Alzheimer's & Dementia 10 (2014) S122-S145

Smoking and increased Alzheimer's disease risk: A review of potential mechanisms☆

Timothy C. Durazzo[a,b,*], Niklas Mattsson[a,b,c], Michael W. Weiner[a,b,d,e,f], for the Alzheimer's Disease Neuroimaging Initiative

[a]*Center for Imaging of Neurodegenerative Diseases (CIND), San Francisco VA Medical Center, San Francisco, CA, USA*
[b]*Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, USA*
[c]*Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*
[d]*Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA*
[e]*Department of Medicine, University of California, San Francisco, San Francisco, CA, USA*
[f]*Department of Neurology, University of California, San Francisco, San Francisco, CA, USA*

Abstract

Background: Cigarette smoking has been linked with both increased and decreased risk for Alzheimer's disease (AD). This is relevant for the US military because the prevalence of smoking in the military is approximately 11% higher than in civilians.

Methods: A systematic review of published studies on the association between smoking and increased risk for AD and preclinical and human literature on the relationships between smoking, nicotine exposure, and AD-related neuropathology was conducted. Original data from comparisons of smoking and never-smoking cognitively normal elders on in vivo amyloid imaging are also presented.

Results: Overall, literature indicates that former/active smoking is related to a significantly increased risk for AD. Cigarette smoke/smoking is associated with AD neuropathology in preclinical models and humans. Smoking-related cerebral oxidative stress is a potential mechanism promoting AD pathology and increased risk for AD.

Conclusions: A reduction in the incidence of smoking will likely reduce the future prevalence of AD.

Keywords: Alzheimer's disease; Cigarette smoking; Tobacco; Risk; Amyloid; Tau; Military; Oxidative stress; U.S. Armed Services

Publication of this article was supported by the United States Army Medical Research and Materiel Command.

M.W.W. has served on the Scientific Advisory Boards for Pfizer, BOLT International, Neurotrope Bioscience, and Eli Lilly. He has provided consulting to Synarc, Pfizer, Janssen, KLJ Associates, Easton Associates, Harvard University, University of California, Los Angeles (UCLA), Alzheimer's Drug Discovery Foundation (ADDF), Avid Radiopharmaceuticals, Clearview Healthcare Partners, Perceptive Informatics, Smartfish AS, Decision Resources, Inc., Araclon, Merck, Defined Health, and Genentech. He served on the Editorial Boards for Alzheimer's & Dementia and MRI. He received honoraria from Pfizer Inc, Tohoku University, and Danone Trading, BV. He received research support from Merck, Avid, the Veterans Administration (VA) and Department of Defense (DOD). The other authors have no conflict of interest to report.

*Corresponding author. Tel.: 415-221-4810 x4157; Fax: 415-668-2864.
E-mail address: timothy.durazzo@ucsf.edu

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http://dx.doi.org/10.1016/j.jalz.2014.04.009

1. Background

1.1. Cigarette smoking prevalence, mortality, and morbidity

In this review, "smoking" refers to chronic smoking of tobacco in the form of cigarettes. Approximately 2 billion people worldwide use tobacco products, mostly in the form of cigarettes, with tobacco smoking–related diseases resulting in at least 4 million global deaths per year [1]. There are an estimated 44 million active smokers in the United States [2]; however, the actual prevalence of smoking in the United States may be underestimated, particularly in younger adults and females [3]. In the United States, smoking-related disease accounts for about one in every five deaths, which equates to more than 440,000 annual deaths, and smoking-related morbidity results in annual direct health-care expenditures and productivity loss of $193 billion [2,4]. The greatest smoking-related mortality is increasingly apparent among economically disadvantaged groups, which, in the United States, includes a disproportionate number of ethnic minorities [5,6]. Over the past 5 years, the prevalence of adult smokers in the United States has remained constant, and the ratio of former to never smokers (quit ratio) has not changed since 1998 [7]. In 2009, the US Food and Drug Administration (FDA) enacted the Family Smoking Prevention and Tobacco Control Act (TCA) to regulate the manufacture, distribution, and marketing of tobacco products to protect the public from smoking-related mortality and morbidity (Public Law 111-31; www.fda.gov/TobaccoControlAct). However, despite the implementation of the TCA, millions of Americans continue to smoke.

Smoking prevalence in active duty US Armed Services personnel is approximately 31% overall [8] and 35% in active duty personnel with high combat exposure [9], which are 11% and 15% higher, respectively, than in the general US population. Smoking among US military personnel is associated with lower productivity and levels of physical fitness, as well as increased risk for injury during training and impaired rate of wound healing (see Refs. [8,10,11] for review); consequently, smoking lowers combat readiness of our active duty personnel [11]. Smoking is among the strongest predictors of premature discharge from the military and is related to more than $130 million in annual excess training costs (see Refs. [10,11] for review). As of 2006, it was estimated that tobacco use costs military approximately $564 million per year from the associated adverse health consequences (e.g., lower productivity and levels of physical fitness) and treatment of tobacco-related diseases (see Refs. [8,11,12] for review).

Cardiovascular disease (CVD), chronic obstructive pulmonary diseases (COPD), and various forms of cancer are the leading causes of smoking-related mortality in the United States [13]. Sustained smoking cessation is associated with significantly decreased risk for these conditions [13], indicating that several adverse health consequences related to smoking are modifiable. It is now apparent that smoking-related morbidity extends beyond CVD, COPD, stroke, and cancer and includes neurobiological and neurocognitive abnormalities (e.g., hippocampal volume loss, learning and memory deficits) that are not solely attributable to the foregoing medical conditions, and some abnormalities show significant progression over time [14–17]. Importantly, some of these smoking-related neurobiological abnormalities may represent risk factors for Alzheimer's disease (AD) [18–21]. Correspondingly, there is now substantial epidemiologic evidence from meta-analyses and cohort-based studies that indicates smoking is associated with a significantly increased risk for AD neuropathology and associated dementia [22–24].

This review will focus on the epidemiologic evidence for smoking as a risk factor for late-onset/sporadic AD dementia, as well as provide a comprehensive review of the potential mechanisms by which smoking may promote increased AD risk. Original and novel data are presented from comparisons of cognitively normal elder smokers and nonsmokers on regional brain β-amyloid (Aβ) deposition, via florbetapir fluorine 18 (F-18) positron emission tomography (PET; see Section 7). A synopsis is provided following each major subsection or section, and an inclusive summary (Section 8) and conclusions (Section 9) are provided after the review of the literature and presentation of original data from our group.

2. Alzheimer's disease

AD is the most common cause of dementia, and late-onset AD (i.e., onset at ≥65 years of age) is the predominant form (>90% of AD cases) [25,26]. More than 35 million individuals worldwide are estimated to suffer from AD, and this number is projected to nearly double by 2030 because of increasing life expectancy [26]. In 2012, an estimated 5.2 million Americans older than 65 years (i.e., one in eight) had AD, resulting in approximately $200 billion in health care–related costs [25]. Recent research criteria recognize that AD is an insidious process, which begins with extended asymptomatic preclinical stages that may last for several decades before dementia symptomatology is exhibited [27]. As the AD-related neuropathologic abnormalities accumulate over time during the preclinical stages, there is a transition from normal neurobiological and neurocognitive function into mild cognitive impairment (MCI), which is most frequently typified by AD-like neuropathology and clinically significant memory deficits [28,29]. MCI patients are at high risk for conversion to AD, with 50% to 70% converting to dementia within 5 to 7 years after MCI onset [29]. The increasing incidence of AD has promoted extensive research into delineating the risk factors associated with the development and progression of this neurodegenerative disease [30]. Despite this major multidisciplinary research effort, the mechanisms associated with

the onset and progression of late-onset AD are not definitively established, and both preclinical and human clinical trials on AD pathology/progression–modifying medications have yielded disappointing results [27,31].

2.1. AD pathophysiology and neuropathology

Two of the hallmark neuropathologic findings in AD are extracellular amyloid and neuritic plaques and intracellular neurofibrillary tangles [32]. Amyloid plaques are primarily formed by aggregation of insoluble Aβ peptides, whereas neuritic plaques are composed of insoluble Aβ peptides, degenerated neurites (dendrites, axons, and/or telodendria), and some contain hyperphosphorylated tau proteins (p-tau) [32]. Neurofibrillary pathology (pretangles, neuropil threads, and neurofibrillary tangles) is primarily composed of intracellular p-tau protein aggregates [32,33]. Insoluble argyrophilic neuropil threads and neurofibrillary tangles develop in the dendrites and cell body, respectively [34]. Aging and *APOE* genotype (ε4 > ε3 > ε2) are independently associated with increased cerebral Aβ deposition [35–37] and may interact where Aβ deposition, beginning in the early 40's, is greater with increasing age in *APOE* ε4 carriers [38]. Aging is also related to cerebral p-tau accumulation and neurofibrillary tangle density [34,36,39].

The current predominant hypothesis (although not universally accepted; for review see Refs. [40–44]) for the development of AD indicates that pathologic Aβ metabolism is the primary event promoting plaque formation, followed by widespread cortical tau pathology, inflammation, synaptic degradation, and neuronal loss (see Refs. [32,40,45] for review). Brain amyloid deposition is indicated to be necessary, but not sufficient, to promote the clinical symptomatology demonstrated in MCI and AD [27]. The pivotal role of Aβ in the development and progression of AD is supported by the genetic link between hereditary/familial AD and mutations in either the gene encoding for the amyloid precursor protein (APP) or in the genes encoding for APP-processing enzymes (presenilin 1 and 2) [46]. Aβ deposition and plaque formation are indicated to begin as early as 20 years (i.e., during middle age) before the onset of AD symptoms [46–49]. Cerebral amyloid and neuritic plaque development follows a predictable pattern of progression, beginning with diffuse amyloid plaques in the inferior/basal temporal neocortex, spreading to the hippocampus and entorhinal cortex, and ultimately, widely distributed amyloid and neuritic plaques are present throughout the neocortex [34]. In AD, amyloid deposition is not exclusively relegated to brain parenchyma but can also be found, in variable levels, in leptomeningeal and intracortical arteries, arterioles, capillaries, venules, and veins [50,51]. Significant vascular amyloid deposition is referred to as cerebral amyloid angiopathy (CAA) [52] and is primarily composed of the $A\beta_{1\text{-}40}$ isoform [53]. Vasculature in the occipital lobe and cerebellum tends to show the greatest level of CAA [54].

The AD amyloidogenic process begins with the proteolysis of the transmembrane APP. If APP is cleaved by α-secretase, extracellular soluble APPα is produced and Aβ peptide formation is inhibited [55]. In contrast, Aβ peptides are created from the sequential cleavage of APP by β- and γ-secretases; β-secretase initially cleaves APP to yield extracellular soluble APP (sAPPβ) and an intracellular carboxyl terminal fragment (β-CTF), which is subsequently cleaved by γ-secretase, and produces Aβ peptides of different lengths [55,56]. $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ are major isoforms [57], and these may aggregate to produce dimers, trimers, oligomers, protofibrils, and insoluble fibrils (which are a fundamental Aβ component of amyloid and neuritic plaques) [58]. $A\beta_{1\text{-}42}$ is considered the greater pathologic isoform because of its strong association with atrophic neurites, reactive astrocytosis, and activated microglia [59]. The redox potential (i.e., ability to acquire electrons) of the primary Aβ species ($A\beta_{1\text{-}42} >> A\beta_{1\text{-}40}$) is consistent with their level of neurotoxicity, and redox-active transition metals (e.g., iron and copper) known to increase reactive oxygen species (ROS) free radical levels bind with high affinity to all Aβ isoforms [60]. It is also established that soluble and oligomeric intracellular Aβ and extracellular neuritic formation are associated with a chronic neuroinflammatory process marked by activated microglia and reactive astrocytes [61,62]. The insertion of $A\beta_{1\text{-}42}$ oligomers into the phospholipid bilayer serves as a source of oxidative stress (OxS) via increased concentrations of reactive oxygen and nitrogen species free radicals, which damage cell membranes and other micro- and macrocellular components, via lipid peroxidation [55]. However, it has also been proposed that some Aβ isoforms may serve as antioxidants, and Aβ production represents a compensatory response to mitigate preexisting chronic OxS (see Refs. [42,63,64] for review). The level of soluble Aβ oligomers, not amyloid or neuritic plaque load, shows a stronger association with cognitive decline and p-tau concentration, in animal models and humans (see Refs. [55,58] for review).

Neurofibrillary tangles show a different regional pattern of development and temporal appearance than Aβ deposition and neuritic plaque formation [36]. In AD, neurofibrillary tangles first appear in the brainstem and transentorhinal cortex, spreading to the entorhinal cortex and hippocampus, and finally showing diffuse distribution throughout the neocortex [34]. Specifically, neurofibrillary tangles localized in the locus coeruleus and entorhinal cortex are common in adults aged 30 to 40 years and precedes the appearance of significant amyloid deposition and neuritic plaques in these regions [39]. Widespread neurofibrillary tangles in neocortical regions are typically not prominent until high amyloid or neuritic plaques levels are present [32], and medial temporal lobe tangle formation is also independently related to age [65]. Currently, there is extensive debate regarding whether the development and progression of Aβ and tau protein pathologies in AD are interrelated or represent independent pathophysiological processes [34,66].

3. Risk factors for AD: Role of smoking

Although the mechanisms responsible for the inception and progression of late-onset AD are not established, increasing age and inheritance of the ε4 allele of the *APOE* gene are the strongest and most consistently replicated risk factors for the development of AD [25,67,68]. Specifically, the risk for AD doubles every 5 years between the ages of 60 to 90 years [68], AD risk for those with one copy of the *APOE* ε4 allele is increased by three to five times, and inheritance of two copies (i.e., *APOE* ε4 homozygotes) is associated with a 12-fold increased risk [69]. Aging and *APOE* genotype may interact with other potential genetic and/or modifiable environmental risk factors to increase AD-related pathophysiology and risk for AD [38,70–72]. CVD, cerebrovascular disease, moderate-to-severe traumatic brain injury (TBI), and race may also be risk factors for AD [25,73]. An increasing number of investigations have focused on the identification of risk factors for AD that are "modifiable," that is, conditions or behaviors that can be effectively treated/altered to reduce their prevalence during the asymptomatic preclinical stage [74], which will promote a significant decrease in the prevalence of AD [70]. However, there is considerable debate on the strength of the association between AD and potentially modifiable risk factors [67,70].

3.1. Modifiable risk factors for AD: Smoking

Cognitive engagement, diet/nutritional supplement intake, physical activity level, type 2 diabetes, alcohol consumption level, mood disorders, hypertension, hypercholesterolemia, and smoking have been proposed as modifiable risk factors for AD [67,70,75,76]. In 2011, a multidisciplinary panel convened by the National Institutes of Health reviewed the cohort studies and randomized controlled trials conducted from 1984 to 2009 on the foregoing potential risk factors and concluded "insufficient evidence exists to draw firm conclusions on the association of any modifiable risk factors with risk of AD." [67] However, for smoking, the panel's rigorous review criteria resulted the consideration of a very limited number of studies, and their conclusions were fundamentally based on a single meta-analysis [77] of 19 prospective cohort studies published up to 2005 and two cohort studies published in 2006 [78] and 2007 [79]. Although the panel's conclusions for many of these modifiable risk factors are likely applicable to the present day, there are substantial additional data that suggest smoking is a significant risk factor for AD. Specifically, a conclusive and authoritative meta-analysis conducted by Cataldo et al. [22] in 2010, on 43 international case-controlled and cohort studies published from 1984 to 2009, revealed that tobacco industry affiliation (e.g., study funding provided by the tobacco company, study author(s) currently/previously employed by tobacco industry) was robustly related to the direction and magnitude of smoking as a risk factor for AD. In case-controlled studies with a tobacco industry affiliation, smoking was associated with a significantly decreased risk for AD (odds ratio [OR] pooled, 0.86; 95% confidence interval [CI], 0.75–0.98), but studies with no tobacco industry affiliation showed no association between smoking and risk for AD. Cohort studies with a tobacco industry affiliation demonstrated a significantly decreased risk for AD (pooled OR, 0.60; 95% CI, 0.27–1.32), whereas those with no tobacco industry affiliation showed a significantly increased risk for AD (pooled OR, 1.45; 95% CI, 1.16–1.80). Some studies in this meta-analysis reported that the risk for development of AD was greater only in smokers who were not *APOE* ε4 carriers [80–83]. After concurrently controlling for study design, quality (based on the impact factor of the journal), secular trend, tobacco industry affiliation, and year of publication, Cataldo et al. indicated that active and former lifetime smoking was a significant risk factor for AD (relative risk, 1.72; 95% CI, 1.33–2.12). Although the year of publication was included as a covariate in their primary analyses, the authors acknowledge that this variable may be systematically related to studies reporting a reduction in AD risk for smokers because all the industry-affiliated/sponsored reviews were published in 1994 or earlier; this may also be attributable to the fact that the tobacco industry ceased funding support for reviews on smoking-related risk for AD after 1994.

