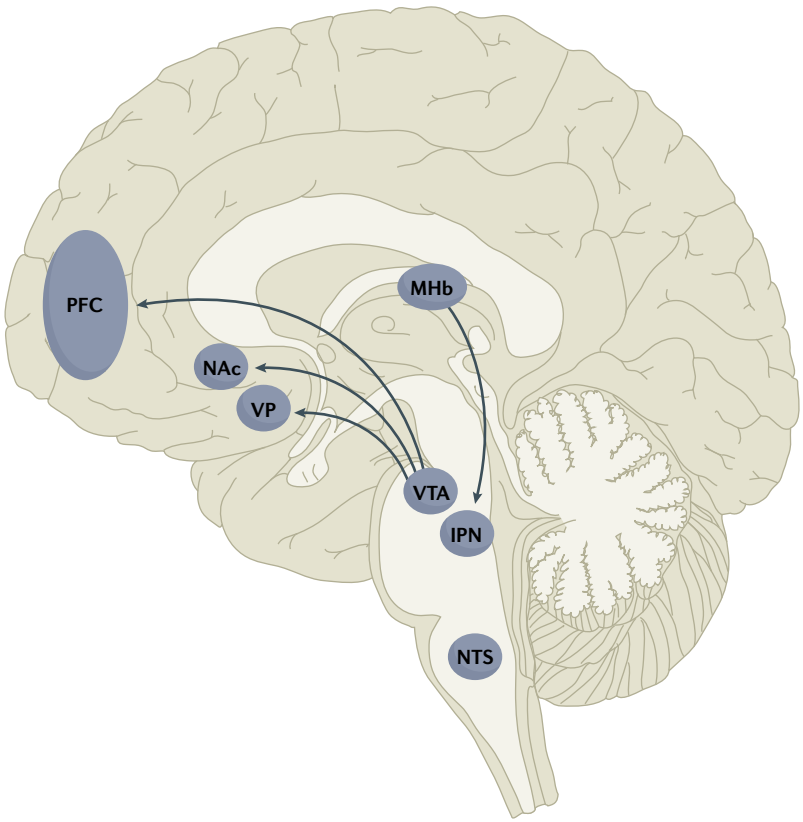

Fig. 5 | **Brain regions involved in nicotine addiction.** Multiple lines of research have demonstrated that nicotine reinforcement is mainly controlled by two brain pathways, which relay predominantly reward-related or aversion-related signals. The rewarding properties of nicotine that promote drug intake involve the mesolimbic dopamine projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). By contrast, the aversive properties of nicotine that limit drug intake and mitigate withdrawal symptoms involve the fasciculus retroflexus projection from the medial habenula (MHb) to the interpeduncular nucleus (IPN). Additional brain regions have also been implicated in various aspects of nicotine dependence, such as the prefrontal cortex (PFC), ventral pallidum (VP), nucleus tractus solitarius (NTS) and insula (not shown here for clarity). All of these brain regions are directly or indirectly interconnected as integrative circuits to drive drug-seeking and drug-taking behaviours.

Nicotine withdrawal in animal models can be assessed by examining somatic signs (such as shaking, scratching, head nods and chewing) and affective signs (such as increased anxiety-related behaviours and conditioned place aversion). Interestingly, few nicotine withdrawal somatic signs are found in mice with genetic knockout of the α_2, α_5 or β_4 nAChR subunits[74,75]. By contrast, β_2 nAChR-knockout mice have fewer anxiety-related behaviours during nicotine withdrawal, with no differences in somatic symptoms compared with wild-type mice[74,76].

In addition to the VTA (mediating reward) and the MHb–IPN pathway (mediating aversion), other brain areas are involved in nicotine addiction (FIG. 5). In animals, the insular cortex controls nicotine taking and nicotine seeking[77]. Moreover, humans with lesions of the insular cortex can quit smoking easily without relapse[78]. This finding led to the development of a novel therapeutic intervention modulating insula function (see Management, below)[79,80]. Various brain areas (shell of nucleus accumbens, basolateral amygdala and prelimbic cortex) expressing cannabinoid CB_1 receptors are also critical in controlling rewarding effects and relapse[81,82]. The α_1-adrenergic receptor expressed in the cortex also control these effects, probably through glutamatergic afferents to the nucleus accumbens[83].

