

Smoking and dementia

May 2021



Key points:

- Dementia is not a normal part of ageing¹
- Approximately 90,000 people in Scotland have dementia, with an estimated 5% (4,500) having early-onset (under age 65) dementia²
- Whilst it is possible to live, and in many cases live well, for many years with dementia, it is an incurable and terminal condition³
- Almost one-third of people in the UK who died over the age of 65 years have had some form of dementia⁴
- 17% of adults smoke in Scotland, contributing to around 9,000 deaths annually, 16% of all deaths^{5,6}
- Smoking is a risk factor for Alzheimer's disease and other forms of dementia⁷⁻¹⁰
- It is estimated that around 14% of all dementia cases worldwide are attributable to smoking¹¹
- Exposure to second-hand smoke may contribute to the development of cognitive decline and dementia¹²⁻¹⁴
- Smoking and exposure to second-hand smoke are risk factors for cardiovascular disease, diabetes and stroke which are in turn underlying risk factors for dementia¹⁵
- The risk of developing dementia, Alzheimer's disease and vascular dementia is drastically higher in heavy smokers than in non-smokers^{7,16}
- Age-related cognitive decline may be accelerated by smoking^{10,16}
- A 2011 YouGov poll found that 31% of those surveyed feared dementia more than cancer or death so there may be smokers for whom dementia risk reduction is an incentive to quit
- Giving up smoking improves health and may reduce the risk of dementia¹⁷⁻¹⁹

This specialist briefing is aimed at professionals and policy makers. It reviews the evidence on smoking and an increased risk of Alzheimer's disease and other forms of dementia, and cognitive impairment. This briefing also examines how continued smoking or exposure to second-hand smoke may affect people with dementia and their carers.

Table of Contents

Introduction	2
What is dementia?.....	2
Smoking and Dementia Risk	3
Neuronal degeneration – amyloid plaques and tau tangles.....	3
Cardiovascular disease.....	3
Diabetes and insulin resistance.....	4
Stroke	4
Smoking and the risk of developing cognitive impairment.....	5
Cognitive Impairment, dementia and exposure to second-hand smoke.....	6
Nicotine	7
Smoking and dementia medication.....	8
When people with dementia smoke	8
Giving up smoking and decreasing the risk of dementia.....	9
People with dementia, carers and exposure to second-hand smoke	9
Professional community carers	10
Conclusion	11
Support to stop smoking.....	12
Short and long term benefits of quitting	13
References.....	14

Introduction

Dementia is a complex illness that impacts on the lives of around 90,000 people in Scotland living with the condition, their families and carers². In 2017 there were close to 50 million people living with dementia globally, which is expected to double every 20 years, reaching 75 million in 2030 and 131.5 million in 2050²⁰. Epidemiological studies have consistently linked smoking to an increased risk of developing dementia^{9-11,15}, and long-term cohort studies suggest that the risk for dementia in former smokers (after several years of not smoking) can be greatly reduced^{16,19}. Indeed, according to a 2020 report from the scientific journal, *The Lancet*, smoking is one of the 12 modifiable risk-factors which can reduce the risk for developing dementia²¹.

What is dementia?

Dementia is not the name of a disease but rather a group of symptoms linked to a decline in brain function. Dementia can be caused by a number of diseases, of which, by far, the most common types are Alzheimer's disease, vascular dementia and frontotemporal dementia, accounting for about 80-90% of all dementias. In reality it is often challenging to attribute a specific cause due to the large overlap in symptoms and co-occurrence of causes, e.g. Alzheimer's disease with vascular dementia.

The decline in brain function follows from the death of brain cells (neurodegeneration) leading to progressive loss of brain functions, including memory loss, mood changes, problems planning and changes in thinking.

Although there are various forms of dementia, one of the key differences between the type of dementias is the part of the brain which is damaged first in the early stages of the disease. The specific pattern of neurodegeneration broadly matches the decline in specific cognitive functions. In Alzheimer's disease, memory is one of the first functions to be affected, whereas for frontotemporal dementia, changes in personality and lack of social tact are likely to be seen first. What all dementias have in common is that they progressively damage the brain. At present, lifestyle changes, such as stopping smoking, taking regular exercise and having a healthy diet, remain one of the best ways to prevent, delay onset or slow progression of dementia. Finally, it should not be forgotten that besides being distressing for the person with dementia, the gradual but pervasive

loss in brain function can also have a very large impact on the health and wellbeing of loved-ones and carers.

Approximately 90,000 people in Scotland have dementia, with an estimated 5% (4,500) having early-onset (under age 65) dementia². Whilst it is possible to live, and in many cases live well, for many years with dementia, it is an incurable and terminal condition³ almost one-third of people in the UK who died over the age of 65 years have had some form of dementia⁴

Smoking and Dementia Risk

Neuronal degeneration – amyloid plaques and tau tangles

Around 60% of all dementias are caused by Alzheimer's Disease (AD). The hallmark of AD is the presence of beta-amyloid (A β) deposits and neurofibrillary tangles (tau tangles) in the brain. Tau which normally produce tiny filaments in neurons, clump together creating 'tau tangles'. Ultimately, dysfunctional A β and tau proteins lead to neuronal dysfunction, followed by neuronal death²². Cigarette smoking is a risk for AD^{23,24}. Both A β and Tau tangle can also be found in many other dementias. The presence of both is considered particularly damaging to neurons²². Whilst more research is needed, it has been speculated that the mechanism underlying the epidemiological association of cigarette smoking with AD might involve the effect of cigarette smoke on amyloid precursor protein processing, a reduction of A β clearance by microglia (immune cells in the brain and spinal system), and/or an increased microglial proinflammatory response²⁵. Further research²⁶, which analysed the brains of transgenic mice exposed to cigarette smoke, also suggests that smoking increases the severity of abnormalities typical of AD, including amyloidogenesis (the production of A β), neuroinflammation and tau phosphorylation (this causes tau tangles within nerve cells). Cigarette smoking may therefore both hasten the onset and cognitive decline of AD, and play a role in other dementias.

