**Graphical Abstract**

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**Beyond the obvious: Smoking and respiratory infection implications on Alzheimer's disease**

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**Abstract**

**Background:** Tobacco smoke is not only a leading cause for chronic obstructive pulmonary disease, cardiovascular disorders, lung and oral cancers but also causes neurological disorders such as Alzheimer’s disease.  Tobacco smoke consists of more than 4500 toxic chemicals, which form free radicals and can cross blood brain barrier resulting in oxidative stress, an extracellular amyloid plaque from the aggregation of amyloid β (Aβ) peptide deposition in the brain. Further, respiratory infections such as *Chlamydia pneumoniae*, respiratory syncytial virus have also been involved in the induction and development of the disease.

**Methods**: The necessary information collated on this review has been gathered from various literature published from 1995 to 2019.

**Findings:** The review article sheds light on the role of smoking and respiratory infections in causing oxidative stress and neuroinflammation resulting in Alzheimer's disease (AD). This review will be of interest to scientists and researchers from biological and medical science disciplines including microbiology, pharmaceutical sciences and the translational researchers, etc.

**Conclusion:** The increasing understanding of the relationship between chronic lung disease and neurological disease are two-fold. First, this would help to identify the risk factors and possible therapeutic interventions to reduce the development and progression of both diseases. Second, this would help to reduce the probable risk of development of AD in the population prone to chronic lung diseases.

**Keywords:** Smoking; Pulmonary infections; Alzheimer’s disease; oxidative stress; infection

1. **Introduction**

Dementia is a heterogeneous syndrome that is primarily characterised by marked reductions in an individual’s cognition levels which leads to impairments in social, professional or personal life [1]. A broad classification of dementia includes patients with dementia being either those who are “neurodegenerative” and non-neurodegenerative [1, 2]. Although simplistic in nature, this categorisation is increasingly being expanded to accommodate newly diagnosed traits associated with dementia [3]. Most common clinical symptoms of dementia include progressive memory impairment, gradual decline in cognition abilities, hallucinations, behavioural alterations (*e.g.,* loss of empathy), aggression, and accidental falls leading to physical injury, headache and malaise [1]. Notably, one of the commonest forms of dementia is AD. This affects a majority of individuals (~70%) with dementia [4, 5].

The burden of dementia has doubled from 1990 (20.2 million) to 2016 globally (43.8 million) [6]. This is primarily due to increasing population growth and ageing. Moreover, the mortality attributed to dementia is now the fifth leading cause of deaths worldwide, accounting for approximately 2.4 million deaths annually [6]. Furthermore, a total of 28·8 million disability-adjusted life years (DALYs) corresponded to dementia. Around 6·4 million of these DALYs may be directly related to major modifiable risk factors. These may include elevated body mass index and smoking [6]. In addition, the economic costs associated with AD is enormous, with total direct expenditure of AD/dementia in USA estimated to be approximately $183 billion, which are predicted to increase to $1.1 trillion by 2050[7].

The key neuropathological biomarkers and/or effectors that are found in cerebrospinal fluid samples of the subjects having AD are outlined below; clumping of senile plaques that are made primarily of β-amyloid (*i.e.*, Aβ42), and substances namely, neurofibrillary tangles (NFTs). These NFTs are primarily made up of a specific protein (tau (τ) protein). These proteins are generally hyperphosphorylated [8]. Novel potential biomarkers include amyloid β oligomers and other synaptic markers [9]. Age is one of the major non-modifiable risk factors in patients having AD. In addition, occurrence of genetic mutations, specifically, in the apolipoprotein E-4 allele (APOE4) is also a major risk factor [10]. In addition to the above, there are several important genetic risk factors that play a significant role. These are alterations within in the amyloid precursor proteins (APP) of the genes, PSEN1 and PSEN2 (presenilin 1 and presenilin 2, respectively). There are several other non-modifiable risk factors in individuals with AD. These constitute female gender, past incidence of head injury/trauma, hereditary incidence of Down syndrome, dementia and other risk factors arising from cerebrovascular issues. In addition, there are several modifiable risk factors attributed to AD, which primarily include lifestyle-related risk factors (*i.e.*, cigarette smoking, stress, depression, inadequate sleep) [11] or acquired diseases that substantially increase the risk of AD, which include diabetes, hypertension, obesity and dyslipidemia [12].