Individual differences in nicotine addiction risk. Vulnerability to nicotine dependence varies between individuals, and the reasons for these differences are multidimensional. Many social factors (such as education level and income) play a role[84]. Broad psychological and social factors also modulate this risk. For example, peer smoking status, knowledge on effect of tobacco, expectation on social acceptance, exposure to passive smoking modulate the risk of initiating tobacco use[85,86].

Genetic factors have a role in smoking initiation, the development of nicotine addiction and the likelihood of smoking cessation. Indeed, heritability has been estimated to contribute to approximatively half of the variability in nicotine dependence[87–90]. Important advances in our understanding of such genetic contributions have evolved with large-scale genome-wide association studies of smokers and non-smokers. One of the most striking findings has been that allelic variation in the *CHRNA5–CHRNA3–CHRNB4* gene cluster, which encodes α_5, α_3 and β_4 nAChR subunits, correlates

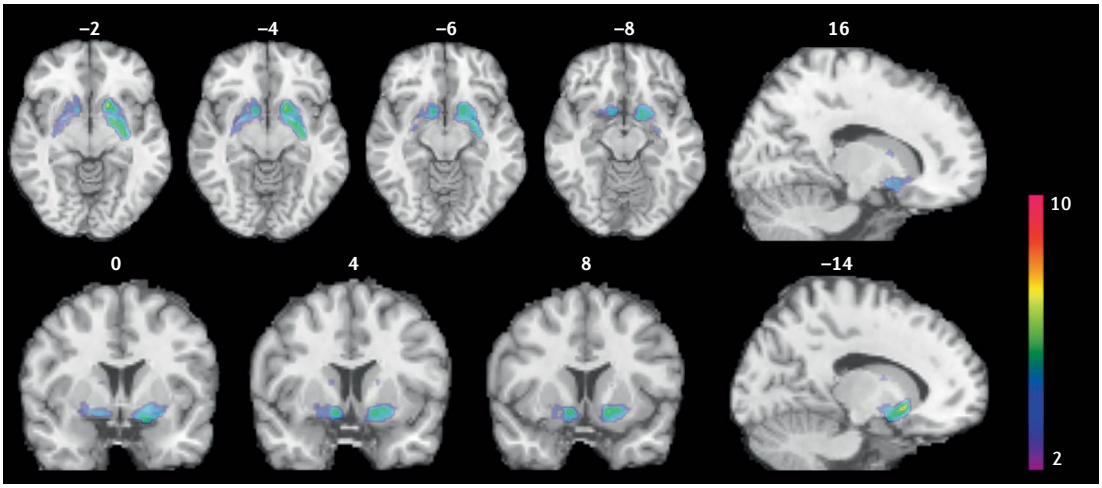

Fig. 6 | **PET imaging shows elevation of dopamine in the human brain after smoking.** Smokers received brain PET scans with [^{11}C]PHNO, a dopamine $D_{2/3}$ PET tracer that has high sensitivity in detecting fluctuations of dopamine. PET scans were performed during abstinence or after smoking a cigarette. Reduced binding potential (BP_{ND}) was observed after smoking, indicating increased dopamine levels in the ventral striatum and in the area that corresponds to the ventral pallidum. The images show clusters with statistically significant decreases of [^{11}C]PHNO BP_{ND} after smoking a cigarette versus abstinence condition. Those clusters have been superimposed on structural T1 MRI images of the brain. Reprinted from REF.[65], Springer Nature Limited.

with an increased vulnerability for nicotine addiction, indicated by a higher likelihood of becoming dependent on nicotine and smoking a greater number of cigarettes per day[91–95]. The most significant effect has been found for a single-nucleotide polymorphism in *CHRNA5* (rs16969968), which results in an amino acid change and reduced function of α_5-containing nAChRs[92].