Cardiovascular disease

Several studies have found that the risks of Alzheimer's disease (AD) and dementia are increased with smoking^{9-11,15}. It is thought that 14% of dementias worldwide are attributable to smoking. Smoking is thought to increase risk for dementia via several mechanisms, of which the most recognized risk factor is via vascular disease^{11,27}. Smoking contributes to a variety of subclinical and clinical vascular disorders including

atherosclerosis and cerebrovascular disease, which, in turn, could lead to increased risk of AD²⁸. However, tobacco smoke also contains hundreds of neurotoxins and could contribute to AD risk through oxidative stress, inflammatory processes, or other mechanisms²⁴. Optimal management of cardiovascular risk factors may therefore improve cognition and delay onset of dementia²¹.

Diabetes and insulin resistance

Many studies have identified a positive association between smoking and the incidence of diabetes^{29–31} and between diabetes and dementia^{21,29,32,33}. Nicotine promotes insulin resistance^{32,34} also called pre-diabetes (which is a risk factor for cardiovascular disease), and there may be a link between pre-diabetes and an increased risk of dementia and Alzheimer's disease^{35,36}. It has also been found that diabetes and pre-diabetes substantially accelerated the progression from mild cognitive impairment (MCI) to dementia^{37,38}.

Stroke

Stroke is a serious medical condition whereby blood flow in the brain is disrupted through a bleed (haemorrhagic stroke) or blockage of blood vessels (ischemic stroke). In addition to fatal or life-changing consequences on their own, strokes are a strong, independent, and potentially modifiable risk factor for dementia³⁹. Ischemic stroke is the second most common cause of death from vascular diseases and the third major cause of disability worldwide⁴⁰, and smoking is a known risk factor for vascular disease²⁸. Pooled data from a meta-analysis of pre- and post-stroke dementia estimates that one in ten patients have dementia prior to first stroke, one in ten patients develop new dementia soon after first stroke, and more than one in three develop dementia after a recurrent stroke⁴¹.

A meta-analysis looking to establish the relationship between smoking and stroke found that for every five cigarettes smoked daily, risk of stroke increased by 12%. This 'dose dependent' effect has been echoed in other studies⁴². Although this study implies that smoking reduction can lead to risk-reduction, this remains unclear. A recent meta-analysis found that not all studies share the finding that smoking reduction leads to risk-reduction⁴³. Some studies indicated that the protective effects are only seen with smoking cessation and not reduction.

Despite that, the link between smoking and the increased risk of stroke is well established. There have been some reports indicating that smoking may lead to a more favorable outcome in stroke, referred to as the 'smoking paradox'. However, a large study – which analysed the findings of 21 other studies, recently established that smoking was definitively not a protective factor for prognosis of ischemic stroke⁴⁴. Smoking patients with ischemic stroke were found to be 10 years younger than nonsmoking patients at the time of the first onset of stroke. Besides vascular disease being known as a main causative link between smoking and stroke, another risk factor is atrial fibrillation (AF). AF doubles the risk of stroke, and smoking increases risk of AF⁴⁵. Research indicates that after being smoke-free for several years, the risk of stroke for former smokers is similar to that of people who have never smoked^{42,45}.

Smoking and the risk of developing cognitive impairment

Decreased brain function (as opposed to the degeneration and death of brain cells in dementia) is a natural part of ageing⁴⁶. It is frequently referred to as age-related cognitive decline (ARCD), although this can develop into dementia, whereas cognitive impairment is a general term, which refers to impaired cognitive functions, due to any cause. Mild Cognitive Impairment (MCI), refers to the stage of dementia where symptoms are still mild but diagnosable. Similar to Alzheimer's Disease and other dementias, many factors can influence the risks and age-of-onset of ARCD and MCI⁴⁷. It is plausible that for many people reducing risk factors can be the difference in progressing from ARCD into a degenerative dementia, or not. A study investigating different strategies for the prevention of ARCD found seven potentially modifiable factors; these include diabetes, obesity or hypertension in middle age, low physical activity, depression, low educational level, and smoking⁴⁷. Research using data from the Whitehall II Cohort study found that compared with never smokers, middle-aged male smokers experienced faster cognitive decline in global cognition and executive function; in ex-smokers, with at least a 10-year cessation period, compared to never smokers, no adverse effects on cognitive decline were found⁴⁸.