In the nontobacco industry–affiliated cohort studies reviewed by Cataldo et al., there were generally consistent findings for smoking exposure variables (i.e., pack-years, a measure of cigarette smoking dose and duration) for AD risk, but mixed results were apparent for former smoking status as a risk factor for AD. With respect to exposure, Ott et al. [80] reported that the risk for AD was significantly increased for active smokers with <20 pack-years (OR, 2.5; 95% CI, 1.1–5.5) and for those with >20 pack-years (OR, 3.0; 95% CI, 1.2–5.4); a corresponding increased risk for AD was observed in former smokers with <20 pack-years (OR, 1.5; 95% CI, 1.0–2.5) and >20 pack-years (OR, 2.1; 95% CI, 1.2–3.7). In a combined group of active and former smokers, Tyas et al. [84] found that smokers with 27 to 41 pack-years (OR, 2.55; 95% CI, 1.22–5.58) and 41 to 56 pack-years (OR, 2.92; 95% CI, 1.37–6.53) had a significantly greater risk for AD compared with those with <27 pack-years; however, those with >56 pack-years showed no statistically significant increased risk for AD (OR, 1.37; 95% CI, 0.53–3.44), which was attributed to a strong survivor bias. Juan et al. [85] in an independent cohort, applied the same pack-year groupings as Tyas et al. and obtained highly similar results. Reitz et al. [79] reported that active smokers with >20 pack-years had a significantly increased risk for AD than active smokers with <20 pack-years (hazard ratio, 1.82; 95% CI, 1.26–2.57). Regarding former smoking status, Launer et al. [86] observed an increased risk for AD in male (relative risk, 1.97; 95% CI, 0.92–4.22) but not in female (relative risk, 1.08; 95% CI, 0.73–1.61) former smokers. Merchant et al. [81] and Reitz et al. [79] reported

that former smokers' risk for AD was not statistically different from never smokers, whereas in Aggarwal et al. [78], former smokers, who were *APOE* ε4 carriers had a significantly lower risk for AD relative to never smokers (OR, 0.27; 95% CI, 0.08–0.93). Notably, greater pack-years were associated with increased mortality in controls and AD [84], and the onset of AD occurred at a significantly younger age in former [80] and active smokers [80,81,87] compared with never smokers.

Subsequent to the meta-analysis by Cataldo et al., a large Finnish cohort study [23] reported that individuals who smoked during midlife and were *APOE* ε4 carriers demonstrated a markedly increased risk for AD (OR, 6.56; 95% CI, 1.80–23.94) [23]. Additionally, a large US cohort study found individuals who smoked >2 packs/day had a significantly increased risk for AD (hazard ratio, 2.57; 95% CI, 1.63–4.03) [24]. Finally, Barnes and Yaffe [70] estimated the influence of the prevalence of several modifiable AD risk factors on AD prevalence. Smoking was projected to account for 574,000 (11%) of AD cases in the United States and 4.7 million (14%) cases worldwide. A 10% reduction in the total number of smokers in the United States and worldwide was projected to decrease the prevalence of AD cases by 51,000 and 412,000, respectively.

For all the aforementioned case-controlled and cohort studies, there was considerable variability in the sample sizes, the duration that participants were followed (for cohort studies), and the covariates (e.g., *APOE* genotype, alcohol consumption, sex, biomedical risk factors) measured and/or controlled for in statistical analyses. Survivor bias has been indicated to promote an underestimation of the smoking-related risk for AD in both case-controlled and cohort studies [88–92]. Specifically, elders who die prematurely from smoking-related diseases are a major source of attrition; this reduces the proportion of smokers who may have ultimately developed AD, creates attrition in cohort studies, and those smokers who do survive are biased toward healthier individuals [92]. The findings regarding the former smoking status as an AD risk factor must be interpreted with caution because some studies were not consistent or explicit about the level of cigarette consumption or duration of smoking cessation [93]. Additionally, the association of other forms of tobacco consumption (e.g., pipe, cigars, cigarillos, smokeless tobacco) and risk for AD was not specifically considered in previous case-controlled and cohort studies.

3.2. Synopsis

The cumulative body of data from international cohort studies, with no affiliation to the tobacco industry, indicate that smoking during lifetime is associated with at least a 1.7 times (70%) greater risk for AD, and the risk markedly increases with greater cumulative cigarette exposure. The relationship between smoking status, exposure, and AD risk may be mediated or moderated by *APOE* genotype. The magnitude of risk for AD associated with smoking is likely to be underestimated in both case-controlled and cohort studies because of attrition/survivor bias resulting from smoking-related mortality and morbidity. Smoking is associated with earlier onset of AD and estimated to account for 4.7 million AD cases worldwide.

4. Neurocognitive and neurobiological consequences of smoking

The vast majority of research investigating the effects of smoking on the human body has focused on the cardiac, pulmonary functions, and vascular systems, as well as on its carcinogenic properties, primarily in the elderly (i.e., >65 years of age) [94–97]. However, outside of cerebrovascular risk factors for stroke, comparatively little research has been devoted to effects of chronic smoking on the brain and its functions, particularly in young/middle-aged adults (i.e., 25–65 years of age) [14,16]. Over the past 12 years, there has been an emergence of studies specifically focusing on the neurocognitive and neurobiological effects of smoking in multiple populations. The findings from these studies suggest that smoking is associated with adverse effects on brain neurobiology and function in those without a history of clinically significant psychiatric and biomedical conditions, with a history of a neuropsychiatric disorder (e.g., schizophrenia, alcohol/substance use disorder), and with a history of mild TBI. Smoking is highly prevalent in these populations in both civilians and US veterans and active duty military personnel [9,98]. The findings for smokers in the above populations are highly relevant because the pattern of neurobiological and neurocognitive abnormalities observed (see the following) are congruent with many of the neuropathologic and neurocognitive abnormalities that characterize the recently proposed "preclinical" stages of AD [27,49], as well as MCI [99–101]. See the studies by Sharma and Brody [15] and Azizian et al. [16] for comprehensive reviews on the effects of smoking on neurobiology and neurocognition in other neuropsychiatric conditions (e.g., schizophrenia).

4.1. Smoking in "healthy" nonclinical cohorts

Smoking in adolescents to young adults (i.e., 17–21 years of age), young to middle-aged adults (i.e., 25–60 years of age), and elders (≥65 years of age) without a history of clinically significant biomedical or psychiatric conditions is associated with significant neurocognitive and/or neurobiological abnormalities.

Adolescent to young adult active smokers showed inferior performance relative to never smokers on measures of attention, learning and memory, processing speed, and impulse control (see Ref. [14] for review).

Young to middle-aged adult active smokers, compared with never smokers, showed poorer performance on multiple neurocognitive domains, predominantly on measures of

executive functions, processing speed, and learning and memory [14,102,103]. Young to middle-aged active smokers also demonstrated abnormalities in regional cortical, hippocampal, and subcortical morphology (volumes and cortical thickness) [16,19,104–108]; biochemistry (markers of neuronal integrity and cell membrane turnover/synthesis) [109,110]; white matter (WM) microstructural integrity [111]; and cortical perfusion [15]. In these studies, the neurobiological abnormalities were predominant in anterior brain regions (e.g., orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, insula), which are cortical components of the brain reward/executive oversight system that is involved in the development and persistence of all addictive disorders [18,112]. The neurobiological abnormalities demonstrated by young to middle-aged adults were also apparent in regions that show significant atrophy (e.g., hippocampus, posterior cingulate, precuneus) and/or glucose metabolism deficits in MCI and/or early stage AD [113,114]. In several studies, pack-years were related to the level of neurobiological [104–107] or neurocognitive [14,103] abnormalities observed.

In the elders, active smokers, relative to never smokers, demonstrated poorer performance in cross-sectional studies, and a greater rate of decline in longitudinal studies in the domains of executive functions, processing speed, and learning and memory (see Ref. [14] for review). Early longitudinal computer tomography studies of elders reported that active smokers showed a greater rate of global brain atrophy relative to never smokers [14]. More recent magnetic resonance imaging (MRI) studies with elder cohorts reported that active smokers showed lower gray matter (GM) density in posterior cingulate gyrus and precuneus bilaterally, right thalamus, and right precentral gyrus [21], and those with any history of smoking demonstrated a greater rate of atrophy over 2 years in anterior frontal, temporal, posterior cingulate, and posterior parietal regions. Primarily in elders, former smokers demonstrated neurocognitive and neurobiological abnormalities that were intermediate to active and never smokers [14].

4.2. Smoking in alcohol use disorders

Smoking is the most prevalent comorbid condition in those with an alcohol use disorder (AUD) [98]. For the past 10 years, we have applied multimodality magnetic resonance neuroimaging methods and comprehensive neurocognitive assessment to investigate the effects of smoking and hazardous alcohol consumption on the brain and its functions in young to elderly adults (25–69 years of age) seeking treatment for AUDs (trsAUD). Most of our trsAUD participants are US Armed Services veterans. At 1 to 4 weeks of abstinence from alcohol, smoking trsAUD consistently demonstrated significantly greater abnormalities than nonsmoking trsAUD on magnetic resonance–derived measures of brain structure, neuronal integrity, and perfusion, primarily in the frontal and temporal lobes (including the hippocampus), as well as poorer performance on measures of learning and memory, cognitive efficiency, executive functions, processing speed, and fine motor skills [112,115–120]. Smoking trsAUD also showed significantly less recovery than nonsmoking trsAUD in brain metabolite markers of neuronal integrity and cell membrane turnover/synthesis in the frontal and medial temporal lobes, frontal GM perfusion and microstructural integrity in the frontal, temporal, and parietal WM, as well as in neurocognition, over 1 month of abstinence [121–123], and multiple domains of neurocognition over 1 month [124] and 9 to 12 months of abstinence [125]. Recently, we also observed that smoking trsAUD relative to nonsmoking trsAUD had thinner cortex and lower N-acetylaspartate levels (marker of neuronal integrity), in anterior frontal and temporal regions at entry into treatment [126]. Recent analyses also indicated that smoking trsAUD showed greater age-related volume loss than nonsmoking trsAUD in the anterior frontal regions and the insula, as well as poorer performance with increasing age on measures of learning and memory, cognitive efficiency, executive functions, processing speed, and fine motor skills at 1 month of abstinence [105,127]. In several of our studies, greater smoking exposure (i.e., lifetime years of smoking or pack-years) was related to greater neurobiological and/or neurocognitive abnormalities in cross-sectional studies or poorer recovery in longitudinal studies [105,115–117,122,125,127,128]. The level of nicotine dependence in these studies showed weak or no association with neurobiological and neurocognitive measures.

4.3. Smoking in mild TBI

In those with a mild TBI, we observed that active smokers demonstrated significantly poorer recovery than never smokers over 6 months post injury on measures of processing speed, visuospatial learning and memory, visuospatial skills, and global neurocognition. Similar to AUD cohorts, greater smoking exposure (i.e., lifetime years of smoking or pack-years) was robustly related to less improvement on measures of visuospatial learning, visuospatial memory, working memory, visuospatial skills, and global cognition [129].

4.4. Synopsis

Smoking in nonclinical and clinical populations is strongly related to multiple neurocognitive and neurobiological abnormalities. Many of the neurocognitive (e.g., learning and memory, executive function, processing speed deficits) and neurobiological (e.g., hippocampal and lateral temporal volume loss, regional cortical thinning, and decreased markers of neuronal integrity) abnormalities demonstrated by nonclinical smokers and smokers with AUD are pathognomonic markers of preclinical stages of AD and MCI. The progressive regional atrophy and

neurocognitive decline observed in elder smokers also represent as risk factors for the transition from MCI to AD [18,20,29,30]. The neurobiological and neurocognitive abnormalities observed in late adolescents through middle-aged adult smokers are highly relevant for the US Armed Services, given that most of active duty personnel are between the ages of 18 and 50 years, and the higher prevalence of smoking compared to civilians in the corresponding age range [9]. The neurobiological and neurocognitive sequelae associated with mild TBI and AUD/hazardous alcohol consumption may be exacerbated by smoking, and impaired recovery from these conditions is associated with smoking. These findings are of considerable import to all branches of the military because personnel engaged in combat operations are at a significantly increased risk for mild TBI and AUD/hazardous alcohol consumption [130,131].

A primary pathophysiological mechanism that is hypothesized to contribute to the neurobiological and neurocognitive abnormalities observed in smokers is cerebral OxS [14,17]. Correspondingly, OxS may serve as a factor promoting the greater risk for AD observed in smokers, which is addressed in the following section.

5. Smoking-related neuropathology: The role of OxS

5.1. Oxidative stress

OxS is indicated by the detection of damage to brain and other organ system tissues that is caused by ROS, or more broadly by damage from ROS, reactive nitrogen species (RNS), and other oxidizing agents [60,63,132]. Increased levels of free radical species (i.e., ROS and RNS) and oxidants result from an imbalance between the generation of these compounds via endogenous (i.e., normal cell metabolism) and/or exogenous sources (e.g., smoking) and their chemical reduction by antioxidants/radical scavengers [60,133,134]. Irrespective of the source, increased free radical concentrations are directly associated with oxidative damage to membrane lipids, proteins, carbohydrates, DNA, and RNA of neuronal, glial, and vascular brain tissue [133,135–141].

Cytokines, which include chemokines, interferons (IFNs), interleukins (ILs), growth factors, and tissue necrosis factors (TNFs), are a major component of a highly complex system that controls immune and inflammatory responses in the peripheral nervous system and central nervous system (CNS) [142]. Oxidative damage from free radical or other oxidants may trigger inflammation via a cytokine-mediated immune response [143] that involves release of anti-inflammatory and proinflammatory cytokines (e.g., TNFα, IL-1, IL-6) by peripheral and CNS cells (e.g., microglia and astrocytes) [142]. Elevated proinflammatory cytokine levels are associated with cerebral OxS and apoptosis through generation of ROS and other inflammatory mediators in the brain (and peripheral organ systems) by immune cells, microglia, and astrocytes [142,144,145]. Therefore, OxS and inflammation often occur in tandem in many diseases/disorders, including AD, smoking, substance use disorders, and AUDs [14,55,62,146–149].

The brain is highly susceptible to OxS caused by free radicals and other oxidizing agents because of its high metabolism and energy demand and vulnerability of membrane phospholipids to peroxidation by radical species [150–154]. The anterior frontal lobe, medial and lateral temporal lobe [155,156], and hippocampus are particularly vulnerable to OxS-mediated cellular damage [60]. See Refs. [143,148,157,158] for details on OxS-mediated cell damage, apoptosis, and neurodegeneration. Smoking-induced OxS, via increased ROS and RNS levels, is also robustly related to an increased risk for atherosclerosis, chronic obstructive pulmonary disease, and carcinogenesis in humans [132,133,141,159–163].

5.2. Cigarette smoke/combustion products, nicotine, and OxS

Cigarette smoke is a complex admixture of approximately 5000 combustion products (including nicotine), which contain a high number of cytotoxic and carcinogenic compounds [164]. The gas and particulate phases of cigarette smoke have extremely high concentrations of short- and long-lived ROS, RNS, and other oxidizing agents [94,133]. In addition to increased free radical concentrations, smoking is associated with markedly elevated carboxyhemoglobin levels [165], altered mitochondrial respiratory chain function [166], and induction of proinflammatory cytokine release by peripheral and CNS glial cells [167], which collectively promote significant cerebral OxS.

