

# TOBACCO & DEMENTIA

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- Smoking is a risk factor for dementia, and quitting could reduce the dementia burden.
- Second-hand smoke exposure may also increase the risk of dementia.
- 14% of Alzheimer's disease cases worldwide are potentially attributed to smoking.
- As no treatments are currently available to cure or alter the progressive course of dementia, it is essential to identify modifiable risk factors for reducing the occurrence of the disease, delaying its onset or reducing its burden.
- Governments should actively implement and enforce the measures of the WHO Framework Convention on Tobacco Control, especially smoke-free environment laws and systematic access to tobacco cessation services.

## What is dementia?

Dementia is a syndrome resulting from disease of the brain, usually of a chronic or progressive nature; it involves a decline in thinking beyond what is normally expected from ageing, and may affect memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded (1). The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. This syndrome occurs in Alzheimer's disease (AD), in cerebrovascular disease (CeVD), and in other conditions primarily or secondarily affecting the brain (1). Dementia is most likely the consequence of interactions between genetic, environmental, and lifestyle factors (2).

**Alzheimer's disease** is a degenerative cerebral disease of unknown etiology with characteristic neuropathological and neurochemical features. AD-related dementia onset is usually subtle and progresses slowly over a period of several years; episodic memory is one of the first cognitive domains to be affected (3).

**Cerebrovascular Disease** refers to the full spectrum of small- and large-vessel vascular pathology in the brain and is highly prevalent in older individuals. Smoking and hypertension are major risk factors for CeVD (4).

**Vascular dementia (VaD)** is linked to CeVD, especially following brain infarcts. Clinical onset typically features impaired frontal-executive function and slowed processing speed (5).

## The problem

Approximately 7.7 million new cases of dementia are identified every year – i.e. a new case identified every 4 seconds (1). Dementia, whose prevalence increases with age, is the leading cause of dependency and disability among older people in both high-income countries (HICs) and low- and middle-income countries (LMICs). In 2010, approximately 36 million adults globally were living with dementia (1).

The combined effects of an ageing global population and the increased risk of dementia with advanced age will dramatically increase the global prevalence of dementia over the next 40 years (1). It is estimated that by 2050, some 2 billion people worldwide will be over the age of 60, and the number of people living with dementia is expected to reach 115 million. This increase is predicted to be especially rapid in LMICs (1).

Dementia is emotionally demanding for patients and caregivers as it can cause severe behavioural and psychological symptoms in the patient. Dementia is also economically burden-

## Tobacco definitions

**Smoked tobacco product:** any product made or derived from tobacco that is intended for human consumption. Examples include manufactured cigarettes, roll-your-own tobacco, cigars, shisha, kreteks and bidis.

**Smokeless tobacco:** any product that consists of cut, ground, powdered, or leaf tobacco and that is intended to be placed in the oral or nasal cavity. Examples include gutka, mishri, and snus.

**Second-hand smoke (SHS):** the combination of "mainstream" smoke exhaled by the smoker, and "side-stream" smoke emitted into the environment from lit cigarettes and other smoked tobacco products. The terms "passive smoking" or "involuntary smoking" are also often used to describe exposure to SHS.

some because of the substantial cost of medical, social and informal care due to the dependency and disabling characteristics of the condition. The average global annual cost of care for a person with dementia is US\$ 17 000. However this cost varies drastically by country – ranging from US\$ 868 in low-income countries, to US\$ 3109 in lower-middle income countries, US\$ 6827 in upper-middle income countries and US\$ 32 865 in high-income countries (6).

In 2010, worldwide costs of dementia were estimated as being approximately US\$ 604 billion (1). Direct medical costs make up the smallest portion of cost, comprising 16% of the global cost of dementia. In HICs, informal social care (family members, friends etc.) and formal social care (nursing home, care facilities etc.) account for the majority of the costs (45% and 40% respectively). In LMICs, informal social care accounts for the majority (almost 60%) of economic costs. In the coming decades, changing population demographics in LMICs is likely to see a reduction in the availability of extended family members for informal social care thus increasing the proportion of direct social care and subsequently the economic burden of dementia (1).

Currently, there are no treatments available to cure or alter the progressive course of dementia, although clinical trials are underway (1). Until effective treatments are identified, strate-



gies for reducing the occurrence of the disease, or delay its onset and lessen the burden must rely on identifying and taking action upon modifiable risk factors (1).

Whilst individual genetic make-up, age and family history cannot be changed, acting on modifiable risk factors may reduce the risk of dementia at both individual and population levels (2). The modifiable risk factors for dementia include tobacco smoking, physical inactivity, hypertension, obesity, diabetes, and low levels of cognitive activity or low educational attainment (7). This document aims to summarise the published links between tobacco use (smoking and smokeless) and exposure to second-hand smoke and dementia.

