EDITORIAL

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No smoke without fire: should we be more concerned about the association between smoking and dementia?

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“...smoking increases an individual's risk of developing dementia, and banning population smoking would reduce the number of dementia cases worldwide.”

The world is facing a dementia epidemic. At present, an estimated 50 million people are living with dementia worldwide, and this figure is expected to triple over the next 40 years [1]. The burden of dementia is already huge, currently contributing towards 11.2% of years lived with a disability in those aged over 60 years, and has a greater burden than stroke (9.5%), musculoskeletal disorders (8.9%), cardiovascular disease (5.0%) and all forms of cancer (2.4%) [2]. A better understanding of the determinants of dementia is essential if we are to slow this epidemic by identifying possible prevention and treatments.

One such determinant that researchers have explored is whether there is a link between cigarette smoking and dementia, following findings that smoking increases the risk of cardiovascular disease. The 1980s and 1990s saw a surge of research into the area, much of which provided inconsistent findings [3]. There are a number of hypotheses that directed this area of research, including that nicotine can play a protective role through improving

short-term cognitive performance [4], and may be beneficial in improving cognitive performance in Alzheimer's patients, both of which have biological plausibility [5]. However, smoking is an established risk factor for vascular disease [6], which in turn is a risk factor for both vascular dementia and Alzheimer's disease (AD) [7].

In 2002, Almeida *et al.* carried out a meta-analysis in an attempt to resolve these conflicting findings, and their results highlighted an important methodological limitation within the then-available literature [3]. The 21 case-control studies they identified suggested that smoking was protective against AD (odds ratio [OR]: 0.74; 95% CI: 0.66–0.84), which remained so, even after adjustment of confounders (OR: 0.82; 95% CI: 0.70–0.97). Whilst fewer cohort studies were identified, the eight included in their meta-analysis indicated the opposite finding, demonstrating a significant association between smoking and AD (relative risk [RR]: 1.10; 95% CI: 0.94–1.29). When this analysis was restricted to only two cohort studies, which included data on participants who

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were smokers at baseline, the RR increased to 1.99 (1.33–2.98). The authors acknowledged that case–control studies are vulnerable to methodological limitations, however, at the time, there were few longitudinal cohort studies to draw from within the literature. It was considered that the use of case–control studies may have not only falsely underestimated the risk of dementia from smoking, but actually suggested that smoking may be beneficial due to limitations, such as survival effects and recall bias, associated with this methodology.

Following the publication of the review by Almeida *et al.* [3], there was continued research into the relationship between smoking and dementia [8]. Anstey *et al.* subsequently conducted a meta-analysis of longitudinal studies that included smoking as a risk factor for cognitive decline and dementia, restricted to studies that had screened for dementia at baseline and had a minimum follow-up of 12 months [8]. Cohort studies of this nature are less susceptible to bias than case–control studies, and it was hoped that these stringent inclusion criteria would give a more accurate picture of the link between smoking and dementia. Their findings presented a more concerning picture to those of Almeida and colleagues [3]. Across the 19 studies identified, they found that those smoking at baseline were at an increased risk of AD (RR: 1.79; 95% CI: 1.43–2.23), vascular dementia (RR: 1.78; 95% CI: 1.28–2.47) and any dementia (RR: 1.27; 95% CI: 1.02–1.60) compared with never smokers.

Although the literature review and meta-analysis conducted by Anstey and colleagues provided what seemed to be undeniable evidence of a significantly increased risk of dementia associated with smoking [8], questions have since been raised as to whether this review is able to give a full picture due to its inclusion of research funded and affiliated with the tobacco industry [9]. Industry sponsorship is highly influential within the tobacco industry, although this is neither uncommon nor unique to this sector [10]. A review found that pharmaceutical research backed by industry was more likely to reach conclusions favorable to the sponsor, and be more prone to publication bias [11].

Cataldo *et al.* found that the tobacco industry began to invest in AD research in 1976 [9], and argued that a major limitation of previous reviews [3,8] was their failure to control for tobacco industry funding or author affiliation.

They conducted a meta-analysis of 43 studies to examine the relationship between smoking and AD after controlling for study design, quality and tobacco industry affiliation. As before [3], they reported that case–control studies yielded lower average risk estimates than cohort studies. Unaffiliated case–control studies had a nonsignificant pooled OR of 0.91 (0.75–1.10), compared with tobacco industry-affiliated case–control studies, which actually suggested a protective effect of tobacco consumption with a significant pooled OR of 0.86 (0.75–0.98). A similar pattern was observed across the cohort studies; unaffiliated studies had an RR of 1.45 (1.16–1.80), demonstrating an increased risk of AD with smoking, whereas tobacco-affiliated studies showed a nonsignificant RR of 0.60 (0.27–1.32). The average risk of AD reported in unaffiliated cohort studies published in 2007 was even higher at 1.72 ($\pm$ 0.19). The results of this meta-analysis clearly show a discrepancy in the findings reported both between different methodologies, and in those studies affiliated with the tobacco industry.

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Cataldo *et al.* further demonstrated that it is not just individual studies that are influenced by the tobacco industry; of the ten systematic reviews examined, four had an affiliation to the tobacco industry and all four reported a protective effect of smoking on AD [9]. Taken as a whole, the findings of Cataldo *et al.* show that much of the early conflict regarding whether smoking is a risk factor for AD was misleading; any protective effects of smoking observed can be attributed to biased study design and affiliation or funding from the tobacco industry [9]. When these factors are controlled for, the evidence is striking. Smoking can increase an individual's risk of developing dementia by as much as 72%.

Research reviewed to date has been predominantly conducted within high-income countries, with few studies being undertaken in low- and middle-income countries. Recently, we have examined a population-based cohort

study in China, and found that compared with never smokers, current smokers at baseline had a substantial excess in incident dementia (i.e., multivariate adjusted odds ratio was 2.39 [1.21–4.72]). Former smokers were also found to have an increase in the risk, but not significantly (OR: 1.66; 95% CI: 0.53–5.16) [12], which is consistent with the findings reported in the review by Anstey *et al.* probably suggesting that giving up smoking would reduce the risk of dementia [8]. This provides further confirmation of the dangers that smoking poses to dementia risk.

Cigarette smoking may also increase the risk of dementia in populations via passive smoking – inhalation of smoke that fills enclosed spaces where individuals burn tobacco products. In recent years, several studies have been published to show an association between passive smoking and cognitive impairment and dementia [13–15]. Passive smoking exposure has many detrimental effects on the cardiovascular system, including increased coagulability of blood platelets, endothelial dysfunction, decreased coronary flow velocity reserves and accelerated atheroma genesis [16]. Moreover, endothelial dysfunction may be related to the reduced clearance of β -amyloid protein, which is considered to be implicated in the pathogenesis of AD [17]. The current findings from passive smoking research, which involves approximately 30% of the world population being exposed, further support that cigarette smoking can substantially increase the risk of individuals with dementia worldwide [18].

Although we have come a long way since the times when smoking was widely reported to be protective against dementia [19], focused

attention on the topic is still needed. The public health message needs to be clear and consistent: smoking increases an individual's risk of developing dementia, and banning population smoking would reduce the number of dementia cases worldwide [1]. As one of the now known preventable risk factors for dementia, it is vital that the public are appropriately educated and government efforts are stepped up to help prevent dementia becoming the worldwide epidemic that it is currently predicted to be. Although reducing smoking is just one arm in the battle to halt the rise of dementia, it is an important one as an estimated 29% of people smoke worldwide today [1]. Effective tobacco control policies can make a significant impact in slowing the epidemic.

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