Smoking of cigarettes is one of the significant and principal modifiable risk factors in the development of AD. Importantly, Cataldo *et al*., found that ever smoking, either active or former, was indeed one of the principal risk factors in the development of AD with a relative risk of 1.72 and a 95% CI (1.33–2.12) [13]. Moreover, a large study (n=21,123) reported that individuals who smoked >2packs/day were at increased risk of developing dementia, where the adjusted hazard ratio was 2.14 and a 95% CI, (1.65-2.78). The study also reported that AD had an adjusted HR of 2.57 at 95% CI, (1.63-4.03). Vascular dementia had an adjusted HR of 2.72 at 95% CI (1.20-6.18) [14]. The potential mechanisms by which former/active smoking may exert its effects on the initiation of AD are speculative and include generation of free radicals that could increase the oxidative stress burden in the host [15]. This leads to activation of immune system and more specifically activation of microglia, which then leads to increased production and release of inflammation triggering cytokines (*e.g.*, tumour necrosis factor (TNF)-α, nitric oxide (NO), interleukin-6 (IL-6), and reactive oxygen species (ROS) [15, 16]. All these pro-inflammatory markers have been shown to be anti-neurogenic, potentially via inducing mitochondrial dysfunction [16]. Additionally, exposure to cigarette smoke is also associated with neuropathology characteristic of AD in both humans and animal models of AD [15].

Recently, emerging data also have outlined and summarised the crucial role of microbes in the development of AD. In particular, several neurotropic viruses, for instance, those related to the family of Herpesviridae namely, Human herpesvirus 1 [HHV-1], Cytomegalovirus (CMV), and Human herpesvirus 2 (HHV-2) are implicated in the neuropathological characteristics of AD [17]. Notably, increased HHV-6A and HHV-7 were detected in the brain sections of subjects having this condition (AD), when studied relatively with subjects who acted as controls [18]. Moreover, Eimer *et al*., have recently showed that amyloid-β peptides bind to the surface glycoproteins of herpesvirus, thereby, accelerating the deposition of β-amyloid in response to the viruses namely, herpes simplex virus 1 (HSV1) and HHV 6A and B [19]. Although this mechanism is presumably protective against the virus-induced damages in the brain, it also leads to increased amyloid-β amyloidosis [19]. Several bacteria, including, *Fusobacterium nucleatum*, *Chlamydia pneumoniae* [20], *Prevotella* *intermedia*, *Helicobacter pylori*, *Porphyromonas gingivalis*, *Borelia burgdorferi*, *Treponema pallidum* and other related bacteria of periodontal origin have also been associated with AD initiation and/or development [17]. The colonisation and/or infection with bacteria could lead to persistent inflammation within the host that could spill-over systemically and lead to damage to the neurons, *i.e.*, neuro-inflammation [21]. This could then lead to hallmark features of AD. A potential role for gut microbiota, especially in the maturation of microglia and systemic immune cells, has been proposed and should be investigated further to tease out specific and most relevant mechanisms associated with infections and AD [22, 23].

1. **Effects of respiratory diseases in Alzheimer’s disease**

 Cognitive impairment in individuals with long term pathological lung conditions is continually shown to be more severe than without it (Figure 1).