## Pathophysiology of tobacco use in dementia

Smoking tobacco is hypothesized to cause dementia via several mechanisms (see Figure 1). The most recognized causal pathway is via vascular risk factors that may ultimately cause cerebrovascular disease, stroke and coronary heart disease (8–10). Smoking increases total plasma homocysteine, an independent risk factor for stroke, cognitive impairment, AD and other dementias (11–14). Smoking also accelerates atherosclerosis, causing a narrowing of blood vessels in the heart and brain that can deprive brain cells of proper oxygen, nutrient and by-product exchange (8). Finally, smoking can cause oxidative stress, which is associated with excitotoxicity, leading to neural death (15). Oxidative stress is also associated with an inflammatory response that may be directly or indirectly related to the neuropathology of AD (16–17). Apolipoprotein E (APOE)  $\epsilon$ 4 allele, is a genetic risk factor for dementia, and smoking tobacco can increase the risk for carriers of this gene (18–19).

The pathophysiological link between second-hand smoke (SHS) exposure and dementia is not well understood. At this time, an indirect causal pathway is biologically plausible because of recognized associations between SHS exposure, increased risk of cardiovascular conditions and stroke (20–21). The cardiovascular effects of second-hand smoke are nearly as great as for smoking, and operate through essentially the same biological mechanisms as described earlier (22–24).

Even less is known about the effects of smokeless tobacco use on dementia. Smokeless tobacco contains over 2000 chemical compounds, including nicotine. It is biologically plausible that the use of smokeless tobacco could increase the risk of dementia through cardiovascular disease-related mechanisms, as use of snus has an increased risk of death from cardiovascular disease (25).

## Tobacco smoking and dementia

There is evidence that current smoking is associated with an increased risk of developing dementia and AD (7, 9,26–37). This evidence was consistent across varied study settings. A meta-analysis of studies undertaken mostly in the 1990s and early 2000s found that relative to never smokers, current smokers had risks of 1.79 (95% CI 1.43–2.23) for AD and 1.78 (95%CI 1.28–2.47) for VaD (27). Another systematic review published at about the same time confirmed the previous findings with risks of 1.59 (95% CI 1.15–2.20) for AD and 1.35 (95%CI 0.90–2.02) for VaD (7). While these findings were

mostly from high income countries, results of studies from low and middle income countries – China, India and Latin America (Cuba, Dominican Republic, Mexico, Peru, Venezuela) – have also concluded a heightened risk of dementia among people with a history of tobacco smoking (37). There is also some evidence of a dose-response relationship, indicating that the more someone smokes, the higher their risk for developing dementia (35). It is estimated that 14% of AD cases worldwide are potentially attributable to smoking (1, 7). Past history of smoking presents less consistent results, possibly indicating that quitting smoking later in life is still beneficial and could reduce the risk of AD or other forms of dementia compared with continued smoking (7, 26–37).

The above findings are in contradiction with several studies that had previously led to an opposite conclusion, namely that use of tobacco was protective against dementia, particularly Alzheimer’s Disease. The review of the literature points to two likely explanations. The first explanation is well summarised in the 2014 US Surgeon General Report which states that “... there is evidence that the tobacco industry influenced many ... epidemiologic studies of smoking and psychiatric disorders ...” (38). Indeed a systematic review of studies conducted by researchers with no links to the tobacco industry found current smoking to be associated with a 45% higher risk of dementia, whereas studies undertaken by scientists with tobacco industry affiliations reported a 40% lower risk of dementia among current smokers (34). The second additional explanation for the apparent protective value of tobacco use relates to study design, in particular, the use of cross-sectional and case control studies. There is widespread agreement in the literature that the use of case-control and cross-sectional study designs can engender multiple avenues for bias, including selection and survival biases (7, 34). A meta-analysis of cohort studies found a risk estimate of 1.99 (95% CI 1.33–2.98) compared with a meta-analysis of case-control studies that produced a pooled estimate of 0.91 (95% CI 0.53–1.27) (26). Additionally, recent research has shown that smokers with dementia are more likely to die earlier than non-smokers with dementia (36).

The literature search did not find any systematic reviews or studies which examined the impact of current or past tobacco smoking on risk of early onset dementia, or on the prognosis of AD or other forms of dementia. Given the benefits that accrue to former smokers relative to current smokers for many other conditions, it is, however, not inconceivable that brain health benefits could also accrue to former smokers.

## Smokeless tobacco and dementia

No systematic reviews have been published on the association between the use of smokeless tobacco and dementia or AD. One population-based cross-sectional study in India evaluated this association and concluded there was not a significant association between smokeless tobacco use and risk of dementia, AD or VaD (37).

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## Second-hand smoke and dementia

At the time of publication no systematic reviews were available on SHS exposure and dementia. However, four publications from two studies have suggested an increased risk of AD or other forms of dementia among those exposed to SHS. These studies also found a dose-response relationship between SHS exposure and risk of dementia (39–42).

Three publications from a large-scale population-based cross-sectional survey in Anhui, China linked SHS exposure with risk of dementia in the general population and among never-smokers (39, 40, 42). These studies also showed that risk of dementia increased with duration and level of exposure. Exposure to SHS at any location (e.g. home or work) increased the risk for all dementias by 78% (RR 1.78, 95% CI 1.18–2.68). The association was strongest for exposure in the home.

Two studies looking at risk of dementia among never-smokers concluded that the risk of AD from SHS is associated with location and duration of exposure. The highest SHS risk from exposure in a single location was in the home (RR 2.15, 95% CI 1.69–2.74), followed by work (RR 2.04, 95% CI 1.72–2.42), and finally other places (RR 1.80, 95% CI 0.96–3.38). The greatest risk for dementia was found following exposure in all three locations (adjusted RR 2.28, 95% CI 1.82–2.84) (39).

A study evaluating dementia severity prior to diagnosis concluded that exposure to SHS significantly increased the risk for severe dementia syndromes (adjusted RR 1.29, 95% CI 1.05–1.59), and this was related to duration and frequency of exposure to SHS in a dose-dependent manner (40).

## Next steps

Although there is relatively strong evidence in the literature of a link between current cigarette smoking and risk of dementia, more well-designed long-term prospective rather than retrospective case-control studies are needed to address smoking and smokeless tobacco products, as well as exposure to second-hand smoke. Also, more research is needed as to the timing of smoking cessation in the lifespan and subsequent normalization of dementia risk. Finally, there is a need for population-based prospective studies that quantitatively measure biomarkers of SHS exposure to more rigorously assess its etiological role in the development of dementia.

## Population level actions

AD, VaD and other forms of dementia place a huge health and socioeconomic burden on individuals, families and communities, in addition to tobacco-related stroke, cardiovascular and cancer burden. Reducing tobacco use and exposure to second-hand smoke are therefore key areas of action. With recent research demonstrating the effectiveness of smoke-free legislation for protecting the health of non-smokers, governments should continue to incorporate the measures relating to create smoke-free environments laid out in the WHO Framework Convention on Tobacco Control (WHO FCTC) (43). This effort should also include regulatory reforms and increasing public awareness of the risk of tobacco-caused dementia. Recommended actions include: the creation of smoke-free public places and workplaces; ensuring the availability of tobacco-cessation services (including tobacco quit lines and the integration of brief advice into the health system at all levels);

health-warning labelling of tobacco products to include the risk of dementia; mass-media campaigns; plain packaging of tobacco products (as has been recently introduced in Australia); establishing and enforcing bans on tobacco advertising, promotion and sponsorship; and raising taxes on tobacco products.

## Individual level action

Given that, at present, no treatments are available to cure or alter the progressive course of dementia, it is essential to identify modifiable risk factors for reducing the occurrence of the disease, delaying its onset or reducing its burden (1). Quitting tobacco use (and controlling other risk factors) could help reduce the risk of cardiovascular diseases and dementia, and encouraging and supporting current tobacco users to quit should be a top priority for prevention of AD and other forms of dementia. Dementia should be added in all educational materials that address the harmful effects of smoking. Clinicians, such as neurologists, psychiatrists, geriatricians and family practitioners should routinely advise their patients about quitting or avoiding tobacco exposure, and about controlling other risk factors. Non-smokers should demand smoke-free legislation and make their homes, workplaces and other places they visit smoke-free.

Information and advice on quitting tobacco use can be found through the following:

- [www.smokefree.gov](http://www.smokefree.gov)
- Quitlines/Helplines
- WHO package of essential noncommunicable (PEN) disease interventions [http://www.who.int/cardiovascular\\_diseases/publications/pen2010/en/](http://www.who.int/cardiovascular_diseases/publications/pen2010/en/)

## Further information

- WHO 2012 Dementia – A Public Health Priority: [http://www.who.int/mental\\_health](http://www.who.int/mental_health)
- WHO Tobacco Free Initiative (TFI): <http://www.who.int/tobacco/en/>
- WHO FCTC: <http://www.who.int/fctc/en/>
- Alzheimer's disease International: <http://www.alz.co.uk/>

## Method

WHO conducted a comprehensive literature review that, in the first instance searched for all systematic reviews that studied smoked, smokeless tobacco, and second-hand smoke and AD and other forms of dementia. The search then focused on identifying as many peer reviewed articles as possible. Although the search focussed on papers published since 2007, the reviews themselves included articles that spanned the period since the mid-1990s. The inclusion criteria included a human study population, a dementia outcome, and tobacco use or exposure at any time over the life course. The review was not limited to any particular study design or language, however very few non-English language studies or reports were identified.

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