5.2.1. In vitro and animal studies

Giunta et al. [168] demonstrated that in vitro exposure of microglia (BV-2) to cigarette smoke condensate promoted significantly increased release of TNF-α and IL-1B proinflammatory cytokines. Barr et al. [169] reported that nicotine administration to rat mesencephalic cells inducted high ROS levels and activated nuclear factor kappa B (NF-*K*B) (involved in inflammation, innate immunity, development, apoptosis, and antiapoptosis). In a series of studies by Anbarasi et al., rats were exposed to daily cigarette smoke for 12 weeks. Homogenized brain tissue showed consistent evidence of OxS (i.e., lipid peroxidation [170], increased creatine kinase [171], and increased apoptotic markers [172]), as well as OxS and dysfunction specifically in mitochondria (i.e., lipid peroxidation, diminished oxidative phosphorylation) [173]. Rueff-Barroso et al. [174] reported that mice exposed to daily cigarette smoke for 15 weeks demonstrated significant OxS in homogenized whole brain tissue as indicated by an elevated malondialdehyde level, a marker of lipid peroxidation. Ho et al. [175] found that rats exposed to daily cigarette smoke for approximately 8 weeks showed significantly increased levels of 8-hydroxyguanine, a marker of

oxidative damage to RNA and DNA nucleosides, in the dentate and CA3 subfields of the hippocampus [175]. Khanna et al. [147] reported that rats exposed to cigarette smoke 5 d/wk for 6 weeks exhibited significantly increased brain IFN-γ and TNF-α proinflammatory cytokine levels, as well as upregulation of the expression of multiple cytokine genes (e.g., TNF-α, IL1-α, IL1-β, Th17). Das et al. [176] observed that rats treated with intraperitoneal nicotine for 7 days showed significant lipid peroxidation and protein oxidation in mitochondria from cortical, diencephalic, and cerebellar tissue.

5.2.2. Human studies

Sonnen et al. [177] conducted postmortem comparisons of human smokers and never smokers (87 ± 6 years of age) without significant AD or microvascular pathology. Active smokers showed significantly higher cortical F_4-neuroprostanes, a measure of neuronal free radical–mediated lipid peroxidation, but groups were not different on measures of cerebellar lipid peroxidation. Additionally, numerous human studies have shown elevated markers of OxS (e.g., F_2-isoprostanes, hydroxycholesterols, C-reactive protein) in the serum or plasma of smokers [132,178–184].

5.3. Cigarette smoke/combustion products and antioxidant depletion

The combined activity of enzyme-based (e.g., superoxide dismutase, catalase, glutathione reductase) and non–enzyme-based (e.g., glutathione and vitamins A, C, and E) antioxidants and radical scavengers is responsible for managing the levels of free radicals and other oxidants in the brain [151,185]. Acute exposure to radical species and oxidizing agents promotes an adaptive increase in the production of enzyme-based antioxidants to mitigate oxidative damage [151]. Deficiencies in the production and/or maintenance of optimal levels of these antioxidant compounds can result in significantly increased radical and oxidant concentrations (via endogenous and/or exogenous sources), which promote OxS [151,157,158,186,187]. Glutathione is the dominant antioxidant in the human brain with regional concentrations from 0.8 to 5.0 mM [188–190], and oxidized forms represent <1% of the total glutathione level [191]. Glutathione is critically involved in the chemical reduction of ROS and hydrogen peroxide and in maintenance of other antioxidants (e.g., vitamins A, C, and E) in their chemically reduced functional forms [135,153,191–193]. Decreased central and peripheral glutathione concentrations is a longstanding and accepted proxy for OxS [134,153,186,187,193–195].

5.3.1. Animal studies

In vivo chronic cigarette smoke exposure to rats was associated with significantly decreased enzyme-based free radical and non–enzyme-based radical scavenger concentrations in brain homogenates [151,196]. Chronic cigarette smoke exposure was specifically associated with a significantly decreased glutathione level in rodent brains [151,170,197]. Das et al. [176] reported that intraperitoneal nicotine administration over 7 days in rats, along with OxS (see Section 5.2.1), significantly decreased multiple enzyme-based radical scavenger levels in brain mitochondria.

5.3.2. Human studies

In humans, smoking was related to significantly reduced glutathione level in plasma/serum across race and sex [64,135,178,179,181,197–199], as well as decreased serum superoxide dismutase and vitamin C [178,179]. Smoking was also shown to directly decrease glutathione production via alterations of its synthetic pathway [135,181], and dietary differences did not account for reduced glutathione levels [178,198]. The decreased glutathione and other antioxidant concentrations in smokers are postulated to result from the amplified demand to detoxify (i.e., chemically reduce) the chronically high ROS and RNS levels delivered in cigarette smoke [151,178,198,200].

5.4. OxS, amyloidogenic pathway, and tau phosphorylation

Aβ isoforms are indicated to promote OxS in brain tissue and AD-related disease progression (see Section 2.1) [55]. However, cerebral OxS has also been hypothesized to be involved in the initiation of AD pathophysiological process, rather than strictly emerging as a physiological consequence of existing amyloid- or tau-based neuropathology [63,201–203]. More specifically, in vitro studies of various brain cell types reported that OxS induced by exogenous agents (e.g., hydrogen peroxide) is associated with increased β-secretase cleavage of APP, under mild and toxic OxS conditions, and amplified OxS does not increase β-secretase levels in cells lacking presenilins or APP [204,205]. Additionally, in vitro and in vivo preclinical models have demonstrated that OxS promotes abnormal tau phosphorylation in the brain (see Refs. [42,149,203] for review). Therefore, smoking-related OxS may serve as a fundamental mechanism contributing to the neurobiological abnormalities (e.g., brain atrophy, regional cortical thinning) observed in smokers in clinical and nonclinical cohorts [14,17], as well as for an increased risk for development of Aβ and tau pathology [63,79,84,168,175,206,207].

5.5. Synopsis

The in vitro and animal studies and literature clearly demonstrate a causal relationship between in vivo chronic cigarette smoke/condensate and nicotine exposure and cerebral OxS; cigarette smoke/condensate, nicotine, and increased proinflammatory cytokines (via activation of immune cells, microglia, and astrocytes) promote high concentrations of ROS, RNS, and other oxidants. Animal models

also showed that cigarette smoke and nicotine exposure were causally linked to significant cerebral antioxidant depletion. The factors promoting cerebral OxS and antioxidant depletion in animal models are hypothesized to be operational, in vivo, in the human brain [132,151,168,177], and evidence of free radical–mediated damage was demonstrated postmortem in the human brain [177]. Taken together, existing literature indicates that smoking and pure nicotine (1) promotes high concentrations of ROS, RNS, and other oxidizing compounds; (2) upregulates activity and release of proinflammatory cytokines in the brain, which promotes immune system–mediated discharge of additional free radicals and oxidizing compounds; and (3) depletes enzyme- and non–enzyme-based antioxidants secondary to increased demand for the chemical reduction of high radical concentrations (from cigarette smoke and proinflammatory cytokine signaling) and inhibits the production of glutathione, the primary antioxidant in the human brain. The combination of these conditions serves to place the brain and other organ systems of smokers under a state of chronic OxS. Importantly, OxS is associated with increased β-secretase cleavage of APP as well as tau phosphorylation; therefore, smoking-related OxS may serve as a fundamental mechanism initiating the AD pathophysiological process.

6. Smoking and nicotine: Relationships to AD pathophysiology

As summarized in Section 5, cerebral OxS has been implicated in the initiation of AD neuropathology, rather than strictly developing as a physiological consequence of existing and/or progressing amyloid- or tau-based pathophysiology [42,63,201,202]. Smoking is strongly associated with cerebral OxS (see Section 5), and OxS promotes increased β-secretase cleavage of APP and abnormal tau phosphorylation. Thus, smoking-related OxS may directly facilitate the amyloidogenic pathway involved in Aβ oligomer production and extracellular fibrillar Aβ aggregation [168], as well as abnormal tau phosphorylation, which is the basis of neurofibrillary tangle pathology.

Nicotine is a main constituent of the particulate phase of cigarette smoke and is principally responsible for promoting physiological dependence on all forms of tobacco [208]. Nicotine consumption has been suggested to be protective against AD neuropathology via activation of nicotinic acetylcholine receptors (nAChRs) [209,210]. Both smoking and pure nicotine significantly upregulate the number of inotropic α4β2 and α7 nAChR subtypes, but the sensitivity of these receptors is diminished [211,212]. Nicotine binding at nAChRs influences neurotransmitter release, signal transduction, gene transcription, and cell survival, apoptosis, and plasticity; α7 nAChRs appear to be centrally involved in survival, apoptotic, and plastic mechanisms [212,213]. A significant loss of neurons and/or synapses expressing nAChRs is apparent in early AD, and Aβ aggregation is frequently pronounced at nAChRs [214]. In this section, we first review the link between smoking/cigarette smoke exposure and AD pathophysiology; we then review the data on the relationship between pure nicotine exposure and AD pathophysiology.

6.1. Smoking, smoke exposure, and AD pathophysiology

6.1.1. In vitro and animal studies

In vitro studies by Giunta et al. [168] showed that cigarette smoke condensate (i.e., the particulate component of tobacco smoke) increased $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ levels in a concentration-dependent manner in cells transfected with human APP (SweAPP N2a cells). In addition to elevated markers of OxS (see Section 5.2.1) in cigarette smoke–exposed rats, Ho et al. [175] reported that these rats concurrently demonstrated significantly increased β-sAPP, but not α-sAPP, levels in homogenized hippocampal tissue and markedly increased Aβ accumulation in the CA3 and dentate subfields of the hippocampus. The smoke-exposed rats also showed significantly increased hippocampal p-tau but not total tau levels. Moreno-Gonzalez et al. [207] exposed 3-month-old APP/presenilin 1(PS1) transgenic mice to high- (one cigarette over 60 minutes) or low-dosage (half of a cigarette over 30 minutes) cigarette smoke 5 d/wk for 4 months. The high-dosage group showed levels of cotinine, the primary metabolite of nicotine, that were physiologically consistent with human smokers. Both high- and low-dosage groups begin to develop neuritic plaques at 5 to 6 months of age. The high-dosage group demonstrated a significantly greater number of Aβ deposits and fibrillar neuritic plaques, increased density of activated microglia and reactive astrocytes, and positive p-tau staining in the majority of the cerebral cortex and hippocampus relative to the low-dosage group and controls.

6.1.2. Postmortem human studies

In a large human autopsy sample, Tyas et al. [84] observed across elder dementia and nondementia groups that active and former smokers demonstrated significantly higher neuritic plaque burden in the cerebral cortex and hippocampus than never smokers, but no differences were apparent between groups on cortical or hippocampal neurofibrillary tangle count. Furthermore, the risk for Consortium to Establish a Registry for Alzheimer's Disease neuropathologically defined AD was more than double for active (OR, 2.64; 95% CI, 0.54–12.88) and former (OR, 2.62; 95% CI, 0.80–11.57) smokers relative to never smokers. Conversely, in a hospital-based autopsy sample, Ulrich et al. [215] observed that female never/former smokers, relative to active smokers, had a lower average density of neuritic plaques in a composite of the hippocampus, entorhinal cortex, and neocortex, but showed a trend for a higher density of neurofibrillary tangles. There were no differences between male smokers and nonsmokers in plaque or neurofibrillary

tangle density. In smokers for both sexes, higher pack-years were significantly correlated with greater neurofibrillary tangle density but not with neuritic plaque density. Sabbagh et al. [87] found no differences in neuritic plaques or neurofibrillary tangle density in the midfrontal cortex (the only region examined) between never, former, and active smokers with AD. Hellstrom-Lindahl et al. [209] observed that soluble and insoluble $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ levels were significantly lower in homogenates of the frontal and temporal cortex, but not the hippocampus, in cognitively normal active smokers compared with never smokers. In the same study, active smoker AD cases had lower insoluble and soluble $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ in the frontal cortex than never smoker AD, but in the temporal cortex and hippocampus, only insoluble and soluble $A\beta_{1\text{-}40}$ levels were significantly lower in active smoker AD. Perry et al. [216] reported that nondemented elders who had smoked within 10 years of (smokers) death had a lower mean neuritic plaque level in the hippocampus, entorhinal cortex, and neocortex than those who had quit smoking more than 10 years before death (nonsmokers); a never smoker group was not available for comparison. No group differences were observed for neurofibrillary tangles in any region, and *APOE* genotype did not mediate the finding for neuritic plaque or neurofibrillary tangle burden in group comparisons on smoking status; however, irrespective of the smoking status, *APOE* ε4 carriers had lower mean neocortical neuritic plaque density than noncarriers, which appeared to be driven by the low density in the small number of smoker *APOE* ε4 carriers (n = 4). In a subsequent study by the same laboratory, Court et al. [217] found that nondemented elders who smoked most of their lives/smoked within 15 years of death showed lower entorhinal cortex levels of total and diffuse Aβ deposits and insoluble $A\beta_{1\text{-}42}$ relative to elders who never smoked/quit smoking at least 25 years before death Higher pack-years were related to lower entorhinal cortex soluble $A\beta_{1\text{-}42}$ level Groups did not differ on p-tau density.

6.1.3. Synopsis

The in vitro and animal studies showed cigarette smoke condensate and cigarette smoke exposure consistently facilitated the amyloidogenic pathway, as well as causally increased tau hyperphosphorylation. Specifically, chronic cigarette smoke exposure in normal and AD model transgenic animals was causally related to significantly increased sAPPβ level, Aβ deposition, and neuritic plaque burden, as well as increased p-tau levels in the cerebral cortex and hippocampus. Cigarette smoke condensate exposure to cells transfected with human APP produced increased $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ levels in a concentration-dependent manner. Markers of increased OxS were concurrently observed in several of studies demonstrating amyloidogenic pathway facilitation and tau accumulation. In contrast, human autopsy studies yielded mixed findings regarding the association between smoking and AD neuropathology. The interpretation of these human studies is obfuscated by inconsistencies in the assignment of smoking status (e.g., never smokers and former smokers with variable lengths of smoking cessation combined into a single group), small sample sizes in some studies, inconsistent consideration of potential sex effects, and survivor bias. In the large-sample study [84] with clear assignment of never/former/active smokers, significantly greater brain Aβ-related neuropathology was observed in active and former smokers compared with never smokers. Conversely, in small sample–sized studies comparing groups of nonsmokers (e.g., combined never and long-term abstinent former smoker) and smokers (combined active or smoked within 15 years of death), smokers showed significantly lower levels of Aβ-related neuropathology. One of the studies [216] reporting smokers showed lower neuritic plaque density reported that irrespective of the smoking status, *APOE* ε4 carriers had lower mean neocortical neuritic plaque density than noncarriers, which is contrary to typically observed effect of *APOE* ε4 genotype on plaque density in humans [68]. Despite the methodological limitations and inconsistent results across the human postmortem studies, these findings, combined with the animal and in vitro data suggest (1) at a minimum, smoking is not protective of AD-related pathophysiological processes, and smoking may facilitate the development of regional Aβ and tau pathology and (2) increased OxS is a robust candidate mechanism contributing to the initiation of the AD pathophysiological process in smokers.

6.2. Nicotine, nAChR agonists and antagonists, and AD pathophysiology

6.2.1. In vitro and animal studies

Hellstrom-Lindahl et al. [218] reported that nicotine or epibatidine (a nonselective nAChR agonist) treatment of the human neuroblastoma cells (SH-SY5Y) caused increased levels of p-tau and total tau. Additionally, nicotine, epibatidine, or $A\beta_{1\text{-}42}$ (as a ligand for nAChRs) administration induced tau phosphorylation in neuroblastoma cells (SK-N-MC) and in hippocampal synaptosomes. In rats, subcutaneous nicotine administration over 2 weeks decreased soluble APP peptides [219,220] but increased levels of total sAPP in the cerebrospinal fluid (CSF) [220]. Over 6 weeks, rats administered intraventricular $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ with concurrent subcutaneous nicotine showed lower levels of $A\beta_{1\text{-}40}$ and β-secretase in the hippocampal CA1 subfield, better memory, and greater hippocampal long-term potentiation compared with rats administered $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ alone [221]. In transgenic mice (expressing Swedish human APP), those administered nicotine in drinking water showed a significant reduction of neuritic plaques and insoluble $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ levels, but no changes in soluble $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ levels, in the cerebral cortex, compared with sucrose-treated mice [210]. Transgenic mice (expressing human Aβ precursor protein and PS1 genes) that were administered cotinine, the

primary metabolite of nicotine, via oral gavage for 3.5 months, showed lower insoluble $A\beta_{1-42}$ in the cortex and $A\beta_{1-40}$ in the hippocampus than control transgenic mice; no differences between treated and control animals were observed for soluble $A\beta_{1-42}$ and $A\beta_{1-40}$ levels in the cortex or hippocampus; decreased $A\beta_{1-42}$ oligomerization was also observed in vitro [222]. Conversely, a study using transgenic mice (3xTg-AD; expressing combination of Swedish human APP and tau_{P30IL}) that were administered nicotine in drinking water for 5 months showed no increase in soluble or insoluble $A\beta_{1-42}$ and $A\beta_{1-40}$ levels in the hippocampus compared with control transgenic mice; however, the nicotine-treated mice exhibited a significant increase of hippocampal tau phosphorylation and aggregation; the increased hippocampal tau aggregation and phosphorylation were related to an age-dependent decreased density of α7 nAChRs in both the nicotine-treated and untreated mice [223]. Additionally, in vitro exposure of mature mouse brain mitochondria to nicotine produced no increase in free radical concentration or corresponding evidence of lipid peroxidation [224].