Allelic variation in *CYP2A6* (encoding the CYP2A6 enzyme, which metabolizes nicotine) has also been associated with differential vulnerability to nicotine dependence[96–98]. *CYP2A6* is highly polymorphic, resulting in variable enzymatic activity[96,99,100]. Individuals with allelic variation that results in slow nicotine metabolism consume less nicotine per day, experience less-severe withdrawal symptoms and are more successful at quitting smoking than individuals with normal or fast metabolism[101–104]. Moreover, individuals with slow nicotine metabolism have lower dopaminergic receptor expression in the dopamine D2 regions of the associative striatum and sensorimotor striatum in PET studies[105] and take fewer puffs of nicotine-containing cigarettes (compared with de-nicotinized cigarettes) in a forced choice task[106]. Slower nicotine metabolism is thought to increase the duration of action of nicotine, allowing nicotine levels to accumulate over time, therefore enabling lower levels of intake to sustain activation of nAChRs[107].

Large-scale genetic studies have identified hundreds of other genetic loci that influence smoking initiation, age of smoking initiation, cigarettes smoked per day and successful smoking cessation[108]. The strongest genetic contributions to smoking through the nicotinic receptors and nicotine metabolism are among the strongest genetic contributors to lung cancer[109]. Other genetic variations (such as those related to cannabinoid, dopamine receptors or other neurotransmitters) may affect certain phenotypes related to smoking (such as nicotine preference and cue-reactivity)[110–115].

Diagnosis, screening and prevention

Screening for cigarette smoking. Screening for cigarette smoking should happen at every doctor's visit[116]. In this regard, a simple and direct question about a person's tobacco use can provide an opportunity to offer information about its potential risks and treatments to assist in quitting. All smokers should be offered assistance in quitting because even low levels of smoking present a significant health risk[33,117,118]. Smoking status can be assessed by self-categorization or self-reported assessment of smoking behaviour (TABLE 1). In people who smoke, smoking frequency can be assessed[119] and a combined quantity frequency measure such as pack-year history (that is, average number of cigarettes smoked per day multiplied by the number of years, divided by 20), can be used to estimate cumulative risk of adverse health outcomes. The Association for the Treatment of Tobacco Use and Dependence recommends that all electronic health records should document smoking status using the self-report categories listed in TABLE 1.

Owing to the advent of e-cigarettes and heat-not-burn products, and the popularity of little cigars in the US that mimic combustible cigarettes, people who use tobacco may use multiple products concurrently[120,121]. Thus, screening for other nicotine and tobacco product use is important in clinical practice. The self-categorization approach can also be used to describe the use of these other products.

Diagnosis. Traditionally tobacco use has been classified according to whether the smoker meets criteria for nicotine dependence in one of the two main diagnostic classifications: the DSM[122] (tobacco use disorder) and the ICD (tobacco dependence)[123]. The diagnosis of tobacco use disorder according to DSM-5 criteria requires the presence of at least 2 of 11 symptoms that have produced marked clinical impairment or distress

within a 12-month period (BOX 2). Of note, these symptoms are similar for all substance use disorder diagnoses and may not all be relevant to tobacco use disorder (such as failure to complete life roles). In the ICD-10, codes allow the identification of specific tobacco products used (cigarettes, chewing tobacco and other tobacco products).

Dependence can also be assessed as a continuous construct associated with higher levels of use, greater withdrawal and reduced likelihood of quitting. The level of dependence can be assessed with the Fagerström Test for Nicotine Dependence, a short questionnaire comprising six questions[124] (BOX 2). A score of ≥4 indicates moderate to high dependence. As very limited time may be available in clinical consultations, the Heaviness of Smoking Index (HSI) was developed, which comprises two questions on the number of cigarettes smoked per day and how soon after waking the first cigarette is smoked[125]. The HSI can guide dosing for nicotine replacement therapy (NRT).

Other measures of cigarette dependence have been developed but are not used in the clinical setting, such as the Cigarette Dependence Scale[126], Hooked on Nicotine Checklist[127], Nicotine Dependence Syndrome Scale[128], the Wisconsin Inventory of Smoking Dependence Motives (Brief)[129] and the Penn State Cigarette Dependence Index[130]. However, in practice, these are not often used, as the most important aspect is to screen for smoking and encourage all smokers to quit smoking regardless of their dependence status.

Prevention. Young people who do not start smoking cigarettes between 15 and 25 years of age have a very low risk of ever smoking[24,131,132]. This age group provides a critical opportunity to prevent cigarette smoking using effective, evidence-based strategies to prevent smoking initiation and reduce escalation from experimentation to regular use[131–135].

Table 1 | **Smoking self-report screening questions**

Type of assessment	Question	Possible responses
Self-categorization	Which of these best describe your smoking history?	Current daily/every day smoker
		Current non-daily/some day smoker
		Former smoker
		Never smoker
		Smoking status unknown
Categorization via assessment of smoking behaviour	Have you ever smoked a cigarette?	N = Never smoker
		Y = Ever smoker
	Have you smoked more than 100 cigarettes in your lifetime?	N = Never smoker
		Y = Ever smoker
	Have you smoked in the last 30 days?	N (but Ever smoker) = Former smoker
		Y = Current smoker
	Do you smoke every day or almost every day of the week?	N (but Current smoker) = Non-daily smoker
		Y = Daily smoker

Effective prevention of cigarette uptake requires a comprehensive package of cost-effective policies[134,136,137] to synergistically reduce the population prevalence of cigarette smoking[131,135]. These policies include high rates of tobacco taxation[30,134,137,138], widespread and rigorously enforced smoke-free policies[139], bans on tobacco advertising and promotions[140], use of plain packaging and graphic warnings about the health risks of smoking[135,141], mass media and peer-based education programmes to discourage smoking, and enforcement of laws against the sale of cigarettes to young people below the minimum legal purchase age[131,135]. These policies make cigarettes less available and affordable to young people. Moreover, these policies make it more difficult for young people to purchase cigarettes and make smoking a much less socially acceptable practice. Of note, these policies are typically mostly enacted in HICs, which may be related to the declining prevalence of smoking in these countries, compared with the prevalence in LMICs.

Management

Pharmacotherapy. Three evidence-based classes of pharmacotherapy are available for smoking cessation: NRT (using nicotine-based patches, gum, lozenges, mini-lozenges, nasal sprays and inhalers), varenicline (a nAChR partial agonist), and bupropion (a noradrenaline/dopamine reuptake inhibitor that also inhibits nAChR function and is also used as an antidepressant). These FDA-approved and EMA-approved pharmacotherapies are cost-effective smoking cessation treatments that double or triple successful abstinence rates compared with no treatment or placebo controls[116,142].

Combinations of pharmacotherapies are also effective for smoking cessation[116,142]. For example, combining NRTs (such as the steady-state nicotine patch and as-needed NRT such as gum or mini-lozenge) is more effective than a single form of NRT[116,142,143]. Combining NRT and varenicline is the most effective smoking cessation pharmacotherapy[116,142,143]. Combining FDA-approved pharmacotherapy with behavioural counselling further increases the likelihood of successful cessation[142]. Second-line pharmacotherapies (for example, nortriptyline) have some potential for smoking cessation, but their use is limited due to their tolerability profile.

All smokers should receive pharmacotherapy to help them quit smoking, except those in whom pharmacotherapy has insufficient evidence of effectiveness (among adolescents, smokeless tobacco users, pregnant women or light smokers) or those in whom pharmacotherapy is medically contraindicated[144]. TABLE 2 provides specific information regarding dosing and duration for each FDA-approved pharmacotherapy. Extended use of pharmacotherapy beyond the standard 12-week regimen after cessation is effective and should be considered[116]. Moreover, preloading pharmacotherapy (that is, initiating cessation medication in advance of a quit attempt), especially with the nicotine patch, is a promising treatment, although further studies are required to confirm efficacy.

Cytisine has been used for smoking cessation in Eastern Europe for a long time and is available in some countries (such as Canada) without prescription[145].

Box 2 | **DSM-5 criteria for tobacco use disorder and items of the Fagerström Test for nicotine dependence**

DSM-5 (REF.[122])

Taxonomic and diagnostic tool for tobacco use disorder published by the American Psychiatric Association.

A problematic pattern of tobacco use leading to clinically significant impairment or distress as manifested by at least two of the following, occurring within a 12-month period.