Similarly, in a prospective cohort study of men and women aged between 43 and 53, smoking was associated with faster declines in verbal memory and with slower visual search speeds; these effects were largely accounted for by individuals who smoked more than 20 cigarettes per day and were independent of sex, socioeconomic status, previous

(adolescent) cognitive ability, and a range of health indicators⁴⁹. In a 2012 population based cohort study, which explored the association between cardiovascular risk and cognitive decline in adults aged 50 and over, smoking was consistently associated with lower performance on the cognitive outcomes measured⁴⁹. Similarly, a 2004 prospective multi-centre cohort study found higher rates of decline by smoking in men and women over 65. This in both persons with and without a family history of dementia it further also showed that higher cigarette pack-year exposure was correlated with a significantly higher rate of decline⁵⁰. All of the above support the theory that age-related cognitive decline is accelerated by smoking⁵¹.

Cognitive Impairment, dementia and exposure to second-hand smoke

Second-hand smoke, also referred to as passive smoking, is associated with a wide range of negative health impacts, including an increased risk for certain cancers and respiratory diseases⁵². Second-hand smoke has also been linked with cognitive deficit in children, adolescents and adults¹³. Although the association is considerably smaller than with smoking, second-hand smoke has also been linked with increased risk for cognitive impairment and dementia^{14,53,54}.

However, not all studies are in agreement over the risk⁵⁵. This is likely due to the vast differences in the settings and frequency of exposure to second-hand smoke, between individuals, and countries with different smoking laws. Over the last few decades, the introduction of laws that prohibit smoking at work and in public places have greatly reduced exposure to second-hand smoke in many countries. One cross sectional study in England¹⁴, which measured cotinine to confirm exposure to second-hand smoke, concluded that exposure to second-hand smoke may increase odds of cognitive impairment. A 2013 study from China concluded that second-hand smoke should be considered an important risk factor for severe dementia syndromes and that avoidance of second-hand smoke might reduce the rates of severe dementia syndromes worldwide. This cohort study assessed almost 6,000 older adults in China, examining their mental state to see if they had dementia and questioning their exposure to second-hand smoke during their lifetime¹². This study had some limitations, including the uncertainty of dementia diagnoses and the self-recall of exposure to second-hand smoke; more research is needed.

It is unclear exactly how the risk of second-hand smoke on dementia is mediated, but it is thought that changes in vascular function and health likely play a critical role. There is indeed evidence that second-hand smoke induced vascular disease is linked to dementia⁵⁹. Exposure to second-hand smoke is associated with an increased risk of endothelial dysfunction, even in healthy young non-smokers⁵⁶⁻⁵⁸, cardiovascular disease^{60,61} and stroke^{62,63} which are themselves associated with an increased risk of cognitive impairment and dementia^{20,21} (See also sections on stroke and cardiovascular disease). Similarly, studies suggest that second-hand smoke exposure increases the risk of developing diabetes⁶⁴⁻⁶⁷ and diabetes in turn is a well-established risk factor for dementia^{21,33}. One review of several large prospective cohort studies estimated that diabetes increased the risk of Alzheimer's disease by 50–100 per cent and of vascular dementia by 100–150 per cent⁶⁸.

Nicotine

Through the inhalation of tobacco smoke, nicotine is rapidly absorbed into the body, where it primarily interacts with nicotinic acetylcholine receptors (nAChR) in the brain, and mediates many cognitive functions, including concentration and memory formation⁶⁹, nicotine is also known to have some anti-inflammatory effects. The binding of nicotine to the nAChR is what causes a 'feel good' effect and makes nicotine highly addictive. It is also interesting to note that in the tobacco plant and small number of other plants, nicotine is produced as a natural pesticide. Nicotine is poisonous to insects. In humans, high doses are similarly highly toxic.

As there are nAChR throughout the cholinergic system in the brain, the idea of nicotine as a mechanism for aiding cognitive function appears plausible. Indeed, there has been some research to suggest that smoking could have a protective effect for some forms of Alzheimer's disease⁷⁰. It is hypothesized that the mechanism behind this is that nicotine can inhibit the formation of amyloid plaques⁷¹. However, a 2010 analysis – which controlled for tobacco industry affiliation, study design and other factors – concluded that smoking is not protective against Alzheimer's disease but is instead a significant and substantial risk factor²³. Indeed, the overwhelming evidence, as laid-out in this document, is that tobacco smoke is a risk factor for all dementias, indicating that nicotine intake through tobacco smoke does not protect against dementia.

Nevertheless, interest remains in the idea that nicotine, through its stimulatory effect on the cholinergic system, could counteract the cholinergic dysfunction, which is known to occur in dementias⁷². A group of approved medications for cognitive decline, called acetylcholine esterase inhibitors, such as Galantamine and Rivastigmine, work by decreasing the breakdown of the signaling molecule acetylcholine, thereby increasing stimulation of the cholinergic system. Hypothetically, nicotine would similarly stimulate the cholinergic system. Research published in 2012 in the journal *Neurology* suggested that wearing a nicotine patch might help improve memory loss in non-smoking older adults with mild cognitive impairment⁷³. However, despite decades of research and clinical trials, according to a review by the Alzheimer Drug Discovery Foundation, the evidence for the use of nicotine in dementia remains uncertain, strongly indicating that nicotine is neither protective, nor meaningfully boosts brain function in dementia⁷⁴.

Smoking and dementia medication

Smoking affects the metabolism of various medications, including diazepam, haloperidol (partial), olanzapine (partial), clozapine, mirtazapine (partial), tricyclic antidepressants, barbiturates and benzodiazepines. Smoking cessation or starting smoking can affect the metabolism of certain medication, which can affect its efficacy⁷⁵.

Similarly, there is some theoretical evidence that smoking can affect the metabolism of the group of dementia medication called, cholinesterase inhibitors (such as donepezil, rivastigmine, and galantamine for mild to moderate Alzheimer's disease)⁷⁶. It is currently unknown if this is clinically relevant.

Those taking these medications should seek guidance from their prescriber when attempting to quit, and similarly be aware that (re)starting smoking may also affect drug efficacy.

When people with dementia smoke

Smoking and dementia are uneasy bedfellows. Many smokers will have occasionally left a lit cigarette unattended; indeed in 2018 – 2019, 7.3% of house fires in Scotland were smoking related⁷⁷. The risk for people with impaired memory and reasoning seems likely to be much higher⁷⁸. While it is important to consider the views of the person with dementia, stopping smoking should be encouraged. If they want to continue to smoke,

they may need support to do this in a way that minimizes the fire risk. When attempting to give up smoking, it is best to get professional advice and support to do so, as this increases the chance of success⁷⁹⁻⁸¹. More advice about smoking cessation can be found in the section 'Support to stop smoking'.

Many people with dementia have other medical conditions which can make their dementia worse and lead to hospital admissions. Not smoking is an important part of staying well for as long as possible yet there is a lack of research about helping people with dementia to stop smoking or finding ways of limiting exposure to second-hand smoke.

Giving up smoking and decreasing the risk of dementia

For those who manage to give up smoking, the risk of dying from lung cancer halves within ten years⁸². Research has shown that the benefits of giving up smoking are evident in all age groups, including participants who are 80 years and older⁹⁰.

The Whitehall II Cohort study found that in ex-smokers with at least a 10-year cessation, there were no adverse effects of their past smoking on cognitive decline⁴⁸. A similar longitudinal study of six years, of participants 65 or older, showed that after abstinence of more than three years, dementia risk became the same as for non-smokers¹⁷. Indeed, a report on the risk reduction of cognitive decline and dementia published in 2019 by the World Health Organization, included smoking cessation as one of 12 strategies to reduce dementia¹⁸. Other long-term cohort studies also suggest that the risk for dementia in former smokers (after several years of not smoking) approaches that of never smokers^{16,18,19}. Giving up smoking confers both immediate and long-term health benefits from improved blood pressure and lung function, reduced risk to infections including influenza⁸³, to decreased cancer and stroke risk⁸⁴ (also see the 'Short and long term benefits of quitting' on the last page).

People with dementia, carers and exposure to second-hand smoke

Direct exposure to second-hand smoke can cause many of the same diseases as active smoking⁸⁵. Whilst less is known about indirect exposure to second-hand smoke, tobacco smoke is a toxic substance with no safe level of exposure although the risks from exposure are largely dose-related^{31,86}. Even low levels of exposure may cause irritation to

eyes and lungs, nausea and headaches as well as creating an unpleasant smell. The 2006 report from the US Surgeon General concluded that ‘second-hand smoke is not a mere annoyance, it is a serious health hazard that leads to disease and premature death in children and non-smoking adults’^{31,87}.

People with dementia already have compromised health and whilst they should avoid exposure to second-hand smoke, they may be unable to remove themselves from smoky settings. Similarly, when people with dementia smoke this may cause carers to be exposed and they too may be reluctant or unable to remove themselves from this situation. Caring for someone with dementia can be a very intensive, challenging, rewarding and at times stressful experience and carers may forget that it’s important to look after themselves.

Professional community carers

The introduction of smoke-free legislation in enclosed public spaces, in many countries, has helped protect workers from exposure to second-hand tobacco smoke. Where smoke-free laws have been implemented there tends to be some exemptions and, as a result, some occupational groups continue to be exposed to second-hand smoke as part of their daily activity. Even though second-hand smoke is a known health hazard, many community staff still find themselves regularly exposed to it on home visits. They may find it difficult to ask clients not to smoke in their own homes, so it is vital that managers and employers have a clear policy on how to protect staff from the harms of second-hand smoke. A rapid review conducted in 2018 at the University of Stirling, aiming to understand the scale of this problem, found that very little is known about home health and community care workers’ exposure to second-hand smoke ⁸⁸. Many carers and nursing organisations may have guidelines in place but these are often not publicly available. The Royal College of Nurses have written a guidance document which can be found here:

- The Royal College of Nurses guidance – Protecting community staff from exposure to second-hand smoke
<http://www.perinatal.nhs.uk/smoking/Final%20RCN%20SHSdoc.pdf>

However, as the rapid review notes “*Guidance prepared by the UK Royal College of Nursing (RCN) in 2006 on protecting community staff from exposure to SHS provides*

recommendations for best practice for staff and managers – although this is now listed by the RCN as “use with caution” due to the fact that it has not been reviewed for over 10 years and may no longer be fully applicable. That guidance suggests educating patients about the need to provide community staff with a smoke-free space and for the patient not to smoke during a home visit. The guidance also advises that patients should ensure the area of the visit has been smoke-free for 1 hour before the visit. This now conflicts, to some extent, with more recent public health messages such as the “Take it Right Outside” campaign in Scotland that have used the message that SHS remains in air for up to 5 hours after a cigarette is extinguished. “

Conclusion

It is well known that smoking damages our health, taking years off of our lives. It is also well known that smoking causes cancers and lung disease, but the awareness of its effect on other diseases, such as dementia, is much smaller. There is sufficient evidence to conclude that current smokers have an increased risk of any dementia, such as Alzheimer’s disease, vascular dementia and cognitive decline, compared to non-smokers. Emerging evidence also indicates that exposure to second-hand smoke can be a risk factor for dementia. In a report in the prominent journal the Lancet, smoking has been identified as one of the 12 critical factors which can reduce dementia²¹. This was similarly echoed in a 2019 report from the WHO ‘Risk reduction of cognitive decline and dementia’. There is some research suggesting nicotine maybe beneficial in cognitive decline and Alzheimer’s disease, there is currently insufficient evidence that nicotine can be effectively used for the protection or treatment of dementia.



For further information and support, Alzheimer Scotland's 24 hour, freephone Dementia Helpline is for people with dementia, those who care for them and anyone with a concern or query regarding dementia. Or email at: helpline@alzscot.org. Also see the Alzheimer Scotland website at: www.alzscot.org

Support to stop smoking

People who smoke have a much better chance of giving up smoking if they get support to do so and there are lots of different ways to find support:

- Quit Your Way advisers provide free advice and information for anyone who wants to stop smoking, or who wants to help someone to quit. Quit Your Way also provides information about the free stop smoking services provided by every health board in Scotland.
- Phone free to Quit Your Way from the NHS on 0800 84 84 84 (9am to 5pm, Mon-Fri)
- Online chat from the Scottish NHS Quit Your Way services
<https://www.nhsinform.scot/campaigns/quit-your-way-scotland>
- The Quit Your Way – My Quit Plan is designed to help plan your smoking cessation attempt <https://www.nhsinform.scot/stopping-smoking/my-quit-plan>
- Pharmacies/local chemists are able to provide quit smoking advice and support. Where appropriate, the pharmacist can identify the most suitable form of nicotine replacement therapy (NRT) and some pharmacies run NHS-funded stop smoking services
- Through the local doctor's surgery

Short and long term benefits of quitting

20 minutes after quitting	Heart rate and blood pressure drop.
12 hours after quitting	The blood carbon monoxide levels return to normal.
2 weeks to 3 months after quitting	Circulation improves and lung function increases.
1 to 9 months after quitting	Coughing and shortness of breath decrease; cilia (tiny hair-like structures that move mucus out of the lungs) start to regain normal function in the lungs, increasing the ability to handle mucus, clean the lungs, and reduce the risk of infection.
1 year after quitting	The excess risk of coronary heart disease is half that of a continuing smoker's.
5 years after quitting	Risk of cancer of the mouth, throat, oesophagus, and bladder are cut in half. Cervical cancer risk falls to that of a non-smoker. Stroke risk can fall to that of a non-smoker after 2-5 years.
10 years after quitting	The risk of dying from lung cancer is about half that of a person who is still smoking. The risk of cancer of the larynx (voice box) and pancreas decreases.
15 years after quitting	The risk of coronary heart disease is that of a non-smoker's.

References

1. WHO. Dementia fact sheet 2019. *World Heal. Organ.* September, (2019).
2. Alzheimer Scotland action on dementia. About dementia. <https://www.alzscot.org/what-is-dementia/about-dementia> (2020).
3. Alzheimer's Research UK. A quick guide to dementia. <https://www.alzheimersresearchuk.org/dementia-info> (2020).
4. Brayne, C., Gao, L., Dewey, M. & Matthews, F. E. Dementia before Death in Ageing Societies—The Promise of Prevention and the Reality. *PLoS Med.* 3, e397 (2006).
5. Cheong, C. K. *et al.* Scottish Health Survey 2018: main report. *Scottish Gov.* 1, (2019).
6. ScotPho. Tobacco use: smoking attributable deaths. *The Scottish Public Health Observatory* (2017).
7. Rusanen, M., Kivipelto, M., Quesenberry, C. P., Zhou, J. & Whitmer, R. A. Heavy Smoking in Midlife and Long-term Risk of Alzheimer Disease and Vascular Dementia. *Arch. Intern. Med.* 171, 333–339 (2011).
8. Wingbermhühle, R., Wen, K. X., Wolters, F. J., Ikram, M. A. & Bos, D. Smoking, APOE Genotype, and Cognitive Decline: The Rotterdam Study. *J. Alzheimer's Dis.* (2017) doi:10.3233/JAD-170063.
9. Zhong, G., Wang, Y., Zhang, Y., Guo, J. J. & Zhao, Y. Smoking is associated with an increased risk of dementia: A meta-analysis of prospective cohort studies with investigation of potential effect modifiers. *PLoS One* 10, 1–23 (2015).
10. North, T. L. *et al.* Effect of smoking on physical and cognitive capability in later life: A multicohort study using observational and genetic approaches. *BMJ Open* 5, 1–12 (2015).
11. McKenzie J, Bhatti L, T. d'Espaignet E. WHO Tobacco Knowledge Summaries: Tobacco and dementia. *World Heal. Organ.* (2015).
12. Chen, R. *et al.* Association between environmental tobacco smoke exposure and dementia syndromes. *Occup. Environ. Med.* 70, 63–69 (2013).
13. Ling, J. & Heffernan, T. The Cognitive Deficits Associated with Second-Hand Smoking. *Front. Psychiatry* 7, 98–103 (2016).
14. Llewellyn, D. J., Lang, L. A., Langa, K. M., Naughton, F. & Matthews, F. E. Exposure to secondhand smoke and cognitive impairment in non-smokers: National cross sectional study with cotinine measurement. *BMJ* 338, (2009).
15. Kuźma, E. *et al.* Which Risk Factors Causally Influence Dementia? A Systematic Review of Mendelian Randomization Studies. *J. Alzheimer's Dis.* 64, 181–193 (2018).
16. Anstey, K. J., Von Sanden, C., Salim, A. & O'Kearney, R. Smoking as a risk factor for dementia and cognitive decline: A meta-analysis of prospective studies. *Am. J. Epidemiol.* 166, 367–378 (2007).
17. Lu, Y., Sugawara, Y., Zhang, S., Tomata, Y. & Tsuji, I. Smoking cessation and incident dementia in elderly Japanese: the Ohsaki Cohort 2006 Study. *Eur. J. Epidemiol.* (2020) doi:10.1007/s10654-020-00612-9.
18. World Health Organization & WHO. *Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines.* World Health Organisation (2019).
19. Choi, D., Choi, S. & Park, S. M. Effect of smoking cessation on the risk of dementia: a longitudinal study. *Ann. Clin. Transl. Neurol.* 5, 1192–1199 (2018).
20. Alzheimer's Disease International (ADI), Wimo, A., Prince, M. & International, A. D. World

Alzheimer Report 2015, The Global Impact of Dementia. *Alzheimer's Dis. Int. (ADI)* <https://www.alz.co.uk/research/world-report-2015> (2015) doi:10.1111/j.0963-7214.2004.00293.x.

21. Livingston, G. *et al.* The Lancet Commissions Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* (2020) doi:10.1016/S0140-6736(20)30367-6.
22. Spiers-Jones, T. L. & Hyman, B. T. The Intersection of Amyloid Beta and Tau at Synapses in Alzheimer's Disease. *Neuron* 82, 756–771 (2014).
23. Cataldo, J. K., Prochaska, J. J. & Glantz, S. A. Cigarette smoking is a risk factor for Alzheimer's disease: An analysis controlling for tobacco industry affiliation. *J. Alzheimer's Dis.* 19, 465–480 (2010).
24. Durazzo, T. C., Mattsson, N. & Weiner, M. W. Smoking and increased Alzheimer's disease risk: A review of potential mechanisms. *Alzheimer's Dement.* 10, S122–S145 (2014).
25. Giunta, B. *et al.* Evaluation Of how Cigarette Smoke Is A Direct Risk Factor For Alzheimer's Disease. *Technol. Innov.* 14, 39–48 (2012).
26. Moreno-Gonzalez, I., Estrada, L. D., Sanchez-Mejias, E. & Soto, C. Smoking exacerbates amyloid pathology in a mouse model of Alzheimer's disease. *Nat. Commun.* 4, (2013).
27. Barnes, D. E. & Yaffe, K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet Neurology* vol. 10 819–828 (2011).
28. Gordon, P. & Flanagan, P. Smoking: A risk factor for vascular disease. *J. Vasc. Nurs.* 34, 79–86 (2016).
29. Maddatu, J., Anderson-Baucum, E. & Evans-Molina, C. Smoking and the risk of type 2 diabetes. *Translational Research* (2017) doi:10.1016/j.trsl.2017.02.004.
30. Willi, C., Bodenmann, P., Ghali, W. A., Faris, P. D. & Cornuz, J. Active smoking and the risk of type 2 diabetes: A systematic review and meta-analysis. *Journal of the American Medical Association* (2007) doi:10.1001/jama.298.22.2654.
31. United States Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress A Report of the Surgeon General. *A Rep. Surg. Gen.* (2014).
32. Judith Maddatu, Emily Anderson-Baucum, and C. E.-M. Smoking and the Risk of Type 2 Diabetes HHS Public Access. *Physiol. Behav.* 176, 139–148 (2017).
33. Li, J. *et al.* Diabetes mellitus and dementia—a systematic review and meta-analysis. *Eur. Rev. Med. Pharmacol. Sci.* 18, 1778–1789 (2014).
34. Bergman, B. C. *et al.* Novel and reversible mechanisms of smoking-induced insulin resistance in humans. *Diabetes* 61, 3156–3166 (2012).
35. Kellar, D. & Craft, S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. *The Lancet Neurology* vol. 19 758–766 (2020).
36. Ferreira, L. S. S., Fernandes, C. S., Vieira, M. N. N. & De Felice, F. G. Insulin resistance in Alzheimer's disease. *Front. Neurosci.* 12, 1–11 (2018).
37. Infante-Garcia, C., Ramos-Rodriguez, J. J., Galindo-Gonzalez, L. & Garcia-Alloza, M. Long-term central pathology and cognitive impairment are exacerbated in a mixed model of Alzheimer's disease and type 2 diabetes. *Psychoneuroendocrinology* 65, 15–25 (2016).
38. Xu, W. *et al.* Accelerated progression from mild cognitive impairment to dementia in people with diabetes. *Diabetes* 59, 2928–2935 (2010).
39. Kuźma, E. *et al.* Stroke and dementia risk: A systematic review and meta-analysis. *Alzheimer's Dement.* 14, 1416–1426 (2018).
40. Tram, L. *et al.* Adipose tissue lipophilic index and risk of ischemic stroke—A danish case-

- cohort study. *Nutrients* (2018) doi:10.3390/nu10111570.
41. Pendlebury, S. T. Stroke-related dementia: Rates, risk factors and implications for future research. *Maturitas* (2009) doi:10.1016/j.maturitas.2009.09.010.
 42. Oshunbade, A. A. *et al.* Cigarette Smoking and Incident Stroke in Blacks of the Jackson Heart Study. *J. Am. Heart Assoc.* (2020) doi:10.1161/JAHA.119.014990.
 43. Chang, J. T., Anic, G. M., Rostron, B. L., Tanwar, M. & Chang, C. M. Cigarette Smoking Reduction and Health Risks: A Systematic Review and Meta-Analysis. *Nicotine Tob. Res.* (2020) doi:10.1093/ntr/ntaa156.
 44. Li, B. *et al.* "Smoking paradox" is not true in patients with ischemic stroke: a systematic review and meta-analysis. *J. Neurol.* (2019) doi:10.1007/s00415-019-09596-3.
 45. Choi, S. *et al.* Association of smoking cessation after atrial fibrillation diagnosis on the risk of cardiovascular disease: A cohort study of South Korean men. *BMC Public Health* 20, 1–8 (2020).
 46. Harada, C. N., Natelson Love, M. C. & Triebel, K. L. Normal cognitive aging. *Clin. Geriatr. Med.* 29, 737–752 (2013).
 47. Shatenstein, B. & Barberger-Gateau, P. Prevention of age-related cognitive decline: Which strategies, when, and for whom? *J. Alzheimer's Dis.* 48, 35–53 (2015).
 48. Sabia, S. *et al.* Impact of smoking on cognitive decline in early old age: The Whitehall II cohort study. *Arch. Gen. Psychiatry* 69, 627–635 (2012).
 49. Richards, M., Jarvis, M. J., Thompson, N. & Wadsworth, M. E. J. Cigarette Smoking and Cognitive Decline in Midlife: Evidence from a Prospective Birth Cohort Study. *Am. J. Public Health* (2003) doi:10.2105/AJPH.93.6.994.
 50. Dregan, A., Stewart, R. & Gulliford, M. C. Cardiovascular risk factors and cognitive decline in adults aged 50 and over: A population-based cohort study. *Age Ageing* (2013) doi:10.1093/ageing/afs166.
 51. Etgen, T., Sander, D., Bickel, H. & Förstl, H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. *Dtsch. Arztebl. Int.* (2011) doi:10.3238/arztebl.2011.0743.
 52. Action on Smoking and Health Scotland. Fastfacts: Secondhand smoke is harmful to others. *ASH Scotl.* 2, <https://www.ashscotland.org.uk/media/801104/2-seco> (2018).
 53. Pan, X., Luo, Y. & Roberts, A. R. Secondhand Smoke and Women's Cognitive Function in China. *Am. J. Epidemiol.* 187, 911–918 (2018).
 54. Orsitto, G., Turi, V., Venezia, A., Fulvio, F. & Manca, C. Relation of secondhand smoking to mild cognitive impairment in older inpatients. *Sci. World J.* 2012, (2012).
 55. Stirland, L. E., O'Shea, C. I. & Russ, T. C. Passive smoking as a risk factor for dementia and cognitive impairment: Systematic review of observational studies. *Int. Psychogeriatrics* 30, 1177–1187 (2018).
 56. Groner, J. A., Huang, H., Nagaraja, H., Kuck, J. & Bauer, J. A. Secondhand Smoke Exposure and Endothelial Stress in Children and Adolescents. *Acad. Pediatr.* 15, 54–60 (2015).
 57. Harbin, M. M. *et al.* Relation of secondhand smoke exposure to vascular phenotypes in children and adolescents. *Pediatr. Res.* 87, 760–766 (2020).
 58. Yang, B., Li, M., Chen, B., Xu, Y. & Li, T. De. Deterioration of endothelial function and carotid intima-media thickness in Tibetan male adolescents exposed to second-hand smoke. *JRAAS - J. Renin-Angiotensin-Aldosterone Syst.* (2012) doi:10.1177/1470320312440901.
 59. Frey, P. F. *et al.* The exposure-dependent effects of aged secondhand smoke on

- endothelial function. *J. Am. Coll. Cardiol.* (2012) doi:10.1016/j.jacc.2012.02.025.
60. Teo, K. K. *et al.* Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* (2006) doi:10.1016/S0140-6736(06)69249-0.
 61. Fischer, F. & Kraemer, A. Meta-analysis of the association between second-hand smoke exposure and ischaemic heart diseases, COPD and stroke Environmental health. *BMC Public Health* (2015) doi:10.1186/s12889-015-2489-4.
 62. Oono, I. P., MacKay, D. F. & Pell, J. P. Meta-analysis of the association between secondhand smoke exposure and stroke. *J. Public Health (Bangkok)*. (2011) doi:10.1093/pubmed/fdr025.
 63. Lin, M. P., Ovbiagele, B., Markovic, D. & Towfighi, A. Association of secondhand smoke with stroke outcomes. *Stroke* (2016) doi:10.1161/STROKEAHA.116.014099.
 64. Eze, I. C. *et al.* Environmental tobacco smoke exposure and diabetes in adult never-smokers. *Environ. Heal. A Glob. Access Sci. Source* 13, 1–9 (2014).
 65. Kermah, D., Shaheen, M., Pan, D. & Friedman, T. C. Association between secondhand smoke and obesity and glucose abnormalities: Data from the national health and nutrition examination survey (NHANES 1999–2010). *BMJ Open Diabetes Res. Care* 5, (2017).
 66. Huang, C. *et al.* Association between environmental tobacco smoke exposure and risk of type 2 diabetes mellitus in Chinese female never smokers: A population-based cohort study. *J. Diabetes* 12, 339–346 (2020).
 67. Kim, D., Choy, Y. S. & Park, E. C. Association between secondhand smoke and glycemic control in adult diabetes patients. *Prev. Med. (Baltim)*. 94, 48–54 (2017).
 68. Biessels, G. J., Staekenborg, S., Brunner, E., Brayne, C. & Scheltens, P. Risk of dementia in diabetes mellitus: A systematic review. *Lancet Neurology* (2006) doi:10.1016/S1474-4422(05)70284-2.
 69. RK, T. *et al.* Nicotine addiction: Neurobiology and mechanism. *J. Pharmacopuncture* 23, 1–7 (2020).
 70. Wang, C. C. *et al.* Cigarette smoking and cognitive impairment: A 10-year cohort study in Taiwan. *Arch. Gerontol. Geriatr.* 51, 143–148 (2010).
 71. Dickerson, T. J. & Janda, K. D. Glycation of the amyloid β -protein by a nicotine metabolite: A fortuitous chemical dynamic between smoking and Alzheimer's disease. *Proc. Natl. Acad. Sci. U. S. A.* (2003) doi:10.1073/pnas.1332847100.
 72. Stanciu, G. D. *et al.* Alzheimer's disease pharmacotherapy in relation to cholinergic system involvement. *Biomolecules* 10, 1–21 (2020).
 73. Newhouse, P. *et al.* Nicotine treatment of mild cognitive impairment: A 6-month double-blind pilot clinical trial. *Neurology* (2012) doi:10.1212/WNL.0b013e31823efcbb.
 74. Alzheimer's Drug Discovery Foundation. *Nicotine. Alzheimer's Drug Discovery Foundation* (2016).
 75. Lucas, C. & Martin, J. Smoking and drug interactions. *Aust. Prescr.* 36, 102–104 (2013).
 76. Maideen, N. M. P. Tobacco smoking and its drug interactions with comedications involving CYP and UGT enzymes and nicotine. *World J. Pharmacol.* 8, 14–25 (2019).
 77. Scottish Fire and Rescue Service. FIRE AND RESCUE INCIDENT STATISTICS (SCOTLAND) 2018–19. *Fire Rescue Scotl.* 2018–2019, (2019).
 78. Heward, M. & Fiona, K. Fire Safety Innovations for People Affected by Dementia: Report on Focus Group and Survey findings. *Bournemouth Univ. - Dement. Inst.* <http://www.cfoa.org.uk/download/63722> (2015).
 79. NICE. Smoking cessation guidelines for health professionals. *Natl. Inst. Clin. Excell.*

- <https://www.nice.org.uk/guidance/ng92/chapter/reco> (2018).
80. NHS Scotland, ASH Scotland & Royal College of Practitioners. A guide to smoking cessation in Scotland 2010 - Planning and providing specialist smoking cessation services. *NHS Heal. Scotl.* <https://healthscotland.scot/media/1096/a-guide-to-> (2017).
 81. West, R., McNeill, A. & Raw, M. Smoking cessation guidelines for health professionals: An update. *Thorax* (2000) doi:10.1136/thorax.55.12.987.
 82. Peto, R. *et al.* Smoking, smoking cessation, and lung cancer in the UK since 1950: Combination of national statistics with two case-control studies. *Br. Med. J.* (2000) doi:10.1136/bmj.321.7257.323.
 83. Han, L. *et al.* Smoking and Influenza-associated Morbidity and Mortality: A Systematic Review and Meta-analysis. *Epidemiology* vol. 30 405–417 (2019).
 84. WHO. Fact sheet about health benefits of smoking cessation. *World Heal. Organ.* <https://www.who.int/tobacco/quitting/benefits/en/>.
 85. Carreras, G. *et al.* Burden of disease attributable to second-hand smoke exposure: A systematic review. *Prev. Med. (Baltim)*. 105833 (2019) doi:10.1016/j.ypmed.2019.105833.
 86. INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). Tobacco Smoke and Involuntary Smoking. *IARC Monogr. Eval. Carcinog. Risks to Humans* 83, Volume 83 (2004).
 87. Al-Sayed, E. M. & Ibrahim, K. S. Second-hand tobacco smoke and children. *Toxicol. Ind. Health* (2014) doi:10.1177/0748233712462473.
 88. Angus, K., Semple, S. Home health and community care workers' occupational exposure to secondhand smoke: a rapid literature review. *Nicotine Tob. Res.* (2018) doi: 10.1093/ntr/nty226.
 89. Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. *Archives of Internal Medicine*, volume 172(11): pp. 837-844, June 2012. <http://archinte.jamanetwork.com/article.aspx?articleid=1182214>



8 Frederick Street | Edinburgh | EH2 2HB.

0131 225 4725

enquiries@ashscotland.org.uk

Action on Smoking & Health (Scotland) (ASH Scotland) is a registered Scottish charity (SC 010412) and a company limited by guarantee (Scottish company no 141711). The registered office is 8 Frederick Street, Edinburgh EH2 2HB.