6.2.2. Postmortem human study

In a human autopsy study, the effect of several nAChRs agonists (but not nicotine) and antagonists on ^{11}C Pittsburgh compound B binding (PiB; shows high affinity binding to fibrillar Aβ [225]) was evaluated in frontal lobe homogenates of elder controls and AD. The smoking status of AD and control cases was not provided. The α7 nAChR agonists varenicline and JN403, but not the α4β2 nAChR agonist cytisine, increased PiB binding in both AD and controls. This effect was abolished by the α7 nAChR antagonists α-bungarotoxin, mecamylamine, and methyllycaconitine, but not by the α4β2 antagonist dihydro-β-erythroidine. Increased PIB binding promoted by varenicline and JN403 was significantly inhibited by preincubation with the amyloid ligand, BF-227. The acetylcholinesterase inhibitor and allosteric nAChR modulator galantamine and the N-methyl-D-aspartate receptor blocker memantine did not significantly influence PiB-binding levels in AD cases [226].

6.2.3. Synopsis

The rodent studies on the effect of chronic nicotine administration on Aβ isoform concentrations and deposition yielded inconsistent results; nicotine administration in transgenic and nontransgenic animals produced significant reductions of neuritic plaques and insoluble $A\beta_{1-40}$ and $A\beta_{1-42}$ levels in brain tissue, or nicotine caused no increase in soluble or insoluble $A\beta_{1-42}$ and $A\beta_{1-40}$ levels. Regardless of the use of different species and genetic modifications, variable routes of nicotine administration, and different assay and quantitation methods in rodent studies, nicotine did not alter soluble $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations in the cortex or hippocampus. This finding is relevant to humans because soluble Aβ oligomer levels, but not fibrillar Aβ-containing compounds, show consistent associations with cognitive decline and tau hyperphosphorylation [55]. In humans, α7 nAChR agonists, but not α4β2 nAChR agonists, increased PiB binding in postmortem frontal lobe homogenates of elder controls and AD. Additionally, chronic nicotine administration to adolescent rats evoked cell damage and loss throughout the brain and with selectively greater effects in the female hippocampus [227,228]. The interpretation of the effects of nicotine on Aβ-related neuropathology in animals and humans is further complicated by the following: (1) AD is associated with a significant reduction in acetylcholinergic neurons, synapses, and nAChR expression; (2) active smoking/nicotine consumption is associated with increased nAChR levels; (3) neuritic plaque and Aβ accumulation show strong co-localization at nAChRs [229]; (4) *APOE* ε4 carriers with carriers with AD may possess fewer nAChR binding regions [80]. Therefore, it is clear that the interplay between nicotine/cholinergic agonists at nAChRs, particularly α7 nAChRs, and Aβ deposition is complex and incompletely understood [6,226,229]. In contrast to Aβ, animal and in vitro models showed that administration of nicotine and nAChR agonists consistently induced tau aggregation and hyperphosphorylation. Overall, the findings across animal and human studies do not provide consistent evidence that nicotine and other α7 nAChR agonists are protective against Aβ production and deposition. Notably, preclinical data indicated that nicotine and nAChR agonists reliably produced tau hyperphosphorylation. Given in vitro and in vivo nicotine exposure induces cerebral OxS, and OxS promotes abnormal tau phosphorylation, the associations observed between nicotine exposure and increased tau phosphorylation may be explained by nicotine-inducted OxS.

7. Comparison of elders with and without a history of smoking on cerebral Aβ deposition: Florbetapir PET

7.1. Background and subjects

To our knowledge, there are no published in vivo human studies that specifically investigated the influence of smoking status on neuroimaging markers of Aβ deposition in cognitively normal elders. Accordingly, we compared a large cross-sectional sample of cognitively normal elder control participants from the Alzheimer's Disease Neuroimaging Initiative who were never smokers (n = 154; 75 ± 7 years of age; 17 ± 3 years of education) with those with at least 1 year of smoking during lifetime (smokers; n = 109; 76 ± 5 years of age; 16 ± 3 years of education; pack-years = 26 ± 21), on cortical Aβ deposition, via florbetapir F-18 PET. Twelve smokers (11%) were active smokers at the time of study; former smokers (n = 97) quit smoking 34 ± 15 years (minimum = 1 year, maximum = 34 years; median = 37 years) before study. Smokers (former and current smokers combined) and never smokers were equivalent on age, education, allowed current

and historical biomedical conditions, and frequency of sex, *APOE* ε4 carriers, antihypertensive, statins and cholesterol absorption blockers, and COPD medication use. Smokers and nonsmokers did not differ on plasma triglyceride and cholesterol levels, the modified Hachinski score (measure of cerebrovascular risk factors), or WM hypointensity volume based on T1-weighted MRI. Smokers had a significantly higher frequency of history of alcohol misuse ($P < .05$), which is consistent with findings from middle-aged cohorts [14].

7.2. Florbetapir F-18 PET and statistical analyses

Florbetapir shows high affinity and specific binding to fibrillar Aβ deposits in neuritic plaques [230] and is strongly correlated with the level of neuritic plaque binding demonstrated by PiB [231]. Mean florbetapir retention was calculated for prefrontal, anterior/posterior cingulate, lateral parietal, and lateral temporal GM, and each region was standardized to whole cerebellar retention. A composite measure was calculated by taking the average of the four cortical regions (see adni.loni.usc.edu/research/pet-analysis/ for details on formation florbetapir quantitation and formation of GM regions of interest). Human fibrillar Aβ deposition, as measured by PET ligands, is highly related to age, beginning in the fifth decade of life and suggested to follow a sigmoid curve through old age [30]. *APOE* genotype is also strongly related to fibrillar Aβ deposition, with *APOE* ε4 carriers typically showing greater deposition than noncarriers, particularly with increasing age [38,232]. Because a history of smoking in cognitively normal elders is associated with greater regional brain atrophy and other neurobiological abnormalities in the anterior and posterior cingulate and anterior frontal and posterior parietal and lateral temporal lobes (see Section 4.3), we predicted that smokers would demonstrate greater florbetapir retention than nonsmokers across these regions. A composite GM florbetapir retention value of ≥1.11 is designated as an "amyloid-positive" cutoff, based on levels demonstrated by individuals who completed a florbetapir PET scan within 12 months of death that showed probable AD at autopsy (see adni.loni.usc.edu/research/pet-analysis/). We predicted that a greater percentage of smokers have ≥1.11 composite GM retention values. Multivariate analysis of covariance (MANCOVA) tested for differences between smokers and never smokers in prefrontal, anterior/posterior cingulate, lateral parietal, and lateral temporal GM and composite florbetapir retention, controlling for *APOE* ε4 carrier status, age, sex, education, and history of alcohol misuse. Effect sizes for mean differences between smokers and nonsmokers on regional florbetapir uptake were calculated with Cohen's *d*. The small number of active smokers (n = 12) had numerically higher florbetapir uptake in all regions than former smokers (data not shown), but these differences were not statistically significant, so active and former smokers were combined into one group. The proportion of smokers and never smokers that were ≥1.11 versus <1.11 for composite GM florbetapir was compared with chi-square. Associations between smoking exposure variables (i.e., pack-years, years of smoking cessation) and regional florbetapir uptake were examined with partial correlations controlling for age, sex, and *APOE* ε4 carrier status.

7.3. Results

MANCOVA yielded a significant omnibus effect for smoking status (active/former smoker vs. never smoker) [$F(5, 252) = 2.75$, $P = .019$]. There were no significant interactions among smoking status and covariates. Follow-up *t* tests (two-tailed, $P \leq .025$ considered statistically significant) indicated that smokers showed greater florbetapir retention than never smokers in the cingulate, temporal, parietal, and composite GM (all $P < .018$; see Fig. 1), with a trend for the frontal GM ($P = .065$). A significantly higher proportion of smokers (44 of 109; 40%) than never smokers (39 of 154; 25%) had florbetapir retention values ≥1.11 for the composite GM (two-tailed $\chi^2 = 6.69$; $P = .01$). Virtually identical results were obtained for the aforementioned analyses when only former smokers (n = 97) were compared with never smokers. In smokers, there were no significant associations between cigarette exposure variables (i.e., pack-years, lifetime years of smoking, years of smoking cessation) and florbetapir retention in any region.

7.4. Discussion

The significantly higher regional florbetapir retention in this large sample of cognitively normal elders with a history of smoking indicated that they had greater fibrillar Aβ deposition in the cingulate, temporal, parietal, and composite cortical GM. The greater in vivo florbetapir retention in these cognitively normal elder smokers is novel and congruent with in vitro, animal, and human postmortem studies that reported cigarette smoke exposure/smoking was associated with significantly increased Aβ-based neuropathology (see Section 5.2). A significantly higher proportion of smokers (40%) than never smokers (25%) had composite GM retention values that fell into the range demonstrated by those with histologically confirmed AD. Human postmortem studies have reported that approximately 30% of cognitively intact elders exhibit levels of amyloid deposition observed in AD cases [48,233]. This suggests that the proportion of smokers in this cohort who demonstrated elevated amyloid deposition is 10% beyond that expected in the general population of cognitively normal elders.

Additionally, research criteria [27] have been recently proposed to stage and operationalize the severity of the neuropathologic correlates of preclinical AD in cognitively normal individuals; the stages are as follows: no indications of elevated amyloid and neuronal injury biomarkers or "subtle" cognitive decline (stage 0), elevated amyloid biomarkers

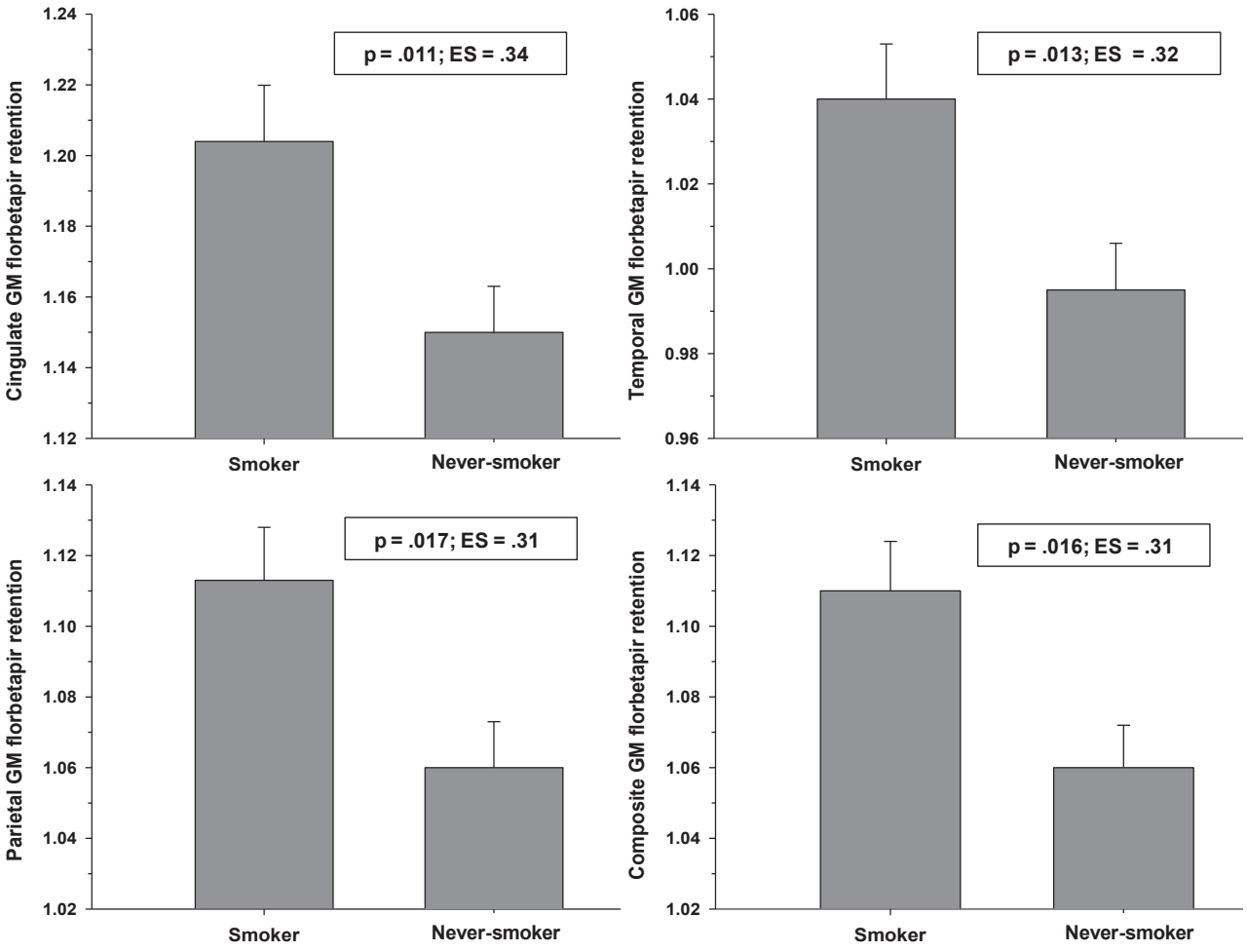

Fig. 1. Regional florbetapir retention for smokers and never smokers. Retention values for each region represent the ratio formed by standardization to whole cerebellar florbetapir retention. Bars represent the group mean and error bars are the standard error of the mean; ES, Cohen's d effect size; GM, gray matter.

only (stage 1), elevated amyloid and neuronal injury biomarkers (stage 2), and elevated amyloid, neuronal injury biomarkers, and subtle cognitive decline (stage 3). Based on the florbetapir findings alone, approximately 33% of the entire cognitively normal elder cohort would have been classified as stage 1 preclinical AD; however, when the smoking status was considered, 40% of smokers versus 25% of never smokers would be classified as stage 1, after controlling for *APOE* ε4 genotype and other relevant covariates. This highlights the importance of consideration of the potential effects of smoking status on AD-related neuropathology. Smokers and never smokers from this cognitively normal cohort will be compared on markers of structural, metabolic, OxS, and neurocognition in future analyses to more accurately determine the number of individuals exhibiting criteria for the various preclinical AD stages.

The 11% active smokers in this cohort is consistent with the estimated prevalence of 10% active smokers in those ≥60 years of age in the general US population [2]. It is noteworthy that 89% of smokers were former smokers, with a wide range of duration of smoking cessation. The lack of differences between smokers and never smokers on CVD and cerebrovascular disease risk factors (e.g., triglyceride and cholesterol levels, modified Hachinski score, use of antihypertensive medications) may be related to the fact that 89% of the smokers were former smokers or potentially to survivor bias in the smoker cohort. Nevertheless, despite 34 ± 15 years of smoking cessation, former smokers demonstrated significantly greater florbetapir retention in the cingulate, temporal, parietal, and composite GM. In the entire smoker sample and in former smokers alone, there were no significant associations between cigarette exposure variables and regional florbetapir retention. These findings suggest that other premorbid and/or comorbid factors not considered in this report may have partially contributed to the greater regional florbetapir retention observed in smokers, or the amyloid deposition in this cohort has been stable for many years. Given the increased rate of amyloid accumulation is associated with an increased risk for cognitive decline in cognitively normal elders, as well as for conversion from MCI to AD [234,235], longitudinal tracking of this cohort of smokers and never smokers may advance our

understanding of the factors related to the increasing dementia incidence in the rapidly growing numbers of the oldest-old (i.e., ≥90 years of age) in the United States [236].