- Tobacco often used in larger amounts or over a longer period of time than intended
- A persistent desire or unsuccessful efforts to reduce or control tobacco use
- A great deal of time spent in activities necessary to obtain or use tobacco
- Craving, or a strong desire or urge to use tobacco
- Recurrent tobacco use resulting in a failure to fulfil major role obligations at work, school or home
- Continued tobacco use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of tobacco (for example, arguments with others about tobacco use)
- Important social, occupational or recreational activities given up or reduced because of tobacco use
- Recurrent tobacco use in hazardous situations (such as smoking in bed)
- Tobacco use continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by tobacco use
- Tolerance, defined by either of the following.
  - A need for markedly increased amounts of tobacco to achieve the desired effect
  - A markedly diminished effect with continued use of the same amount of tobacco
- Withdrawal, manifesting as either of the following.
  - Withdrawal syndrome for tobacco
  - Tobacco (or a closely related substance, such as nicotine) taken to relieve or avoid withdrawal symptoms

Fagerström Test for Nicotine Dependence[124]

A standard instrument for assessing the intensity of physical addiction to nicotine.

- How soon after you wake up do you smoke your first cigarette?
  - Within 5 min (scores 3 points)
  - 5 to 30 min (scores 2 points)
  - 31 to 60 min (scores 1 point)
  - After 60 min (scores 0 points)
- Do you find it difficult not to smoke in places where you should not, such as in church or school, in a movie, at the library, on a bus, in court or in a hospital?
  - Yes (scores 1 point)
  - No (scores 0 points)
- Which cigarette would you most hate to give up; which cigarette do you treasure the most?
  - The first one in the morning (scores 1 point)
  - Any other one (scores 0 points)
- How many cigarettes do you smoke each day?
  - 10 or fewer (scores 0 points)
  - 11 to 20 (scores 1 point)
  - 21 to 30 (scores 2 points)
  - 31 or more (scores 3 points)
- Do you smoke more during the first few hours after waking up than during the rest of the day?
  - Yes (scores 1 point)
  - No (scores 0 points)
- Do you still smoke if you are so sick that you are in bed most of the day or if you have a cold or the flu and have trouble breathing?
  - Yes (scores 1 point)
  - No (scores 0 points)

A score of 7–10 points is classified as highly dependent; 4–6 points is classified as moderately dependent; <4 points is classified as minimally dependent.

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Cytisine is a partial agonist of nAChRs and its structure was the precursor for the development of varenicline[145]. Cytisine is at least as effective as some approved pharmacotherapies for smoking cessation, such as NRT[146–148], and the role of cytisine in smoking cessation is likely to expand in the future, notably owing to its much lower cost than traditional pharmacotherapies. E-cigarettes also have the potential to be useful as smoking cessation devices[149,150]. The 2020 US Surgeon General's Report concluded that there was insufficient evidence to promote cytisine or e-cigarettes as effective smoking cessation treatments, but in the UK its use is recommended for smoking cessation (see REF.[15] for regularly updated review).

Counselling and behavioural treatments. Psychosocial counselling significantly increases the likelihood of successful cessation, especially when combined with pharmacotherapy. Even a counselling session lasting only 3 minutes can help smokers quit[116], although the 2008 US Public Health Service guidelines and the Preventive Services Task Force[151] each concluded that more intensive counselling (≥20 min per session) is more effective than less intensive counselling (<20 min per session). Higher smoking cessation rates are obtained by using behavioural change techniques that target associative and self-regulatory processes[152]. In addition, behavioural change techniques that will favour commitment, social reward and identity associated with changed behaviour seems associated with higher success rates[152]. Evidence-based counselling focuses on providing social support during treatment, building skills to cope with withdrawal and cessation, and problem-solving in challenging situations[116,153]. Effective counselling can be delivered by diverse providers (such as physicians, nurses, pharmacists, social workers, psychologists and certified tobacco treatment specialists)[116].

Counselling can be delivered in a variety of modalities. In-person individual and group counselling are effective, as is telephone counselling (quit lines)[142]. Internet and text-based intervention seem to be effective in smoking cessation, especially when they are interactive and tailored to a smoker's specific circumstances[142]. Over the past several years, the number of smoking cessation smartphone apps has increased, but there the evidence that the use of these apps significantly increases smoking cessation rates is not sufficient.

Contingency management (providing financial incentives for abstinence or engagement in treatment) has shown promising results[154,155] but its effects are not sustained once the contingencies are removed[155,156]. Other treatments such as hypnosis, acupuncture and laser treatment have not been shown to improve smoking

cessation rates compared with placebo treatments[116]. Moreover, no solid evidence supports the use of conventional transcranial magnetic stimulation (TMS) for long-term smoking cessation[157,158].

Although a variety of empirically supported smoking cessation interventions are available, more than two-thirds of adult smokers who made quit attempts in the USA during the past year did not use an evidence-based treatment and the rate is likely to be lower in many other countries[142]. This speaks to the need to increase awareness of, and access to, effective cessation aids among all smokers.

Brain stimulation. The insula (part of the frontal cortex) is a critical brain structure involved in cigarette craving and relapse[78,79]. The activity of the insula can be modulated using an innovative approach called deep insula/prefrontal cortex TMS (deep TMS), which is effective in helping people quit smoking[80,159]. This approach has now been approved by the FDA as an effective smoking cessation intervention[80]. However, although this intervention was developed and is effective for smoking cessation, the number of people with access to it is limited owing to the limited number of sites equipped and with trained personnel, and the cost of this intervention.

Quality of life

Generic instruments (such as the Short-Form (SF-36) Health Survey) can be used to evaluate quality of life (QOL) in smokers. People who smoke rate their QOL lower than people who do not smoke both before and after they become smokers[160,161]. QOL improves when smokers quit[162]. Mental health may also improve on quitting smoking[163]. Moreover, QOL is much poorer in smokers with tobacco-related diseases, such as chronic respiratory diseases and cancers, than in individuals without tobacco-related diseases[161,164]. The dimensions of QOL that show the largest decrements in people who smoke are those related to physical health, day-to-day activities and mental health such as depression[160]. Smoking also increases the risk of diabetes mellitus[165,166], which is a major determinant of poor QOL for a wide range of conditions.

The high toll of premature death from cigarette smoking can obscure the fact that many of the diseases that cause these deaths also produce substantial disability in the years before death[1]. Indeed, death in smokers is typically preceded by several years of living with the serious disability and impairment of everyday activities caused by chronic respiratory disease, heart disease and cancer[2]. Smokers' QOL in these years may also be adversely affected by the adverse effects of the medical treatments that they receive for these smoking-related diseases (such as major surgery and radiotherapy).

Outlook

Expanding cessation worldwide. The major global challenge is to consider individual and population-based strategies that could increase the substantially low rates of adult cessation in most LMICs and indeed

Table 2 | **FDA-approved smoking cessation pharmacotherapies**

Medication	Cautions or warnings	Side effects	Use	Availability
Combination nicotine replacement therapy: patch plus lozenge or patch plus gum	Follow instructions for individual medications	See individual medications below	See individual medications below	See individual medications below
Varenicline	Use with caution in patients with significant renal impairment, serious psychiatric illness or undergoing dialysis	Nausea, insomnia and abnormal dreams	Start 1 week before quit date and use for 3–6 months; typically quit on day 8; optional quit between days 8 and 35	Prescription only
Nicotine patch	Do not use if you have severe eczema or psoriasis	Local skin reaction and insomnia	After quitting: 12 weeks; optional before quitting up to 6 months prior to quit date with smoking reduction	OTC or prescription
Nicotine lozenge	Do not eat or drink 15 min before or during use; consume one lozenge at a time with a limit of 20 lozenges in 24 h	Hiccups, cough and heartburn	3–6 months; optional before quitting up to 6 months before quit date with smoking reduction; recommend mini-lozenge owing to more rapid nicotine blood level and ease of use	OTC only
Nicotine gum	Caution with dentures; do not eat or drink 15 min before or during use	Mouth soreness and stomach ache	After quitting: up to 12 weeks; optional before quitting up to 6 months before quit date with smoking reduction	OTC only
Nicotine inhaler	May irritate mouth or throat at first (improves with use)	Local irritation of mouth and throat	After quitting: up to 6 months, taper at end; optional before quitting up to 6 months before quitting with smoking reduction	Prescription only
Nicotine nasal spray	Not in patients with asthma; may irritate nose (improves over time) and may cause dependence	Nasal irritation	3–6 months, taper at end	Prescription only
Bupropion SR 150	Not in patients taking a monoamine oxidase inhibitor, using bupropion in any other form, or with a history of seizures or eating disorders	Insomnia and dry mouth	Start 1–2 weeks before quit date; use for 2–6 months	Prescription only

OTC, over the counter. Adapted with permission from Chris Hollenback (CTRI website).

Table 3 | **Smoking cessation approaches recommended for further research**

Drug class or intervention	Medication	Approved for management of other addictions	Main findings and limitations	Future research foci
Cannabinoid drugs	CBD	No	A pilot study found an effect with short-term treatment on the number of cigarettes smoked[175]	Proof-of-principle RCT
			CBD has been suggested to have anti-addictive properties[175,176]	
	FAAH inhibitor (PF-04457845)	No	FAAH inhibitor blocks relapse in animal models[177]	Proof-of-principle RCT
			Attenuation of cannabis withdrawal in cannabis users, but no exploration yet in people who smoke tobacco[178]	
	Neutral cannabinoid antagonist	No	Rimonabant (a CB_1 inverse agonist) has some efficacy for smoking cessation[179]; however, CB_1 inverse agonist had psychiatric adverse effects, leading to withdrawal from the market	Proof-of-principle RCT
			Neutral CB_1 antagonist may keep the therapeutic potential without the negative profile[180]	
Nicotinic drug	Cytisine	Yes	Some efficacy demonstrated for smoking cessation[146–148]	Large-scale RCT to compare effectiveness, tolerability and cost
			Cheaper than varenicline, it is widely use in Eastern Europe but its use is limited in developed countries	Possible use in specific populations
GLP1 receptor agonists	Exendin-4 or liraglutide, for example	No	This class of drug has some promise to reduce smoking and weight gain associated with cessation[181,182]	Proof-of-principle RCT
Noradrenergic drug	Clonidine, prazosin or β-blockers	No	Animal studies suggest that the α_1-noradrenergic receptor controls nicotine taking and seeking[83]	Proof-of-principle RCT
			Clonidine has some efficacy for smoking cessation (but modest effect)	
			Prazosin and beta-blockers have not been tested for smoking cessation[183]	
Dopamine D3 antagonist	Various drugs	No	Animal studies suggest that blocking D3 receptors reduces motivation for nicotine and relapse[184]	Proof-of-principle RCT required
			No clinical trial has been done for smoking cessation	
Opioid antagonists	Naltrexone	Approved for alcohol and opioid addiction	Naltrexone alone or combined with nicotine replacement therapy[185] or with varenicline[186] seems not to be effective for smoking cessation	Large-scale study testing the combination of naltrexone and bupropion
			The combination of naltrexone and bupropion may be effective[187]	
GABAergic, glutamatergic and anticonvulsant drugs	Baclofen and experimental drugs	No	Preclinical studies suggest that drugs modulating GABAergic and glutamatergic transmission may be beneficial[188,189]	Studies validating the use of topiramate
			Baclofen reduced the number of cigarettes smoked in a pilot study[190]	Testing of baclofen
			Topiramate increased abstinence rates in some studies[191]	
Serotonin $5\text{-}HT_{2C}$ receptor agonist	Lorcaserin	No	Lorcaserin seems to help in smoking cessation and in preventing weight gain related to cessation[192]	More studies of this class of drug
			Lorcaserin has been withdrawn from the market owing to small cancer risk, but other serotonin $5\text{-}HT_{2C}$ receptor agonists may be valuable[193]	
Brain stimulation	TMS, deep insula TMS, transcranial direct current stimulation	No	Emerging studies suggest some potential of brain stimulation approaches; the deep coils targeting the insula and prefrontal cortex are effective for smoking cessation[80]	More validation trials for deep insula/prefrontal cortex rTMS; notably, cost-effectiveness studies and comparison with standard pharmacotherapies approved for smoking cessation

CB_1, cannabinoid receptor 1; CBD, cannabidiol; FAAH, fatty acid amide hydrolase; GLP1, glucagon-like peptide 1; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation.

strategies to ensure that even in HICs, cessation continues to increase. In general, the most effective tools recommended by WHO to expand cessation are the same tools that can prevent smoking initiation, notably higher tobacco taxes, bans on advertising and promotion, prominent warning labels or plain packaging, bans on public smoking, and mass media and educational efforts[29,167]. The effective use of these policies, particularly taxation, lags behind in most LMICs compared with most HICs, with important exceptions such as Brazil[167]. Access to effective pharmacotherapies and counselling as well as support for co-existing mental health conditions would also be required to accelerate cessation in LMICs. This is particularly important as smokers living in LMICs often have no access to the full range of effective treatment options.

Regulating access to e-cigarettes. How e-cigarettes should be used is debated within the tobacco control field. In some countries (for example, the UK), the use of e-cigarettes as a cigarette smoking cessation aid and as a harm reduction strategy is supported, based on the idea that e-cigarette use will lead to much less exposure to toxic compounds than tobacco use, therefore reducing global harm. In other countries (for example, the USA), there is more concern with preventing the increased use of e-cigarettes by youths that may subsequently lead to smoking[25,26]. Regulating e-cigarettes in nuanced ways that enable smokers to access those products whilst preventing their uptake among youths is critical.

Regulating nicotine content in tobacco products. Reducing the nicotine content of cigarettes could potentially produce less addictive products that would allow a gradual reduction in the population prevalence of smoking. Some clinical studies have found no compensatory increase in smoking whilst providing access to low nicotine tobacco[168]. Future regulation may be implemented to gradually decrease the nicotine content of combustible tobacco and other nicotine products[169–171].

Tobacco end games. Some individuals have proposed getting rid of commercial tobacco products this century or using the major economic disruption arising from the COVID-19 pandemic to accelerate the demise of the tobacco industry[172,173]. Some tobacco producers have even proposed this strategy as an internal goal, with the idea of switching to nicotine delivery systems that are less harmful (Philip Morris International). Some countries are moving towards such an objective; for example, in New Zealand, the goal that fewer than 5% of New Zealanders will be smokers in 2025 has been set (REF.[174]). The tobacco end-game approach would overall be the best approach to reduce the burden of tobacco use on society, but it would require coordination of multiple countries and strong public and private consensus on the strategy to avoid a major expansion of the existing illicit market in tobacco products in some countries.

Innovative interventions. The COVID-19 pandemic has shown that large-scale investment in research can lead to rapid development of successful therapeutic interventions. By contrast, smoking cessation has been underfunded compared with the contribution that it makes to the global burden of disease. In addition, there is limited coordination between research teams and most studies are small-scale and often underpowered[79]. It is time to fund an ambitious, coordinated programme of research to test the most promising therapies based on an increased understanding of the neurobiological basis of smoking and nicotine addiction (TABLE 3). Many of those ideas have not yet been tested properly and this could be carried out by a coordinated programme of research at the international level.

Published online: 24 March 2022

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Acknowledgements
B.Le F. is supported by a clinician-scientist award from the Department of Family and Community Medicine at the University of Toronto and the Addiction Psychiatry Chair from the University of Toronto. The funding bodies had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication. The authors thank H. Fu (University of Toronto) for assistance with Figs 1–3.

Author contributions
Introduction (B.Le F.); Epidemiology (P.J. and W.D.H.); Mechanisms/pathophysiology (C.D.F., L.B., L.L. and B.Le F.); Diagnosis, screening and prevention (P.J., M.E.P., S.T. and B.Le F.); Management (M.E.P., S.T., W.D.H., L.L. and B.Le F.); Quality of life (P.J. and W.D.H.); Outlook (all); Conclusions (all). All authors contributed substantially to the review and editing of the manuscript.

Competing interests
B.Le F. has obtained funding from Pfizer (GRAND Awards, including salary support) for investigator-initiated projects. B.Le F. has received some in-kind donations of cannabis product from Aurora and medication donation from Pfizer and Bioprojet and was provided a coil for TMS study from Brainsway. B.Le F. has obtained industry funding from Canopy (through research grants handled by CAMH or the University of Toronto), Bioprojet, ACS, Indivior and Alkermes. B.Le F. has received in-kind donations of nabiximols from GW Pharma for past studies funded by CIHR and NIH. B.Le F. has been an advisor to Shinoghi. S.T. has received honoraria from Pfizer the manufacturer of varenicline for lectures and advice. All other authors declare no competing interests.

Peer reviewer information
Nature Reviews Disease Primers thanks Jamie Brown, Elisardo Iglesias and Ming Li for their contribution to the peer review of this work.

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