**Figure 1: Inter-relationship of AD with respiratory diseases.**

* 1. **Chronic obstructive pulmonary disease (COPD)**

The occurrence of cognitive disorders in COPD is between 10% and 61% based on population of the study and neuropsychological evaluation methodology. Chronic pulmonary obstructive disease has an effect on 210 million individuals, and 60 percent of certain groups have cognitive impairment [24-27]. A one year study involving 126,106 U.S. citizens in nursing homes found a combined diagnosis of COPD and dementia in mentally impaired health, showing substantial data to justify the link to poor quality of living standards, hospitalization and diminished survival. Moderate to severe cognitive dysfunction was reported to occur in around 61% of extremely hypoxaemic COPD individuals. Some studies show a global disability or lack of attention, memory and thinking and motor functions of COPD patients [28, 29]. A majority of the 42 percent of COPD patients showed severe dysfunction of cognition when compared to 22 percent for the patients who were in the group that was labelled as control as reported by the combined Nocturnal Oxygen Therapy and Intermittent Positive Pressure Breathing trials [30].

* 1. **Asthma**

The major clinically defined symptoms of asthma are breathlessness, wheezing, chest and throat tightness, repeated cough along with obstruction in the airflow [31-36]. The characteristics feature of asthma includes goblet cell hyperplasia, alterations in extracellular matrix component, denudation of epithelial lining, increased airway smooth muscle cell proliferation and angiogenesis [37]. Some studies suggest that neurocognitive dysfunction has an association with asthma, citing causes such as systemic inflammation, medication effects and sleep disorders [38, 39]. The incidences of cognitive dysfunction along with dementia were particularly related with mid-life asthma, and risks with exacerbations and hospitalization further increased. Cognitive function was assessed in baseline subjects, 6 weeks after administering inhaled bronchodilators and steroids. The sample size was 46, who were primarily atopic subjects suffering from asthma [40]. The intervention showed an enhancement in cognitive capacities, which is reported to have a connection with improved respiratory function variability. However, it is not evident that median effects have been fully taken into consideration in practice and regress [41].

* 1. **Pneumonia**

Pneumonia, in particular for older adults, is a main cause of hospitalization and mortality. The importance of the clinical management of pneumonia is growing with the rapid growth of the older population [42]. The aging phenomenon is followed by a growing number of Alzheimer's patients, a major challenge for healthcare. Previous research has shown that Alzheimer's is a risk factor for pneumonia in older adults. Several studies have also shown that people with Alzheimer's tend to die from pneumonia more often. A study reported on this has shown the risk of pneumonia-associated mortality is more than twice higher for Alzheimer's patients than for those without Alzheimer's. Nevertheless, the estimated rate of death from pneumonia among older adults with dementia ranges from 12% to 70% [43, 44].

* 1. **Lung Cancer**

Among cancer related death, lung cancer is the leading cause of mortality globally primarily due to lack of effective early diagnostic markers and treatments [45]. About 30 percent of small cell lung cancer (SCLC) patients suffer from a form of neurological disorder in course of the condition [46]. A majority of them are due to cerebral metastases. Some of these are metastases to locations other than the cerebrum. But, due to other factors there is a small percentage of them. These may result from comorbid conditions, chemical therapy and/or radiation, paraneoplastic neurological syndrome (PNS), aging, or immunological deterioration. A 59-year-old subject who was diagnosed with small-cell lung cancer (SCLC) received full response to chemoradiation in one case study in October 2008, which included a prophylactic cranial irradiation (PCI) with (25 Gy at 250 cGy per fraction). He was reported to have anorexia, weight loss, fatigue, and short-term loss of memory, and eventually developed Alzheimer's and weakness in his muscles, three months afterwards. Magnetic resonance imaging showed the progression of diffuse atrophy without evidence of metastasis of SCLC [47].

**3.** **Role of nicotine in the pathology of Alzheimer’s disease**

The hallmark features observed in AD pathology is the accumulation of two types of proteins, the naturally occurring Aβ peptide which accumulates as extracellular amyloid plaques and the intracellular hyperphosphorylated τ proteins aggregated as neurofibrillary tangles in various regions of the brain modulating the cholinergic system [48-50].

The Cholinergic system consists of the enzyme choline acetylcholine transferase (ChAT) that induces the production of the neurotransmitter acetylycholine (ACh) at the synaptic junction, the receptors nicotinic acetylcholine receptors (nAChRs) and muscarinic receptors which form a complex responsible for the neurotransmission, ACh esterase which metabolises the ACh after the signal transduction and the regulatory of ACh esterase and inhibitors [51-53]. The accumulation of amyloid plaques and τ proteins leads to decreased activity of ChATs that impairs the secretion of the neurotransmitters [53, 54], reduction in nACh receptors and increased stimulation of ACh esterases results in synaptic and neuronal loss causing brain atrophy and dementia observed in AD [55]. Thus, in AD the cholinergic and the synaptic mechanism are impaired affecting the nerve cell communication that results in the loss of cognitive and noncognitive functions such as memory, learning, attention, anxiety and balance and movement [56, 57].

Nicotine is the active component of tobacco, a natural product produced by plants of nightshade family and prepared synthetically as well. It is one of the commonly abused drugs and is highly addictive that augments individuals’ addiction to tobacco usage [58, 59]. Several studies proved the involvement of nicotine in AD pathogenesis and showed their protective and degenerative functions in the disease [59-62].

Homeostasis of metals in the body plays an important role in AD pathogenesis as it primarily affects the development of Aβ dimers and trimers [63]. Tobacco contains a high amount of other metals such as Al, As, Cd, Co, Cr, Cu, Hg, Mn, Ni, Pb, Se and Zn other than nicotine, at non-negligible amounts, out of which many are considered neurotoxic [64, 65]. Heavy metals such as Pb, Cd, As etc. increases the expression of amyloid precursor protein (APP) and β-secretase 1(BACE1) and interferes with the functioning of microglia and increases the accumulation of Aβ and plaque formation in hippocampus and cortex area [66, 67]. Moreover the exposure to heavy metals activates toll like receptors (TLR4) which induces rise in proinflammatory proteins such as Interleukins (IL)-1β, IL-8, tumor necrosis factor alpha (TNF-α), IL-6 and iNOS which intensifies the neuroinflammation [68].

Cadmium ions induce conformational changes (coil structure to α-helix structure) in the third repeat (R3) τ domain resulting in τ self-aggregation [69]. While aluminium improve the performance of τ kinases such as cyclin-dependent kinase 5 (CDK5), prevents dephosphorylation and enhances its aggregation [70]. Evidences showed that Alzheimer's disease (AD) pathology can be partly caused or worsened by inorganic mercury. Its strong affinity to selenium and selenoprotein indicates that inorganic mercury can promote neurodegenerative diseases through redox-regulation degradation. This can also enhance the effect of other metals on pathogenesis of AD [71].

Lovell *et al*. linked AD to the transition metals such as Cu, Fe, and Zn and showed that they are raised in phosphorylated τ tangles and in AD plaques (AD neuropil) as compared with adjacent nervous tissue [72]. In contrast to AD neuropil, copper was considerably higher (P<0.05) in the rim of senile plaques and Zn expedite the accumulation of amyloid beta peptide [73]. Another research revealed unique binding of these ions (Cu(II), Fe(II) and Zn(II)) to the Aβ peptide and modified its aggregation pathways [74]. Exposure to chronic copper worsened Aβ's accumulation and impair cognition ability [75]. Cu(II) and Fe(III) ions easily bound by Aβ peptide 64, produce harmful ROS which can potentially lead to neuroinflammatory symptoms correlated with AD [76, 77].

Nicotine is both a potent stimulant and relaxant, it activates the nAChRs of the parasympathetic nervous system and mimics the effects ACh [78]. However, there are a five nAChR subunits consisting of α (2-7, 9 and 10), β (2-4), γ, δ, and ε that form functional heteromeric and homomeric pentamers which modulate various functions of the nervous system [53, 78, 79]. Nicotine intake was first shown to be protective in an experimental rodent model of AD by Nordberg and his colleagues [80]. They observed that in transgenic mice with mutation in human amyloid precursor protein (APP) when supplied by adding nicotine in the drinking water, had 80% reduction in the Aβ peptide plaques compared with the controls [80].

Several other investigations also showed the decrease in Aβ peptide pathology with nicotine treatment through the activation of nAChRs, α 4 and 7, β 2 and more specifically via the stimulation of the nicotinic receptor α7 [62, 81-83]. Further, it was reported that in APP mutated transgenic mice, nicotine administration reduces the cellular concentration of the metal copper which decreases Aβ-mediated neurodegeneration and is independent of nChRs activation [84]. In AD, in addition to the dysfunctional cholinergic system, the Aβ plaques modulate the secretion of the neurotransmitter glutamate that overstimulates its receptor N-methyl-D-aspartate (NMDA) inducing neurotoxicity [85]. Moreover, various studies also showed that nicotine induced nAChRs stimulation attenuate glutamate mediated neurodegeneration as shown in figure 2 [86-88].

In contrast to Aβ aggregation, nicotine treatment showed increased hyperphosphorylation and aggregation of τ proteins in both *in vitro* and *in vivo* models [61, 89, 90]. Whereas, a recent study has reported that nicotine does not interact with Aβ and has no effect on Aβ accumulation in AD pathology [60]. The neurotoxic effects of nicotine may be mediated through the increased levels of oxygen free radicals which modulates the pro-inflamamtory transcription factor nuclear factor kappa-B [91]. Similarly, Das *et al*., performed *in-vivo* studies and demonstrated that intraperitoneal administration of nicotine for a week in rats resulted nitic oxide production that decreased the level of mitochondrial free radical scavenger levels in the brain [92].

The toxic effect of acute and chronic nicotine exposure was observed in adolescent female rats which showed significant brain damage compared with male rats [93]. Additionally, in a short randomized controlled clinical trial, high dosage of nicotine (16mg) was shown to impair sleep in healthy adults [94]. However, in other small clinical trials aimed at aged adults, nicotine therapy aided in improving their cognitive performance but not in other aspects of AD [95, 96]. Thus, understanding the effects of nicotine in alleviating AD pathologies is complex and further studies are required to bridge the gaps in the knowledge surrounding the mechanism of Aβ-mediated neurodegeneration to posit nicotine as a potential pharmacological target in the treatment of AD.



**Figure 2: Role of nicotine in AD and cell death.**

1. **Smoking and oxidative stress, a symbiotic association contributing Alzheimer disease**

The abnormal dumping of both τ and Aβ protein is the important causative factors of Alzheimer's disease. These are primarily initiated and enhanced due to the oxidative stress (OxS) which is the imbalance between endogenous free radical production and antioxidant defences [32, 97, 98]. OxS produced by exogenous source such as smoking has been linked with peroxidation of membrane lipids, proteins DNA and RNA which impairs cellular function [99-103]. Along with more than 400 chemical compounds, cigarette smoke possesses elevated levels of free radical and several oxidising agents. Study have shown that cigarette smoking promotes the endogenous production of free radical species *via* activation of inflammatory cells as well as reducing antioxidant defence mechanism [104]. Cigarette smoking associated OxS promotes the amyloidogenic pathway resulting neurotoxic Aβ oligomers generation as well as the abnormal phosphorylation of τ, which is the aetiology of AD. Low level of serum enzymes functioning against oxidation (glutathione reductase, glutathione peroxidase) and antioxidants molecules (ascorbic acid, melatonin, β-carotene, α-carotene) as well as elevated level of malondialdehyde (oxidative stress markers) were observed in smokers [105-108]. In central and peripheral nervous systems, cytokines such as IL, TNF-α and interferons (IFN) influences the inflammatory and immune responses [109]. OxS mediated by free radical may activate inflammatory pathway through a cytokine induce immune response [16, 110] resulting in generation of proinflammatory and anti-inflammatory molecules, for example IL-6, IL-1 TNFα from brain cells [109]. High level of proinflammatory molecules are linked with cerebral OxS leading to cell apoptosis due to ROS and other mediator in brain by astrocytes, microglia and immune cells [48, 111, 112]. The brain cells are highly prone to oxidative damages induced by reactive free radicals because of enhanced metabolism and increased energy demand, as well as easy target of oxidizing agents to membrane phospholipids that are abundant with polyunsaturated fatty acids leading to lipid peroxidation by ROS as shown in figure 3 [113-117].

*In vitro* study has shown that condensate of cigarette smoke elevates the concentrations of Aβ1–40 along with the concentrations of Aβ1–42 with respect to various dose in human amyloid precursor protein (APP) transfected SweAPP N2a cells [118]. Wallin *et al*., 2017 used fluorescence, atomic force microscopy imaging, mass spectrometry, nuclear magnetic resonance techniques to record *in vitro* if Aβ accumulation is influenced by the chemicals present in cigarette such as polycyclic aromatic hydrocarbons (PAHs), nicotine, and metal ions Pb(II), Pb(IV), Cd(II), Cr(III). This study demonstrated that entire metal ions and PAHs modulated the Aβ accumulation process. Among metals ions, Pb(II) Cd(II) and Cr(III) showed common electrostatic associations with Aβ, whereas Pb(IV) displayed distinct temporary binding to N-end of Aβ. Therefore, Pb(IV) ions may be mostly liable to interact with dimer and trimer form of Aβ as well as influence its aggregation. In contrast, hydrophobic toluene mostly influences formation of bigger aggregates, for example tetramers. However, hydrophilic and uncharged molecule such as nicotine displayed no straight interactions with Aβ as well as no effect on its aggregation. This study provides a clear justification for the increased prevalence of AD among smokers highlighting the roles of Pb(IV) as a risk factor for AD [60].

Rat exposed to cigarette smoke increased β-soluble APP concentration in hippocampal tissue homogenate and Aβ accumulation in the cornu ammonis 3 region as well as dentate hippocampal subfield. Also, the rats exposed to smoke demonstrated remarkable upregulation in hyperphosphorylation of τ protein and OxS markers in hippocampal [119]. Exposure APP/presenilin1 transgenic mice (3 months old) to high dose of cigarette (one cigarette over 1 hour, 5 days/week for 4 months) showed an increased formation of fibrillar neuritic plaques and Aβ deposits. Mice also displayed a drastic increase in overall activated microglia density and reactive astrocytes, and τ hyperphosphorylation in the brain cerebral cortex and brain hippocampus compared to the low dosage group (half of cigarette given in 30 minutes) and controls [120].

Tyas *et al*., 2003 compared the level of neuritic plaque burden between never smoker and active, former smokers using autopsy sample of elderly patient with or without dementia. This study found that active and former smoker exhibit remarkably high burden in cerebral cortex as well as hippocampus. However, there were no significant differences between the samples with regard to hippocampal or cortical neurofibrillary tangle count [121]. In contrast, Ulrich *et al*., 1997 found that the level of neurotic plaques in autopsy sample was lower in entorhinal cortex, hippocampus and neocortex in female former/non-smoker compared to active smokers. However, the density of neurofibrillary tangles was higher. Likewise, among male non-smoker and active smokers, there was no significant difference in neurofibrillary tangle or plaque density. In either of the gender, smoking higher pack annually was closely related with increased density of neurofibrillary tangle, whilst not linked with the density of the neurotic plaque [122]. Furthermore, Sabbagh *et al*., 2005, in addition reported no significant alterations in neurofibrillary tangle density or neuritic plaques selectively in the mid-frontal cortex between active smokers, non-smokers and former smokers with AD [123]. These *in vitro* and *in vivo* (mice, rats and human) studies explain the clear symbiotic association of smoking and oxidative stress on progression of Alzheimer disease.



**Figure:3 Smoking mediated OxS and inflammation resulting in neurotoxicity and AD**

1. **Role of respiratory infection in AD**

AD patients are highly susceptible to peripheral infections compared to healthy individuals of the same age. Different bacteria, virus, fungal infections are correlated to disease development, either by directly causing AD or through infiltration causing neuroinflammation [124, 125]. *Chlaymdia pneumonia*, intracellular gram negative bacteria has been widely reported to be associated with AD. It increases AD progression by five folds [126]. It has been reported that *C.pneumonia* crosses the blood brain barrier by infected monocytes or olfactory route and can infect astrocytes, microglia and neurons [127]. Further, it can inhibit neuronal apoptosis and facilitates persistence of chronic infection. Intranasal delivery of *C. pneumonia* in mice has shown to induce Aβ deposition in brain and its localisation in glia. *C. pneumonia* combines with factors like apolipoprotein E4 (APOE4) for the progression of AD [128]. It activates and stimulates the production of pro-inflammatory cytokines including TNF-β, IL-6, IL-1and IL-10 in the brain of AD patients [129-131]. Mahony [128]and co-workers studied the brain of AD patients via PCR screening technique and reported the correlation of AD with *C.pneumonia* [132]. Another study by Paradowski *et al*., performed ante-mortem screening of cerebrospinal fluid (CSF) of AD, which represents a positive correlation with *C.pneumonia* [133]. However, a little is known about the exact pathogenesis of *C.pneumonia* in AD. A well designed mice model may help to evaluate the colonisation of bacteria/ infection involved in AD.

1. **Conclusion**

Smoking is associated with early onset of AD, reducing the life expectancy by atleast 10 years resulting in significant morbidity. Prolonged exposure to cigarette smoke and nicotine is associated with OxS which corresponds to cerebral cellular damage. OxS elevates proteolytic pathways resulting in Aβ isoforms and τ phosphorylation. These exogenous sources of OxS facilitate the pathophysiology of AD. Further, the available evidences in human show that respiratory infections may be cause direct β amyloidogenesis and indirectly contribute to pathogenesis of AD via microglial and inflammatory response in the brain. However, further studies using appropriate animal model are essential to decipher the mechanism of cigarette smoke and respiratory infection related progression of AD which can direct for potential prevention and treatment strategies.

**Conflict of Interest**

The authors have no conflict of interest to declare.

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**List of abbreviations**

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| **Abbreviation** | **Full form** |
| Aβ | Amyloid β |
| AD | Alzheimer’s disease |
| DALYs | Disability-adjusted life years |
| NFTs | Neurofibrillary tangles |
| APOE4 | Apolipoprotein E-4 allele |
| APP | Amyloid precursor protein |
| PSEN1 | Presenilin 1 |
| PSEN2 | Presenilin 2 |
| TNF-α | Tumor necrosis factor alpha |
| HHV-1 | Human herpesvirus 1 |
| CMV | Cytomegalovirus |
| HHV-2 | Human herpesvirus 2 |
| HSV1 | Herpes simplex virus 1 |
| COPD | Chronic obstructive pulmonary disease  |
| SCLC | Small cell lung cancer |
| PNS | Paraneoplastic neurological syndrome |
| PCI | Prophylactic cranial irradiation |
| CHAT | Choline acetylcholine transferase |
| ACh | Acetylycholine |
| nAChRs | Nicotinic acetylcholine receptors |
| BACE1 | β-secretase 1 |
| TLR4 | Toll like receptors |
| IL | Interleukins |
| TNF-α | Tumor necrosis factor alpha |
| CDK5 | cyclin-dependent kinase 5 |
| ROS | reactive oxygen species |
| NMDA | N-methyl-D-aspartate |
| OxS | Oxidative stress |
| IFN | Interferons |
| PAH | Polycyclic aromatic hydrocarbons |
| CSF | Cerebrospinal fluid |
| τ | Tau |