8. Summary

1. The cumulative body of research considered in this review strongly indicates that a history of smoking (i.e., former and active) is a significant and modifiable risk factor for AD, and increasing smoking exposure is related to greater AD risk. Smoking is associated with earlier onset of AD symptomatology and is estimated to account for 4.7 million AD cases worldwide. In the United States, smoking is associated with at least a 10-year reduction in life expectancy [237], which will decrease the number of elder smokers participating in both case-controlled and cohort studies, and creates a survivor bias due to premature death. In other words, the study of smoking-related risk for AD in elders will be inescapably biased toward the healthiest smokers—individuals who survived or did not experience significant smoking-related morbidity [91,92]. Furthermore, Chang et al. [92] clearly demonstrated how competing risk due to death (i.e., a smoker dies of another cause before manifesting AD) may obscure the association between smoking and risk for AD. The development of common clinically significant smoking-related morbidity (e.g., CVD, COPD, cancer, multiple cerebrovascular accidents) may be exclusionary in some studies or limit the functional ability and/or motivation of individuals to participate in longitudinal studies. This may also create a selection bias in which the characteristics of study participants free from these conditions are not representative of the comparably aged smokers in the general population. Taken together, the actual magnitude of risk for AD associated with smoking is likely underestimated because of survivor bias.
2. Chronic exposure to cigarette smoke and nicotine is consistently and causally linked to OxS in vitro and in animal models and is associated with OxS and corresponding cerebral cellular damage in postmortem human studies. The animal models used a wide variety of smoke exposure levels and durations, which should be considered when interpreting the findings from these studies. OxS is related to increased activity of the proteolytic pathway responsible for generating Aβ isoforms, as well as abnormal tau phosphorylation. Therefore, exogenous sources of OxS may facilitate the onset of AD pathophysiology/neuropathology, rather than simply emerge as a physiological consequence of existing amyloid or tau pathology. Given the strong association between cigarette smoke exposure and increased brain OxS, smoking in humans may serve as a fundamental mechanism promoting development of AD pathophysiology and neuropathology. This assertion is supported by (1) in vitro data demonstrating chronic cigarette smoke condensate exposure and nicotine to various cell types is causally related to increased cerebral Aβ isoforms and p-tau concentrations; (2) data from animal studies showing cigarette smoke exposure causally increases brain fibrillar Aβ deposition and nicotine administration promoted p-tau levels; and (3) data from large–sample size human postmortem studies and our novel in vivo PET neuroimaging findings (see Section 7) showing that cognitively normal former/active smoking is robustly associated with significantly increased cortical fibrillar amyloid deposition (former/active smokers and never smokers were also equivalent on cerebrovascular risk factors in our cohort). Taken together, smoking-related OxS may increase the risk for AD through the initiation and progression of the core amyloid and tau pathologies that are hypothesized to lead to neurodegeneration, cell death, and neurocognitive decline.
3. Pure nicotine administration in vitro and in animal models yielded variable findings for Aβ pathology but consistent results for tau pathology. In humans, we are not aware of any published in vivo or postmortem studies on the effects of pure nicotine consumption on AD pathophysiology. In animals, chronic nicotine administration was shown to significantly decrease neuritic plaques and insoluble $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ levels in the cortex or hippocampus but did not alter soluble $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ concentrations in these regions. The findings for the soluble Aβ isoforms are significant for humans because soluble Aβ oligomer levels may be more strongly related to cognitive decline and tau hyperphosphorylation than fibrillar Aβ-containing compounds. In vitro exposure of nicotine and nicotine agonists causally increased p-tau and total tau levels, and in animals, chronic nicotine administration causally and significantly increased hippocampal tau aggregation and phosphorylation. The animal research reviewed used a wide variety of animal types (e.g., mice, rats, transgenic animals) and routes of nicotine administration and dosages, which may have contributed to the variability of the findings in these preclinical studies. In humans, α7 nAChR agonists increased PiB binding (shows high affinity binding to fibrillar amyloid), postmortem, in frontal lobe homogenates of elder AD and controls. Currently, the combined findings from animal and human studies do not provide consistent evidence that nicotine and other α7 nAChR agonists are protective against Aβ deposition. Importantly, in vitro and animal models showed administration of nicotine and nAChR agonists consistently and causally induced tau hyperphosphorylation and aggregation. The association between nicotine administration and

abnormal tau phosphorylation is consistent with nicotine serving as a source of OxS.

4. Smoking in clinical and nonclinical cohorts across adulthood is strongly related to multiple neurobiological and neurocognitive abnormalities (see Section 4). In humans, smoking is consistently associated with biomarkers of compromised neuronal integrity and degeneration (e.g., regional volume loss, cortical thinning, decreased N-acetylaspartate levels) and neurocognitive deficiencies. Smoking-related deficiencies in learning/memory, processing speed, and executive skills, as well as regional brain structural abnormalities may show progression over time in the middle-aged to elder adults. In cognitively normal elders, several of the reviewed postmortem studies indicated that smokers showed significant Aβ deposition and increased tau pathology. Additionally, we observed that cognitively normal elder controls with a history of smoking demonstrated significantly higher retention of florbetapir, a marker of fibrillar Aβ deposition, in multiple brain regions. Taken together, several of these neurobiological and neurocognitive abnormalities exhibited by cognitively normal middle-aged and elder adults are consistent with the recently proposed preclinical stages of AD (see Section 7.4 for description of pathology associated with each stage) [27,49]. It is important to recognize that some of the neurobiological and neurocognitive abnormalities demonstrated may also be, least partially, related to unrecognized genetic and/or premorbid/comorbid factors, rather than solely to the effects of smoking [14,112,129].
5. The relationship between midlife smoking and risk for AD may also be influenced by potential differences between smokers and nonsmokers on brain reserve, cognitive reserve [238], and other unrecognized genetic and/or premorbid/comorbid factors, as well as other modifiable factors such as diet, physical activity, and cognitive engagement [14,70]. Smoking is associated with an increased risk for CVD [13] and cerebrovascular disease [167,239]; OxS is suggested as a mechanism for both CVD and cerebrovascular disease [94,141]. Because individuals with AD frequently manifest evidence of cerebrovascular pathology (e.g., WM hyperintensities/lesions, subcortical nuclei lesions) [240,241], smoking-related OxS also potentially contributes to an increased risk for AD via CVD/cerebrovascular disease (i.e., atherosclerosis and associated vascular dysfunction) [70,73], rather than exclusively through the facilitation of the amyloidogenic pathway. However, compromised cerebrovascular function may also be related to CAA, which is more severe and widespread across the brain in *APOE* ε4 carriers [52]. The reviewed in vitro and preclinical animal findings, indicate that both cigarette smoke condensate and smoke exposure causally facilitate the amyloid and tau pathologies, and healthy young/middle-aged adults exhibit significant neurobiological and neurocognitive abnormalities that are apparent in the preclinical stages of AD (see Section 4.3). Therefore, smoking-related subclinical or clinically significant CVD and/or cerebrovascular diseases may contribute to, but likely do not completely account for, the link between midlife smoking and increased risk for AD.
6. Approximately 31% of active military personnel are active smokers, which is 11% higher than in the general US population, and cigarette use approaches 35% in personnel with high combat exposure. Smoking in active duty personnel is clearly linked to decreased combat readiness and diminished general health [8,11,242]. TBI and posttraumatic stress disorder (PTSD) are prevalent conditions in active duty personnel serving in Iraq and Afghanistan, and increasing evidence suggests that these conditions increase the risk for AD [243]. Smoking is a highly comorbid condition in TBI [129], PTSD [200], and other anxiety disorders [244]; consequently, it is imperative to consider the potential mediating or moderating effect of the smoking status on the association between TBI, PTSD, and the risk for AD in future case-controlled or cohort studies. The smoking-related neurobiological and neurocognitive abnormalities observed in nonclinical cohorts of late adolescents through middle-aged adults are highly relevant for the US Armed Services, given most active duty personnel are between the ages of 18 and 50 years. Additionally, the neurobiological and/or neurocognitive sequelae associated with both mild TBI and hazardous alcohol consumption appear to be exacerbated by smoking, and diminished recovery from these conditions is associated with smoking. These findings are of critical import to the US Armed Services because of the significantly increased risk for mild TBI and hazardous levels of alcohol consumption in active duty personnel. The Department of Defense (DoD) clearly recognizes the adverse effects of smoking on the well-being of active duty personnel [9] and has promoted the "Quit Tobacco. Make Everyone Proud" education campaign. Also, the Code of Federal Regulations, Title 32, Part 85, specifically outlines DoD policies to prevent smoking and encourage cessation, which dictate that each armed service develop its own health promotion plans [8]. However, the efficacy of such programs and policies have been questioned, and unfortunately, there currently appears to be many logistical and political issues that obstruct the enactment of more stringent tobacco control in the US Armed Services [8,10–12,242].

7. Future research opportunities:
   - Currently, the interplay between *APOE* genotype and smoking on risk for AD is unclear and requires further prospective cohort-based research.
   - Additional prospective longitudinal studies with former smokers that are fully characterized on smoking exposure variables, cessation periods, diet, and exercise are necessary to better understand the association between former smoking status/smoking cessation and risk for AD.
   - The association between smoking and risk for MCI has received little attention [245,246] and warrants future research because MCI is considered to be the prodromal stage of AD [28,247].
   - Longitudinal in vivo measurements of multiple biomarkers of brain Aβ burden, tau, and OxS in smokers and nonsmokers during middle age (i.e., 40-65 years of age) will promote a better understanding on how smoking relates to the onset and trajectory of AD pathophysiology and neuropathology. The interplay between nicotine/cholinergic agonists at nAChRs and Aβ- and tau-related neuropathology is clearly multifaceted, and additional prospective research is needed to clarify their effects on AD-related neuropathology and utility as potential disease-modifying agents. These research objectives may be accomplished via florbetapir for fibrillar amyloid, new PET tracers for tau [248], and with magnetic resonance spectroscopy of glutathione concentration, an established marker of OxS [249]. Alternately, concurrent measurement of CSF concentrations of Aβ and tau isoforms combined with CSF isoprostanoids, a measure of ROS-mediated OxS (see Refs. [141,154,250] for review), may also provide parallel information. Additionally, examination of the association between smoking and soluble Aβ oligomers (e.g., Aβ trimers, Aβ*56) may be informative as recent research has reported the strong relationships between these oligomers and age, neurocognition, neuritic plaque load, and soluble tau levels [58,251].

9. Conclusions

- The cumulative body of research to date indicates that previous and active smoking is associated with a significantly increased risk for AD, and previous research reporting that smoking was related to a significantly decreased risk for AD appears to be highly confounded by selection/survivor bias and affiliation with the tobacco industry. Correspondingly, in humans, there is no consistent evidence demonstrating that smoking or pure nicotine confers any protection from the development of AD neuropathology or is associated with a decreased risk for AD.
- Late-onset AD is characterized by an extended preclinical stage, and smoking has been associated with earlier onset of AD symptomatology. We hypothesize that smoking during middle age, via chronic OxS, may shorten the length of the preclinical period by shifting the inception of AD-related pathologic Aβ processing, tau protein hyperphosphorylation, and, potentially, mild cerebrovascular dysfunction (via subclinical cerebrovascular disease and/or CAA) to a significantly younger age. We predict that the greatest AD pathologic findings will be most apparent in actively smoking *APOE* ε4 carriers.
- CVD, stroke, diabetes, hypertension, and hypercholesterolemia have been individually proposed as potential modifiable risk factors for AD [25,70,252], and these conditions are also associated with an increased risk for vascular dementia [253,254]. Because smoking is moderately to strongly associated with an increased risk for the development of the aforementioned medical conditions [13,70,206,255], a global decrease in the prevalence of smoking would also likely promote a further reduction in the number of people who develop and suffer from AD [70,206] and vascular dementia.
- The significantly increased risk for smoking-related CVD, COPD, and cancer has been recognized by most health-care providers and the general public for decades, but, unfortunately, tobacco use is treated at a much lower frequency than other chronic conditions (e.g., diabetes, hypertension) [256]. Additionally, it has been argued that if health-care providers have the perception that smoking does not increase the risk for, or is somehow protective of, AD, this may serve as an additional barrier to encourage engagement in smoking cessation interventions, particularly in elders [206]. The aforementioned may act in concert to contribute to the general undertreatment of tobacco use in the United States, which may have even greater adverse ramifications for active duty military personnel, given their higher prevalence of smoking. We fully recognize the challenges associated with maintenance of sustained smoking cessation with currently available behavioral and pharmacological interventions [7,257]; however, more aggressive global efforts aimed at smoking prevention in youth and facilitation of sustained smoking cessation in adults may ultimately promote a significant decrease in the prevalence of future AD cases worldwide.
- Considering multiple studies observed former smoking (i.e., individuals who quit) during lifetime was associated with AD-related neuropathology and increased risk for AD, we strongly support that the FDA Family Smoking Prevention and Tobacco

Control Act to impose even greater restrictions on tobacco product advertising and marketing to youth to prevent the onset of smoking. We also support more vigorous efforts by the DoD to incentivize new US Armed Service recruits not to smoke and active duty personnel to stop smoking.

- Given there are no currently available pharmacological interventions that prevent the onset of AD pathophysiology or significantly alter its clinical course, it is imperative to delineate the mechanisms by which potentially "modifiable" risk factors, such as smoking, confer increased risk for AD during the preclinical stages. This will assist in the identification of those at elevated AD risk and potentially inform development of more efficacious treatment interventions [27]. Specifically, if we understand how smoking increases the risk for AD during the preclinical stages, the associated pathophysiological mechanisms (e.g., OxS) [203] may be mitigated through targeted treatment, or more ideally, the mechanisms halted via smoking cessation. Furthermore, determining if smoking is associated with greater AD-related pathophysiology and neuropathology during the specific preclinical AD stages is highly relevant, as those who are in stages 1 to 3 may be at risk for clinically significant cognitive and functional decline over time [258]. Prospective longitudinal research specifically focusing on the neurobiological consequences of smoking (including the potential interactions among smoking status, age, *APOE* genotype, and other emerging AD risk factors), as well as the neurobiological effects of sustained smoking cessation, in adolescents to elders, is clearly warranted and necessary to delineate the potential mechanisms by which smoking places individuals at greater risk for AD. The study of young to middle-aged adults has the advantage of minimizing the likelihood of clinically significant smoking-related diseases [259] that may affect brain neurobiology and contribute to survivor bias. Such research must also be conducted to better inform and change perceptions among health-care providers, civilians, veterans, and active duty military about the adverse effects of smoking on the brain and its functions. Finally, expanded research efforts focusing on the longitudinal neurobiological and neurocognitive consequences of chronic smoking in conditions in which it is highly prevalent (e.g., AUDs, schizophrenia-spectrum disorders, mood disorders, PTSD) are required to further inform policy on regulation of the manufacture, distribution, and marketing of tobacco products in the United States and abroad.

Acknowledgments

T.C.D. was responsible for the concept and design of the review, completed all statistical analyses on the original data presented, and wrote the original and revised versions of the manuscript. N.M. and M.W.W. were involved in manuscript editing, data interpretation, and manuscript draft revisions. T.C.D. had full access to all the original data presented study and takes responsibility for the integrity of the data and the accuracy of the data analyses. This work was supported by the National Institutes of Health (NIH DA24136 to T.C.D.) and by the use of resources and facilities at the San Francisco Veterans Administration Medical Center. Florbetapir data collection and sharing for this project was funded by ADNI. ADNI is funded by the National Institute on Aging (U01 AG024904), the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Abbott; AstraZeneca AB; Bayer Schering Pharma AG; Bristol-Myers Squibb; Eisai Global Clinical Development; Elan Corporation; Genentech; GE Healthcare; GlaxoSmithKline; Innogenetics; Johnson and Johnson; Eli Lilly and Co.; Medpace, Inc.; Merck and Co., Inc.; Novartis AG; Pfizer Inc; F. Hoffman-La Roche; Schering-Plough; Synarc, Inc.; and Wyeth, as well as nonprofit partners such as the Alzheimer's Association and Alzheimer Drug Discovery Foundation, with participation from the U.S. Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (www.fnih.org; http://www.fnih.org; http://www.fnih.org; http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University Southern California. This research was also supported by National Institutes of Health grants P30 AG010129, K01 AG030514, R01 AG010897, and R01 AG012435, and The Dana Foundation and by resources by resources and the use of facilities at the San Francisco Veterans Administration Medical Center, San Francisco, CA. The aforementioned funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Original data used in preparation of this article were obtained from the ADNI database (www.loni.usc.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Authorship_List.pdf

T.C.D., N.M., and M.W.W. have no conflicts of interest to report.

References

[1] DeMarini DM. Genotoxicity of tobacco smoke and tobacco smoke condensate: a review. Mutat Res 2004;567:447–74.

[2] Dube SR, McClave A, James C, Caraballo R, Kaumann R, Pechacek TF, et al. Vital signs: current cigarette smoking among adults aged ≥ 18 years—United States, 2009. MMWR Morb Mortal Wkly Rep 2010;59:1135–40.
[3] Delnevo CD, Gundersen DA, Hagman BT. Declining estimated prevalence of alcohol drinking and smoking among young adults nationally: artifacts of sample undercoverage? Am J Epidemiol 2008; 167:15–9.
[4] Current cigarette smoking among adults—United States, 2011. MMWR Morb Mortal Wkly Rep 2012;61:889–94.
[5] Jha P, Peto R, Zatonski W, Boreham J, Jarvis MJ, Lopez AD. Social inequalities in male mortality, and in male mortality from smoking: indirect estimation from national death rates in England and Wales, Poland, and North America. Lancet 2006;368:367–70.
[6] Dome P, Lazary J, Kalapos MP, Rihmer Z. Smoking, nicotine and neuropsychiatric disorders. Neurosci Biobehav Rev 2010; 34:295–342.
[7] Alpert HR, Connolly GN, Biener L. A prospective cohort study challenging the effectiveness of population-based medical intervention for smoking cessation. Tob Control 2013;22:32–7.
[8] Bondurant S, Wedge R. Combating tobacco use in military and veteran populations: Institute of Medicine of the National Academies; 2009. Available at: http://www.nap.edu/catalog/12632.html. Accessed May 12, 2014.
[9] Bray RM, Pemberton MR, Hourani LL, Witt, M, Rae-Olmsted KL, Brown JM, et al. 2008 Department of Defense survey of health related behaviors among active duty military personnel. Research Triangle Park, North Carolina: Research Triangle Institute (RTI) International. Technical Report RTI/10940-FR, 2009. Available at: www.tricare.mil/tma/2008HealthBehaviors.pdf. Accessed May 12, 2014.
[10] Smith EA, Malone RE. Military exceptionalism or tobacco exceptionalism: how civilian health leaders' beliefs may impede military tobacco control efforts. Am J Public Health 2013; 103:599–604.
[11] Haddock CK, Jahnke SA, Poston WS, Williams LN. Cigarette prices in military retail: a review and proposal for advancing military health policy. Mil Med 2013;178:563–9.
[12] Smith EA, Malone RE. Why strong tobacco control measures "can't" be implemented in the U.S. Military: a qualitative analysis. Mil Med 2012;177:1202–7.
[13] Services US Dept of Health and Human Services. The health consequences of smoking: a report of the surgeon general. Centers for Disease Control and Prevention, 2004. Available at: http://www.cdc.gov/tobacco/data_statistics/sgr/2004/. Accessed May 12, 2014.
[14] Durazzo TC, Meyerhoff DJ, Nixon SJ. Chronic cigarette smoking: implications for neurocognition and brain neurobiology. Int J Environ Res Public Health 2010;7:3760–91.
[15] Sharma A, Brody A. In vivo brain imaging of human exposure to nicotine and tobacco. In: Nicotine psychopharmacology. Springer-Verlag Berlin Heidelberg; 2009. p. 145–71.
[16] Azizian A, Monterosso J, O'Neill J, London ED. Magnetic resonance imaging studies of cigarette smoking. In: Nicotine psychopharmacology. Springer-Verlag Berlin Heidelberg; 2009. p. 113–43.
[17] Swan GE, Lessov-Schlaggar CN. The effects of tobacco smoke and nicotine on cognition and the brain. Neuropsychol Rev 2007; 17:259–73.
[18] Durazzo T, Insel PS, Weiner MW, The Alzheimer's Disease Neuroimaging Initiative. Greater regional brain atrophy rate in healthy elders with a history of cigarette smoking. Alzheimers Dement 2012; 8:513–9.
[19] Durazzo T, Meyerhoff DJ, Nixon SJ. Interactive effects of chronic cigarette smoking and age on hippocampal volumes. Drug Alcohol Depend 2013;133:704–11.
[20] Almeida OP, Garrido GJ, Alfonso H, Hulse G, Lautenschlager NT, Hankey GJ, et al. 24-month effect of smoking cessation on cognitive function and brain structure in later life. Neuroimage 2011; 55:1480–9.
[21] Almeida OP, Garrido GJ, Lautenschlager NT, Hulse GK, Jamrozik K, Flicker L. Smoking is associated with reduced cortical regional gray matter density in brain regions associated with incipient Alzheimer disease. Am J Geriatr Psychiatry 2008;16:92–8.
[22] Cataldo JK, Prochaska JJ, Glantz SA. Cigarette smoking is a risk factor for Alzheimer's disease: an analysis controlling for tobacco industry affiliation. J Alzheimers Dis 2010;19:465–80.
[23] Rusanen M, Rovio S, Ngandu T, Nissinen A, Tuomilehto J, Soininen H, et al. Midlife smoking, apolipoprotein E and risk of dementia and Alzheimer's disease: a population-based cardiovascular risk factors, aging and dementia study. Dement Geriatr Cogn Disord 2010;30:277–84.
[24] Rusanen M, Kivipelto M, Quesenberry CP Jr, Zhou J, Whitmer RA. Heavy smoking in midlife and long-term risk of Alzheimer disease and vascular dementia. Arch Intern Med 2011;171:333–9.
[25] 2012 Alzheimer's disease facts and figures. Alzheimers Dement 2012;8:131–68.
[26] Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement 2013;9:63–752.
[27] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:280–92.
[28] Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, et al. Mild cognitive impairment: ten years later. Arch Neurol 2009;66:1447–55.
[29] Drago V, Babiloni C, Bartres-Faz D, Caroli A, Bosch B, Hensch T, et al. Disease tracking markers for Alzheimer's disease at the prodromal (MCI) stage. J Alzheimers Dis 2011;26(Suppl 3):159–99.
[30] Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet neurology 2013;12:207–16.
[31] Schneider LS, Insel PS, Weiner MW. Treatment with cholinesterase inhibitors and memantine of patients in the Alzheimer's Disease Neuroimaging Initiative. Arch Neurol 2011;68:58–66.
[32] Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J Neuropathol Exp Neurol 2012;71:362–81.
[33] de Calignon A, Polydoro M, Suarez-Calvet M, William C, Adamowicz DH, Kopeikina KJ, et al. Propagation of tau pathology in a model of early Alzheimer's disease. Neuron 2012;73:685–97.
[34] Braak H, Zetterberg H, Del Tredici K, Blennow K. Intraneuronal tau aggregation precedes diffuse plaque deposition, but amyloid-beta changes occur before increases of tau in cerebrospinal fluid. Acta Neuropathol 2013;126:631–41.
[35] Vemuri P, Wiste HJ, Weigand SD, Knopman DS, Shaw LM, Trojanowski JQ, et al. Effect of apolipoprotein E on biomarkers of amyloid load and neuronal pathology in Alzheimer disease. Ann Neurol 2010;67:308–16.
[36] Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol 2011;70:960–9.
[37] Risacher SL, Kim S, Shen L, Nho K, Foroud T, Green RC, et al. The role of apolipoprotein E (APOE) genotype in early mild cognitive impairment (E-MCI). Front Aging Neurosci 2013;5:1–12. article 11.
[38] Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, et al. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Ann Neurol 2010;67:122–31.

[39] Braak H, Del Tredici K. The pathological process underlying Alzheimer's disease in individuals under thirty. Acta Neuropathol 2011;121:171–81.
[40] Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. Arch Neurol 2011;68:1062–4.
[41] Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. Int J Alzheimers Dis 2012; http://dx.doi.org/10.1155/2012/369808. article ID 369808.
[42] Mondragon-Rodriguez S, Basurto-Islas G, Lee HG, Perry G, Zhu X, Castellani RJ, et al. Causes versus effects: the increasing complexities of Alzheimer's disease pathogenesis. Expert Rev Neurother 2010;10:683–91.
[43] Herrup K. Reimagining Alzheimer's disease—an age-based hypothesis. J Neurosci 2010;30:16755–62.
[44] Pimplikar SW, Nixon RA, Robakis NK, Shen J, Tsai LH. Amyloid-independent mechanisms in Alzheimer's disease pathogenesis. J Neurosci 2010;30:14946–54.
[45] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297:353–6.
[46] Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367:795–804.
[47] Masdeu JC, Zubieta JL, Arbizu J. Neuroimaging as a marker of the onset and progression of Alzheimer's disease. J Neurol Sci 2005;236:55–64.
[48] Price JL, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Ann Neurol 1999;45:358–68.
[49] Jack CR Jr, Knopman DS, Weigand SD, Wiste HJ, Vemuri P, Lowe V, et al. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. Ann Neurol 2012;71:765–75.
[50] Castellani RJ, Smith MA, Perry G, Friedland RP. Cerebral amyloid angiopathy: major contributor or decorative response to Alzheimer's disease pathogenesis. Neurobiol Aging 2004;25:599–602. discussion 3–4.
[51] Thal DR, Ghebremedhin E, Orantes M, Wiestler OD. Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. J Neuropathol Exp Neurol 2003;62:1287–301.
[52] Allen N, Robinson AC, Snowden J, Davidson YS, Mann DM. Patterns of cerebral amyloid angiopathy define histopathological phenotypes in Alzheimer's disease. Neuropathol Appl Neurobiol 2014;40:136–48.
[53] Iwatsubo T, Odaka A, Suzuki N, Mizusawa H, Nukina N, Ihara Y. Visualization of A beta 42(43) and A beta 40 in senile plaques with end-specific A beta monoclonals: evidence that an initially deposited species is A beta 42(43). Neuron 1994;13:45–53.
[54] Attems J, Jellinger K, Thal DR, Van Nostrand W. Review: sporadic cerebral amyloid angiopathy. Neuropathol Appl Neurobiol 2011;37:75–93.
[55] Butterfield DA, Swomley AM, Sultana R. Amyloid beta-peptide (1-42)-induced oxidative stress in Alzheimer disease: importance in disease pathogenesis and progression. Antioxid Redox Signal 2013;19:823–35.
[56] Selkoe DJ, Schenk D. Alzheimer's disease: molecular understanding predicts amyloid-based therapeutics. Annu Rev Pharmacol Toxicol 2003;43:545–84.
[57] Revett TJ, Baker GB, Jhamandas J, Kar S. Glutamate system, amyloid β peptides and tau protein: functional interrelationships and relevance to Alzheimer disease pathology. J Psychiatry Neurosci 2013;38:6–23.
[58] Lesne SE, Sherman MA, Grant M, Kuskowski M, Schneider JA, Bennett DA, et al. Brain amyloid-beta oligomers in ageing and Alzheimer's disease. Brain 2013;136:1383–98.
[59] Bulic B, Ness J, Hahn S, Rennhack A, Jumpertz T, Weggen S. Chemical biology, molecular mechanism and clinical perspective of gamma-secretase modulators in Alzheimer's disease. Curr Neuropharmacol 2011;9:598–622.
[60] Wang X, Michaelis EK. Selective neuronal vulnerability to oxidative stress in the brain. Front Aging Neurosci 2010;30:12.
[61] Minghetti L. Role of inflammation in neurodegenerative diseases. Curr Opin Neurol 2005;18:315–21.
[62] Khandelwal PJ, Herman AM, Moussa CE. Inflammation in the early stages of neurodegenerative pathology. J Neuroimmunol 2011;238:1–11.
[63] Sutherland GT, Chami B, Youssef P, Witting PK. Oxidative stress in Alzheimer's disease: primary villain or physiological by-product? Redox Rep 2013;18:134–41.
[64] Waseem SM, Mobarak MH, Islam N, Ahmad Z. Comparative study of pulmonary functions and oxidative stress in smokers and non-smokers. Indian J Physiol Pharmacol 2012;56:345–52.
[65] Mungas D, Tractenberg R, Schneider JA, Crane PK, Bennett DA. A 2-process model for neuropathology of Alzheimer's disease. Neurobiol Aging 2013;35:301–8.
[66] Luan K, Rosales JL, Lee KY. Viewpoint: crosstalks between neurofibrillary tangles and amyloid plaque formation. Ageing Res Rev 2013;12:174–81.
[67] Daviglus ML, Plassman BL, Pirzada A, Bell CC, Bowen PE, Burke JR, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science. Arch Neurol 2011;68:1185–90.
[68] Raber J, Huang Y, Ashford JW. ApoE genotype accounts for the vast majority of AD risk and AD pathology. Neurobiol Aging 2004;25:641–50.
[69] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–3.
[70] Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819–28.
[71] Kivipelto M, Rovio S, Ngandu T, Kareholt I, Eskelinen M, Winblad B, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med 2008;12:2762–71.
[72] Jun G, Naj AC, Beecham GW, Wang LS, Buros J, Gallins PJ, et al. Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. Arch Neurol 2010;67:1473–84.
[73] van Norden AG, van Dijk EJ, de Laat KF, Scheltens P, Olderikkert MG, de Leeuw FE. Dementia: Alzheimer pathology and vascular factors: from mutually exclusive to interaction. Biochim Biophys Acta 2012;1822:340–9.
[74] Jagust W. Apolipoprotein E, neurodegeneration, and Alzheimer disease. JAMA Neurol 2013;70:299–300.
[75] Ersche KD, Barnes A, Jones PS, Morein-Zamir S, Robbins TW, Bullmore ET. Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. Brain 2011;134(Pt 7):2013–24.
[76] Etgen T, Sander D, Bickel H, Forstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. Dtsch Arztebl Int 2011;108:743–50.
[77] Anstey KJ, 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 2007;166:367–78.
[78] Aggarwal NT, Bienias JL, Bennett DA, Wilson RS, Morris MC, Schneider JA, et al. The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. Neuroepidemiology 2006;26:140–6.
[79] Reitz C, den Heijer T, van Duijn C, Hofman A, Breteler MM. Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. Neurology 2007;69:998–1005.
[80] Ott A, Slooter AJ, Hofman A, van Harskamp F, Witteman JC, Van Broeckhoven C, et al. Smoking and risk of dementia and Alzheimer's

disease in a population-based cohort study: the Rotterdam Study. Lancet 1998;351:1840–3.
[81] Merchant C, Tang MX, Albert S, Manly J, Stern Y, Mayeux R. The influence of smoking on the risk of Alzheimer's disease. Neurology 1999;52:1408–12.
[82] Dufouil C, Tzourio C, Brayne C, Berr C, Amouyel P, Alperovitch A. Influence of apolipoprotein E genotype on the risk of cognitive deterioration in moderate drinkers and smokers. Epidemiology 2000; 11:280–4.
[83] Reitz C, Luchsinger J, Tang MX, Mayeux R. Effect of smoking and time on cognitive function in the elderly without dementia. Neurology 2005;65:870–5.
[84] Tyas SL, White LR, Petrovitch H, Webster Ross G, Foley DJ, Heimovitz HK, et al. Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study. Neurobiol Aging 2003; 24:589–96.
[85] Juan D, Zhou DH, Li J, Wang JY, Gao C, Chen M. A 2-year follow-up study of cigarette smoking and risk of dementia. Eur J Neurol 2004; 11:277–82.
[86] Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, et al. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology 1999;52:78–84.
[87] Sabbagh MN, Tyas SL, Emery SC, Hansen LA, Alford MF, Reid RT, et al. Smoking affects the phenotype of Alzheimer disease. Neurology 2005;64:1301–3.
[88] Weuve J, Tchetgen Tchetgen EJ, Glymour MM, Beck TL, Aggarwal NT, Wilson RS, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. Epidemiology 2012;23:119–28.
[89] Debanne SM, Bielefeld RA, Cheruvu VK, Fritsch T, Rowland DY. Alzheimer's disease and smoking: bias in cohort studies. J Alzheimers Dis 2007;11:313–21.
[90] Hernan MA, Alonso A, Logroscino G. Cigarette smoking and dementia: potential selection bias in the elderly. Epidemiology 2008; 19:448–50.
[91] Kukull WA. The association between smoking and Alzheimer's disease: effects of study design and bias. Biol Psychiatry 2001; 49:194–9.
[92] Chang CC, Zhao Y, Lee CW, Ganguli M. Smoking, death, and Alzheimer disease: a case of competing risks. Alzheimer Dis Assoc Disord 2012;26:300–6.
[93] Peters R, Poulter R, Warner J, Beckett N, Burch L, Bulpitt C. Smoking, dementia and cognitive decline in the elderly, a systematic review. BMC Geriatr 2008;8:36.
[94] Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 2004; 43:1731–7.
[95] Boudreaux ED, Francis JL, Carmack Taylor CL, Scarinci IC, Brantley PJ. Changing multiple health behaviors: smoking and exercise. Prev Med 2003;36:471–8.
[96] Casasola GG, Alvarez-Sala JL, Marques JA, Sanchez-Alarcos JM, Tashkin DP, Espinos D. Cigarette smoking behavior and respiratory alterations during sleep in a healthy population. Sleep Breath 2002; 6:19–24.
[97] Bartal M. Health effects of tobacco use and exposure. Monaldi Arch Chest Dis 2001;56:545–54.
[98] Durazzo TC, Meyerhoff DJ. Neurobiological and neurocognitive effects of chronic cigarette smoking and alcoholism. Front Biosci 2007; 12:4079–100.
[99] Davatzikos C, Bhatt P, Shaw LM, Batmanghelich KN, Trojanowski JQ. Prediction of MCI to AD conversion, via MRI, CSF biomarkers, and pattern classification. Neurobiol Aging 2011; 32:2322.e19–27.
[100] Misra C, Fan Y, Davatzikos C. Baseline and longitudinal patterns of brain atrophy in MCI patients, and their use in prediction of short-term conversion to AD: results from ADNI. Neuroimage 2009; 44:1415–22.
[101] de Jager CA, Schrijnemaekers AC, Honey TE, Budge MM. Detection of MCI in the clinic: evaluation of the sensitivity and specificity of a computerised test battery, the Hopkins Verbal Learning Test and the MMSE. Age Ageing 2009;38:455–60.
[102] Wagner M, Schulze-Rauschenbach S, Petrovsky N, Brinkmeyer J, von der Goltz C, Grunder G, et al. Neurocognitive impairments in non-deprived smokers-results from a population-based multi-center study on smoking-related behavior. Addict Biol 2012;18:752–61. http://dx.doi.org/10.1111/j.1369-1600.2011.00429.x.
[103] Durazzo TC, Meyerhoff DJ, Nixon SJ. A comprehensive assessment of neurocognition in middle-aged chronic cigarette smokers. Drug Alcohol Depend 2012;122:105–11.
[104] Kuhn S, Schubert F, Gallinat J. Reduced thickness of medial orbitofrontal cortex in smokers. Biol Psychiatry 2010;68:1061–5.
[105] Durazzo TC, Mon A, Pennington D, Abe C, Gazdzinski S, Meyerhoff DJ. Interactive effects of chronic cigarette smoking and age on brain volumes in controls and alcohol-dependent individuals in early abstinence. Addict Biol 2014;19:132–43. http://dx.doi.org/10.1111/j.1369-1600.2012.00492.
[106] Brody AL, Mandelkern MA, Jarvik ME, Lee GS, Smith EC, Huang JC, et al. Differences between smokers and nonsmokers in regional gray matter volumes and densities. Biol Psychiatry 2004; 55:77–84.
[107] Gallinat J, Meisenzahl E, Jacobsen LK, Kalus P, Bierbrauer J, Kienast T, et al. Smoking and structural brain deficits: a volumetric MR investigation. Eur J Neurosci 2006;24:1744–50.
[108] Kuhn S, Romanowski A, Schilling C, Mobascher A, Warbrick T, Winterer G, et al. Brain grey matter deficits in smokers: focus on the cerebellum. Brain Struct Funct 2012;217:517–22.
[109] Gallinat J, Schubert F. Regional cerebral glutamate concentrations and chronic tobacco consumption. Pharmacopsychiatry 2007; 40:64–7.
[110] Gallinat J, Lang UE, Jacobsen LK, Bajbouj M, Kalus P, von Haebler D, et al. Abnormal hippocampal neurochemistry in smokers: evidence from proton magnetic resonance spectroscopy at 3 T. J Clin Psychopharmacol 2007;27:80–4.
[111] Zhang X, Salmeron BJ, Ross TJ, Geng X, Yang Y, Stein EA. Factors underlying prefrontal and insula structural alterations in smokers. Neuroimage 2011;54:42–8.
[112] Durazzo TC, Mon A, Gazdzinski S, Meyerhoff DJ. Chronic cigarette smoking in alcohol dependence: associations with cortical thickness and N-acetylaspartate levels in the extended brain reward system. Addict Biol 2011;18:379–91.
[113] Langbaum JB, Chen K, Lee W, Reschke C, Bandy D, Fleisher AS, et al. Categorical and correlational analyses of baseline fluorodeoxyglucose positron emission tomography images from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Neuroimage 2009; 45:1107–16.
[114] De Santi S, de Leon MJ, Rusinek H, Convit A, Tarshish CY, Roche A, et al. Hippocampal formation glucose metabolism and volume losses in MCI and AD. Neurobiol Aging 2001;22:529–39.
[115] Durazzo TC, Fryer SL, Rothlind JC, Vertinski M, Gazdzinski S, Mon A, et al. Measures of learning, memory and processing speed accurately predict smoking status in short-term abstinent treatment-seeking alcohol-dependent individuals. Alcohol Alcohol 2010; 45:507–13.
[116] Durazzo TC, Rothlind JC, Gazdzinski S, Banys P, Meyerhoff DJ. A comparison of neurocognitive function in nonsmoking and chronically smoking short-term abstinent alcoholics. Alcohol 2006; 39:1–11.
[117] Durazzo TC, Gazdzinski S, Banys P, Meyerhoff DJ. Cigarette smoking exacerbates chronic alcohol-induced brain damage: a preliminary metabolite imaging study. Alcohol Clin Exp Res 2004;28:1849–60.
[118] Gazdzinski S, Durazzo T, Jahng GH, Ezekiel F, Banys P, Meyerhoff D. Effects of chronic alcohol dependence and chronic

cigarette smoking on cerebral perfusion: a preliminary magnetic resonance study. Alcohol Clin Exp Res 2006;30:947–58.
[119] Gazdzinski S, Durazzo TC, Studholme C, Song E, Banys P, Meyerhoff DJ. Quantitative brain MRI in alcohol dependence: preliminary evidence for effects of concurrent chronic cigarette smoking on regional brain volumes. Alcohol Clin Exp Res 2005;29:1484–95.
[120] Gazdzinski S, Durazzo TC, Ezekiel F, Jahng G-H, Meyerhoff DJ. Effects of chronic alcohol dependence and chronic cigarette smoking on cerebral perfusion. In: Proc Intl Soc Mag Reson Med; 2005 May 7-13, 2005; Miami Beach, FL; 2005. p. 1138.
[121] Gazdzinski S, Durazzo TC, Mon A, Yeh PH, Meyerhoff DJ. Cerebral white matter recovery in abstinent alcoholics—a multimodality magnetic resonance study. Brain 2010;133:1043–53.
[122] Mon A, Durazzo TC, Gazdzinski S, Meyerhoff DJ. The impact of chronic cigarette smoking on recovery from cortical gray matter perfusion deficits in alcohol dependence: longitudinal arterial spin labeling MRI. Alcohol Clin Exp Res 2009;33:1314–21.
[123] Gazdzinski S, Durazzo TC, Yeh PH, Hardin D, Banys P, Meyerhoff DJ. Chronic cigarette smoking modulates injury and short-term recovery of the medial temporal lobe in alcoholics. Psychiatry Res 2008;162:133–45.
[124] Pennington DL, Durazzo TC, Schmidt T, Mon A, Abe C, Meyerhoff DJ. The effects of chronic cigarette smoking on cognitive recovery during early abstinence from alcohol. Alcohol Clin Exp Res 2013;37:1220–7.
[125] Durazzo TC, Rothlind JC, Gazdzinski S, Banys P, Meyerhoff DJ. Chronic smoking is associated with differential neurocognitive recovery in abstinent alcoholic patients: a preliminary investigation. Alcohol Clin Exp Res 2007;31:1114–27.
[126] Durazzo TC, Tosun D, Buckley S, Gazdzinski S, Mon A, Fryer SL, et al. Cortical thickness, surface area, and volume of the brain reward system in alcohol dependence: relationships to relapse and extended abstinence. Alcohol Clin Exp Res 2011;35:1187–200.
[127] Durazzo TC, Pennington DL, Schmidt TP, Mon A, Abe C, Meyerhoff DJ. Neurocognition in 1-month-abstinent treatment-seeking alcohol-dependent individuals: interactive effects of age and chronic cigarette smoking. Alcohol Clin Exp Res 2013;37:1794–803.
[128] Durazzo TC, Rothlind JC, Gazdzinski S, Meyerhoff DJ. The relationships of sociodemographic factors, medical, psychiatric, and substance-misuse co-morbidities to neurocognition in short-term abstinent alcohol-dependent individuals. Alcohol 2008;42:439–49.
[129] Durazzo TC, Abadjian L, Kincaid A, Bilovsky-Muniz T, Boreta L, Gauger GE. The influence of chronic cigarette smoking on neurocognitive recovery after mild traumatic brain injury. J Neurotrauma 2013;30:1013–22.
[130] Petraglia AL, Maroon JC, Bailes JE. From the field of play to the field of combat: a review of the pharmacological management of concussion. Neurosurgery 2012;70:1520–33. discussion 33.
[131] Wilk JE, Bliese PD, Kim PY, Thomas JL, McGurk D, Hoge CW. Relationship of combat experiences to alcohol misuse among U.S. soldiers returning from the Iraq war. Drug Alcohol Depend 2010;108:115–21.
[132] Seet RC, Lee CY, Loke WM, Huang SH, Huang H, Looi WF, et al. Biomarkers of oxidative damage in cigarette smokers: which biomarkers might reflect acute versus chronic oxidative stress? Free Radic Biol Med 2011;50:1787–93.
[133] Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. Int J Environ Res Public Health 2009;6:445–62.
[134] Schulz JB, Lindenau J, Seyfried J, Dichgans J. Glutathione, oxidative stress and neurodegeneration. Eur J Biochem 2000;267:4904–11.
[135] Moriarty SE, Shah JH, Lynn M, Jiang S, Openo K, Jones DP, et al. Oxidation of glutathione and cysteine in human plasma associated with smoking. Free Radic Biol Med 2003;35:1582–8.
[136] Fowles J, Bates M, Noiton D. The chemical constituents in cigarettes and cigarette smoke: priorities for harm reduction. Porirua, New Zealand: Epidemiology and Toxicology Group, Institute of Environmental Science and Research Ltd, 2000. Available at: http://legacy.library.ucsf.edu/documentStore/s/v/h/svh93a00/Ssvh93a00.pdf. Accessed May 12, 2014.
[137] Gonthier B, Signorini-Allibe N, Soubeyran A, Eysseric H, Lamarche F, Barret L. Ethanol can modify the effects of certain free radical-generating systems on astrocytes. Alcohol Clin Exp Res 2004;28:526–34.
[138] Wu D, Cederbaum AI. Alcohol, oxidative stress, and free radical damage. Alcohol Res Health 2003;27:277–84.
[139] Vallett M, Tabatabaie T, Briscoe RJ, Baird TJ, Beatty WW, Floyd RA, et al. Free radical production during ethanol intoxication, dependence, and withdrawal. Alcohol Clin Exp Res 1997;21:275–85.
[140] Brooks PJ. Brain atrophy and neuronal loss in alcoholism: a role for DNA damage? Neurochem Int 2000;37:403–12.
[141] Pratico D. Prostanoid and isoprostanoid pathways in atherogenesis. Atherosclerosis 2008;201:8–16.
[142] Crews FT, Bechara R, Brown LA, Guidot DM, Mandrekar P, Oak S, et al. Cytokines and alcohol. Alcohol Clin Exp Res 2006;30:720–30.
[143] Volobouev LA, Giffard RG. Inflammation, mitochondria, and the inhibition of adult neurogenesis. J Neurosci Res 2011;89:1989–96.
[144] Guerri C, Pascual M. Mechanisms involved in the neurotoxic, cognitive, and neurobehavioral effects of alcohol consumption during adolescence. Alcohol 2010;44:15–26.
[145] Perricone C, De Carolis C, Perricone R. Glutathione: a key player in autoimmunity. Autoimmun Rev 2009;8:697–701.
[146] Crews FT, Nixon K. Mechanisms of neurodegeneration and regeneration in alcoholism. Alcohol Alcohol 2009;44:115–27.
[147] Khanna A, Guo M, Mehra M, Royal W 3rd. Inflammation and oxidative stress induced by cigarette smoke in Lewis rat brains. J Neuroimmunol 2013;254:69–75.
[148] Gill R, Tsung A, Billiar T. Linking oxidative stress to inflammation: toll-like receptors. Free Radic Biol Med 2010;48:1121–32.
[149] Enciu AM, Gherghiceanu M, Popescu BO. Triggers and effectors of oxidative stress at blood-brain barrier level: relevance for brain ageing and neurodegeneration. Oxid Med Cell Longev 2013;2013:297512.
[150] Kovacic P. Unifying mechanism for addiction and toxicity of abused drugs with application to dopamine and glutamate mediators: electron transfer and reactive oxygen species. Med Hypotheses 2005;65:90–6.
[151] Anbarasi K, Vani G, Balakrishna K, Devi CS. Effect of bacoside A on brain antioxidant status in cigarette smoke exposed rats. Life Sci 2006;78:1378–84.
[152] Chalela JA, Wolf RL, Maldjian JA, Kasner SE. MRI identification of early white matter injury in anoxic-ischemic encephalopathy. Neurology 2001;56:481–5.
[153] Mueller SG, Trabesinger AH, Boesiger P, Wieser HG. Brain glutathione levels in patients with epilepsy measured by in vivo (1)H-MRS. Neurology 2001;57:1422–7.
[154] Pratico D. The neurobiology of isoprostanes and Alzheimer's disease. Biochim Biophys Acta 2010;1801:930–3.
[155] Kochunov P, Thompson PM, Lancaster JL, Bartzokis G, Smith S, Coyle T, et al. Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: tract-based spatial statistics study of aging. Neuroimage 2007;35:478–87.
[156] Bartzokis G. Quadratic trajectories of brain myelin content: unifying construct for neuropsychiatric disorders. Neurobiol Aging 2004;25:49–62.
[157] Circu ML, Aw TY. Reactive oxygen species, cellular redox systems, and apoptosis. Free Radic Biol Med 2010;48:749–62.
[158] Halliwell B. Oxidative stress and neurodegeneration: where are we now? J Neurochem 2006;97:1634–58.

[159] Tsiara S, Elisaf M, Mikhailidis DP. Influence of smoking on predictors of vascular disease. Angiology 2003;54:507–30.
[160] Shields PG. Tobacco smoking, harm reduction, and biomarkers. J Natl Cancer Inst 2002;94:1435–44.
[161] Kurth T, Kase CS, Berger K, Schaeffner ES, Buring JE, Gaziano JM. Smoking and the risk of hemorrhagic stroke in men. Stroke 2003; 34:1151–5.
[162] Ryu JH, Colby TV, Hartman TE, Vassallo R. Smoking-related interstitial lung diseases: a concise review. Eur Respir J 2001; 17:122–32.
[163] Kuschner WG, D'Alessandro A, Wong H, Blanc PD. Dose-dependent cigarette smoking-related inflammatory responses in healthy adults. Eur Respir J 1996;9:1989–94.
[164] Talhout R, Schulz T, Florek E, van Benthem J, Wester P, Opperhuizen A. Hazardous compounds in tobacco smoke. Int J Environ Res Public Health 2011;8:613–28.
[165] Deveci S, Deveci F, Acik Y, Ozan A. The measurement of exhaled carbon monoxide in healthy smokers and non-smokers. Respir Med 2004;98:551–6.
[166] Alonso JR, Cardellach F, Casademont J, Miro O. Reversible inhibition of mitochondrial complex IV activity in PBMC following acute smoking. Eur Respir J 2004;23:214–8.
[167] Mazzone P, Tierney W, Hossain M, Puvenna V, Janigro D, Cucullo L. Pathophysiological impact of cigarette smoke exposure on the cerebrovascular system with a focus on the blood-brain barrier: expanding the awareness of smoking toxicity in an underappreciated area. Int J Environ Res Public Health 2010;7:4111–26.
[168] Giunta B, Deng J, Jin J, Sadic E, Rum S, Zhou H, et al. Evaluation of how cigarette smoke is a direct risk factor for Alzheimer's disease. Technol Innov 2012;14:39–48.
[169] Barr J, Sharma CS, Sarkar S, Wise K, Dong L, Periyakaruppan A, et al. Nicotine induces oxidative stress and activates nuclear transcription factor kappa B in rat mesencephalic cells. Mol Cell Biochem 2007;297:93–9.
[170] Anbarasi K, Vani G, Balakrishna K, Devi CS. Effect of bacoside A on membrane-bound ATPases in the brain of rats exposed to cigarette smoke. J Biochem Mol Toxicol 2005;19:59–65.
[171] Anbarasi K, Vani G, Balakrishna K, Devi CS. Creatine kinase isoenzyme patterns upon chronic exposure to cigarette smoke: protective effect of bacoside A. Vascul Pharmacol 2005; 42:57–61.
[172] Anbarasi K, Kathirvel G, Vani G, Jayaraman G, Shyamala Devi CS. Cigarette smoking induces heat shock protein 70 kDa expression and apoptosis in rat brain: modulation by bacoside A. Neuroscience 2006; 138:1127–35.
[173] Anbarasi K, Vani G, Devi CS. Protective effect of bacoside A on cigarette smoking-induced brain mitochondrial dysfunction in rats. J Environ Pathol Toxicol Oncol 2005;24:225–34.
[174] Rueff-Barroso CR, Trajano ET, Alves JN, Paiva RO, Lanzetti M, Pires KM, et al. Organ-related cigarette smoke-induced oxidative stress is strain-dependent. Med Sci Monit 2010;16:BR218–26.
[175] Ho YS, Yang X, Yeung SC, Chiu K, Lau CF, Tsang AW, et al. Cigarette smoking accelerated brain aging and induced pre-Alzheimer-like neuropathology in rats. PLoS One 2012;7:e36752.
[176] Das S, Gautam N, Dey SK, Maiti T, Roy S. Oxidative stress in the brain of nicotine-induced toxicity: protective role of Andrographis paniculata Nees and vitamin E. Appl Physiol Nutr Metab 2009; 34:124–35.
[177] Sonnen JA, Larson EB, Gray SL, Wilson A, Kohama SG, Crane PK, et al. Free radical damage to cerebral cortex in Alzheimer's disease, microvascular brain injury, and smoking. Ann Neurol 2009; 65:226–9.
[178] Kim SH, Kim JS, Shin HS, Keen CL. Influence of smoking on markers of oxidative stress and serum mineral concentrations in teenage girls in Korea. Nutrition 2003;19:240–3.
[179] Kim SH, Ensunsa JL, Zhu QY, Kim JS, Shin HS, Keen CL. An 18-month follow-up study on the influence of smoking on blood antioxidant status of teenage girls in comparison with adult male smokers in Korea. Nutrition 2004;20:437–44.
[180] Reichert V, Xue X, Bartscherer D, Jacobsen D, Fardellone C, Zolan P, et al. A pilot study to examine the effects of smoking cessation on serum markers of inflammation in women at risk for cardiovascular disease. Chest 2009;136:212–9.
[181] Bloomer RJ. Decreased blood antioxidant capacity and increased lipid peroxidation in young cigarette smokers compared to non-smokers: impact of dietary intake. Nutr J 2007;6:39.
[182] Box HC, O'Connor RJ, Patrzyc HB, Iijima H, Dawidzik JB, Freund HG, et al. Reduction in oxidatively generated DNA damage following smoking cessation. Tob Induc Dis 2011;9:5.
[183] Reilly M, Delanty N, Lawson JA, FitzGerald GA. Modulation of oxidant stress in vivo in chronic cigarette smokers. Circulation 1996;94:19–25.
[184] Milne GL, Musiek ES, Morrow JD. F2-isoprostanes as markers of oxidative stress in vivo: an overview. Biomarkers 2005;10(Suppl 1):S10–23.
[185] Slemmer JE, Shacka JJ, Sweeney MI, Weber JT. Antioxidants and free radical scavengers for the treatment of stroke, traumatic brain injury and aging. Curr Med Chem 2008;15:404–14.
[186] Gawryluk JW, Wang JF, Andreazza AC, Shao L, Young LT. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. Int J Neuropsychopharmacol 2011;14:123–30.
[187] Townsend DM, Tew KD, Tapiero H. The importance of glutathione in human disease. Biomed Pharmacother 2003;57:145–55.
[188] Srinivasan R, Ratiney H, Hammond-Rosenbluth KE, Pelletier D, Nelson SJ. MR spectroscopic imaging of glutathione in the white and gray matter at 7 T with an application to multiple sclerosis. Magn Reson Imaging 2010;28:163–70.
[189] Kaiser LG, Marjanska M, Matson GB, Iltis I, Bush SD, Soher BJ, et al. (1)H MRS detection of glycine residue of reduced glutathione in vivo. J Magn Reson 2010;202:259–66.
[190] Wood SJ, Berger GE, Wellard RM, Proffitt TM, McConchie M, Berk M, et al. Medial temporal lobe glutathione concentration in first episode psychosis: a 1H-MRS investigation. Neurobiol Dis 2009;33:354–7.
[191] Lu SC. Regulation of glutathione synthesis. Mol Aspects Med 2009; 30:42–59.
[192] Dringen R, Hirrlinger J. Glutathione pathways in the brain. Biol Chem 2003;384:505–16.
[193] Cruz R, Almaguer Melian W, Bergado Rosado JA. Glutathione in cognitive function and neurodegeneration. Rev Neurol 2003; 36:877–86.
[194] Reichelt KL, Fonnum F. Subcellular localization of N-acetyl-aspartyl-glutamate, N-acetyl-glutamate and glutathione in brain. JNeurochem 1969;16:1409–16.
[195] Meister A, Anderson ME. Glutathione. Annu Rev Biochem 1983; 52:711–60.
[196] Mendez-Alvarez E, Soto-Otero R, Sanchez-Sellero I, Lopez-Rivadulla Lamas M. In vitro inhibition of catalase activity by cigarette smoke: relevance for oxidative stress. J Appl Toxicol 1998; 18:443–8.
[197] Panda K, Chattopadhyay R, Chattopadhyay DJ, Chatterjee IB. Vitamin C prevents cigarette smoke-induced oxidative damage in vivo. Free Radic Biol Med 2000;29:115–24.
[198] Northrop-Clewes CA, Thurnham DI. Monitoring micronutrients in cigarette smokers. Clin Chim Acta 2007;377:14–38.
[199] Abdul-Rasheed OF, Al-Rubayee WT. Effects of cigarette smoking on lipid peroxidation and antioxidant status in Iraqi men at Baghdad city. International Journal of Basic and Applied Sciences 2012; 2:47–50.
[200] Almansa I, Fernandez A, Garcia-Ruiz C, Muriach M, Barcia JM, Miranda M, et al. Brain mitochondrial alterations after chronic alcohol consumption. J Physiol Biochem 2009;65:305–12.
[201] Pratico D, Clark CM, Liun F, Rokach J, Lee VY, Trojanowski JQ. Increase of brain oxidative stress in mild cognitive impairment: a

possible predictor of Alzheimer disease. Arch Neurol 2002; 59:972–6.
[202] Swerdlow RH. Alzheimer's disease pathologic cascades: who comes first, what drives what. Neurotox Res 2012;22:182–94.
[203] Mondragon-Rodriguez S, Perry G, Zhu X, Moreira PI, Acevedo-Aquino MC, Williams S. Phosphorylation of tau protein as the link between oxidative stress, mitochondrial dysfunction, and connectivity failure: implications for Alzheimer's disease. Oxid Med Cell Longev 2013;2013:940603.
[204] Tamagno E, Guglielmotto M, Aragno M, Borghi R, Autelli R, Giliberto L, et al. Oxidative stress activates a positive feedback between the gamma- and beta-secretase cleavages of the beta-amyloid precursor protein. J Neurochem 2008;104:683–95.
[205] Tan JL, Li QX, Ciccotosto GD, Crouch PJ, Culvenor JG, White AR, et al. Mild oxidative stress induces redistribution of BACE1 in non-apoptotic conditions and promotes the amyloidogenic processing of Alzheimer's disease amyloid precursor protein. PLoS One 2013; 8:e61246.
[206] Cataldo JK, Glantz SA. Smoking cessation and Alzheimer's disease: facts, fallacies and promise. Expert Rev Neurother 2010;10:629–31.
[207] Moreno-Gonzalez I, Estrada LD, Sanchez-Mejias E, Soto C. Smoking exacerbates amyloid pathology in a mouse model of Alzheimer's disease. Nat Commun 2013;4:1495.
[208] Benowitz NL, Hukkanen J, Jacob P 3rd. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol 2009; 192:29–60.
[209] Hellstrom-Lindahl E, Mousavi M, Ravid R, Nordberg A. Reduced levels of Abeta 40 and Abeta 42 in brains of smoking controls and Alzheimer's patients. Neurobiol Dis 2004;15:351–60.
[210] Nordberg A, Hellstrom-Lindahl E, Lee M, Johnson M, Mousavi M, Hall R, et al. Chronic nicotine treatment reduces beta-amyloidosis in the brain of a mouse model of Alzheimer's disease (APPsw). J Neurochem 2002;81:655–8.
[211] Mansvelder HD, McGehee DS. Cellular and synaptic mechanisms of nicotine addiction. J Neurobiol 2002;53:606–17.
[212] Mudo G, Belluardo N, Fuxe K. Nicotinic receptor agonists as neuroprotective/neurotrophic drugs. Progress in molecular mechanisms. J Neural Transm 2007;114:135–47.
[213] Yakel JL. Cholinergic receptors: functional role of nicotinic ACh receptors in brain circuits and disease. Pflugers Arch 2013; 465:441–50.
[214] Buckingham SD, Jones AK, Brown LA, Sattelle DB. Nicotinic acetylcholine receptor signalling: roles in Alzheimer's disease and amyloid neuroprotection. Pharmacol Rev 2009;61:39–61.
[215] Ulrich J, Johannson-Locher G, Seiler WO, Stahelin HB. Does smoking protect from Alzheimer's disease? Alzheimer-type changes in 301 unselected brains from patients with known smoking history. Acta Neuropathol 1997;94:450–4.
[216] Perry E, Martin-Ruiz C, Lee M, Griffiths M, Johnson M, Piggott M, et al. Nicotinic receptor subtypes in human brain ageing, Alzheimer and Lewy body diseases. Eur J Pharmacol 2000;393:215–22.
[217] Court JA, Johnson M, Religa D, Keverne J, Kalaria R, Jaros E, et al. Attenuation of Abeta deposition in the entorhinal cortex of normal elderly individuals associated with tobacco smoking. Neuropathol Appl Neurobiol 2005;31:522–35.
[218] Hellstrom-Lindahl E, Moore H, Nordberg A. Increased levels of tau protein in SH-SY5Y cells after treatment with cholinesterase inhibitors and nicotinic agonists. J Neurochem 2000;74:777–84.
[219] Utsuki T, Shoaib M, Holloway HW, Ingram DK, Wallace WC, Haroutunian V, et al. Nicotine lowers the secretion of the Alzheimer's amyloid beta-protein precursor that contains amyloid beta-peptide in rat. J Alzheimers Dis 2002;4:405–15.
[220] Lahiri DK, Utsuki T, Chen D, Farlow MR, Shoaib M, Ingram DK, et al. Nicotine reduces the secretion of Alzheimer's beta-amyloid precursor protein containing beta-amyloid peptide in the rat without altering synaptic proteins. Ann N Y Acad Sci 2002; 965:364–72.
[221] Srivareerat M, Tran TT, Salim S, Aleisa AM, Alkadhi KA. Chronic nicotine restores normal Abeta levels and prevents short-term memory and E-LTP impairment in Abeta rat model of Alzheimer's disease. Neurobiol Aging 2011;32:834–44.
[222] Echeverria V, Zeitlin R, Burgess S, Patel S, Barman A, Thakur G, et al. Cotinine reduces amyloid-beta aggregation and improves memory in Alzheimer's disease mice. J Alzheimers Dis 2011;24:817–35.
[223] Oddo S, Caccamo A, Green KN, Liang K, Tran L, Chen Y, et al. Chronic nicotine administration exacerbates tau pathology in a transgenic model of Alzheimer's disease. Proc Natl Acad Sci U S A 2005; 102:3046–51.
[224] Yang YM, Liu GT. Injury of mouse brain mitochondria induced by cigarette smoke extract and effect of vitamin C on it in vitro. Biomed Environ Sci 2003;16:256–66.
[225] Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh compound-B. Ann Neurol 2004;55:306–19.
[226] Ni R, Marutle A, Nordberg A. Modulation of alpha7 nicotinic acetylcholine receptor and fibrillar amyloid-beta interactions in Alzheimer's disease brain. J Alzheimers Dis 2013;33:841–51.
[227] Abreu-Villaca Y, Seidler FJ, Tate CA, Slotkin TA. Nicotine is a neurotoxin in the adolescent brain: critical periods, patterns of exposure, regional selectivity, and dose thresholds for macromolecular alterations. Brain Res 2003;979:114–28.
[228] Slotkin TA. Nicotine and the adolescent brain: insights from an animal model. Neurotoxicol Teratol 2002;24:369–84.
[229] Oz M, Lorke DE, Yang KH, Petroianu G. On the interaction of beta-amyloid peptides and alpha7-nicotinic acetylcholine receptors in Alzheimer's disease. Curr Alzheimer Res 2013;10:618–30.
[230] Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 2011;305:275–83.
[231] Landau SM, Breault C, Joshi AD, Pontecorvo M, Mathis CA, Jagust WJ, et al. Amyloid-beta imaging with Pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. J Nucl Med 2013;54:70–7.
[232] Tosun D, Schuff N, Truran-Sacrey D, Shaw LM, Trojanowski JQ, Aisen P, et al. Relations between brain tissue loss, CSF biomarkers, and the ApoE genetic profile: a longitudinal MRI study. Neurobiol Aging 2010;31:1340–54.
[233] Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, et al. Neuropathology of older persons without cognitive impairment from two community-based studies. Neurology 2006; 66:1837–44.
[234] Small GW, Siddarth P, Kepe V, Ercoli LM, Burggren AC, Bookheimer SY, et al. Prediction of cognitive decline by positron emission tomography of brain amyloid and tau. ArchNeurol 2012;69:215–22.
[235] Villemagne VL, Pike KE, Chetelat G, Ellis KA, Mulligan RS, Bourgeat P, et al. Longitudinal assessment of Abeta and cognition in aging and Alzheimer disease. Ann Neurol 2011;69:181–92.
[236] Corrada MM, Brookmeyer R, Paganini-Hill A, Berlau D, Kawas CH. Dementia incidence continues to increase with age in the oldest old: the 90+ study. Ann Neurol 2010;67:114–21.
[237] Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013;368:341–50.
[238] Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 2012;11:1006–12.
[239] Filion KB, Luepker RV. Cigarette smoking and cardiovascular disease: lessons from Framingham. Global Heart 2013;8:35–41.
[240] Gootjes L, Teipel SJ, Zebuhr Y, Schwarz R, Leinsinger G, Scheltens P, et al. Regional distribution of white matter hyperintensities in vascular dementia, Alzheimer's disease and healthy aging. Dement Geriatr Cogn Disord 2004;18:180–8.
[241] Bhargava D, Weiner MF, Hynan LS, Diaz-Arrastia R, Lipton AM. Vascular disease and risk factors, rate of progression, and survival in Alzheimer's disease. J Geriatr Psychiatry Neurol 2006;19:78–82.

[242] Jahnke SA, Hoffman KM, Haddock CK, Long MA, Williams LN, Lando HA, et al. Military tobacco policies: the good, the bad, and the ugly. Mil Med 2011;176:1382–7.
[243] Weiner MW, Friedl KE, Pacifico A, Chapman JC, Jaffee MS, Little DM, et al. Military risk factors for Alzheimer's disease. Alzheimers Dement 2013;9:445–51.
[244] Moylan S, Jacka FN, