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Smoking cessation and Alzheimer's disease: facts, fallacies and promise

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Over 37 million people suffer with Alzheimer's disease (AD), a number that will quadruple by 2050 [1]. Delaying the onset of AD by just 5 years would reduce the number of cases by 50% [1]. Current US FDA-approved AD drugs do not prevent or reverse the disease and provide only moderate symptomatic benefits. Lacking a cure, there is growing interest in prevention and treatment to slow AD progression. In a recent review, we found that smoking almost doubled the risk of AD [2]. Smoking cessation is an intervention that contributes to a reduction of both cardiovascular disease (CVD) and AD risk factors, which strongly suggests that smoking cessation could prevent or slow the development of AD.

Despite strong evidence linking smoking with AD, beliefs prevail in both scholarly journals and lay publications that smoking protects against AD [2]. The tobacco industry has played an important role in the development of this myth. In the mid-1970s the tobacco industry began to invest in AD research, efforts that intensified in 1981 following published anecdotal observations of low rates of tobacco use among people with AD [3,101]. The reason for this interest in AD research was to understand the role of smoking in AD in order to develop and market early diagnostics and therapeutics, such as nicotine analogs [102]. Early work on smoking and AD, mostly case-control studies performed by investigators with funding or other relations with the tobacco industry, generally showed a protective effect of smoking on AD. Later work, performed with stronger cohort designs by investigators independent of the tobacco industry, revealed increased risk of AD associated with smoking [2]. Our analysis of 43 studies published through 2007 showed that case-control studies tended to yield lower average risk estimates than cohort studies (by -0.27 ± 0.15 ; $p = 0.075$), lower risk estimates for studies performed by authors affiliated with the tobacco industry (by -0.37 ± 0.13 ; $p = 0.008$), no effect of the quality of the journal in which the study was published (measured by impact factor; $p = 0.828$) and an increasing secular trend in risk estimates (0.031 per year ± 0.013 ; $p = 0.02$). The average risk of AD for cohort studies without tobacco industry affiliation of average quality published in 2007 was estimated to be 1.72 ± 0.19 ($p < 0.0005$), showing that smoking is a significant and

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substantial risk factor for AD. Even more important, smoking is also a modifiable risk factor.

The paper 'Causes versus effects: the increasing complexities of AD pathogenesis' in this issue of *Expert Review of Neurotherapeutics* reports that oxidative stress is emerging as a primary causal factor in AD neurodegeneration [4]. Oxidative stress is a disturbance in the redox state of an organism or a disturbance in the balance between production of reactive oxygen species and endogenous antioxidant defenses, leading to oxidation of lipids, proteins and DNA in ways that impair cellular function [5,6]. Cigarette smoke is a complex mixture of more than 4000 chemical compounds, including high concentrations of free radicals and other reactive oxidant species [7]. Smoking increases oxidative stress by the direct delivery of reactive oxidant species and by promoting the endogenous generation of reactive oxidant species by activation of inflammatory cells while, at the same time, weakening anti-oxidant defense systems [7]. The direct delivery of oxidants and the subsequent promotion of platelet and neutrophil activation suggest the importance of oxidative stress in the pathogenesis of smoking-induced tissue injury [5]. Empirical evidence has demonstrated the important pathophysiological role of increased reactive oxygen species production leading to oxidative stress in neurodegenerative disorders (including AD). The brain is susceptible to oxygen free radical damage, because of the prevalence of oxidizable poly-unsaturated fatty acids in membranes, the presence of redox-active metal ions and the high metabolic requirement for oxygen [8].

Free radicals and lipid peroxidation also have roles in the pathogenesis of CVD [7]. In addition, many of the risk factors for CVD are also risk factors for cognitive decline and dementia, and smoking increases the risk of both CVD and dementia [9,10]. CVD involves hypoperfusion and ischemia and these events can result in damage to the areas of the brain that are responsible for cognition and lead to dementia and AD [11]. Cigarette smoking cessation leads to a marked increase in plasma antioxidant concentrations and provides a substantial improvement in plasma resistance towards oxidative challenge [12].

Studies have reported that a decrease in cardiovascular reactivity (a pattern that is elicited when the homeostasis of the cardiovascular system is challenged, i.e., a change in blood pressure or heart rate [13]) and cerebrovascular events predicts cognitive and functional progression in AD [14,15]. The presence of individual vascular risk factors, such as hypertension, atherosclerosis, atrial fibrillation and stroke, at the time of AD diagnosis impacts on the rate of AD progression [16]. Smoking is independently related to the onset of hypertension [17], atrial fibrillation [18] and diabetes mellitus [19], and there is a dose-response relationship between the amount of cigarettes smoked per day and the risk of stroke [20]. Treating vascular risk factors in AD patients, with or without CVD, slows cognitive decline. Slowing dementia progression could reduce both the prevalence of AD and the prevalence of later severe stages of AD [21]. Given that later stages of AD are responsible for most dementia burden in terms of personal suffering and healthcare costs, any intervention modifying dementia progression could have a tremendous impact [22]. Thus, smoking cessation may play an important role in not only primary, but also secondary prevention of AD.

Smoking cessation, even in older adults who are frail, produces objective benefits in terms of mortality, reversed respiratory symptoms, disability level, decreased psychological distress, quality of life and cost of care [23]. There are substantial short-term benefits from assisting older smokers in stopping smoking and the cardiovascular benefits accrue rapidly [24]. Smoking cessation leads to a marked increase in plasma antioxidant concentrations and substantially improves plasma resistance towards oxidative challenge [12]. The risk of CVD,

a major risk factor for AD, falls by half within the first year following cessation and is nearly back to that of a nonsmoker in 3 years [25].

Even though smoking cessation can provide older smokers with increased quality and quantity of life, older smokers are asked to quit less often, given fewer resources and provided with less guidance than younger smokers [23,26]. The myth that smoking protects against AD may discourage cessation attempts among older smokers and contribute to the reluctance of healthcare providers to treat tobacco dependence in older smokers [23]. While there is not yet any research on the effects of smoking cessation on AD risk and progression, given that smoking is a significant risk factor for CVD and AD, it makes sense that smoking cessation should become an integral part of the prevention and treatment of AD. Even as we research the specific effects of smoking cessation as an intervention to prevent or slow AD, because of its many other benefits, smoking cessation needs to become a priority in the care of all older smokers.

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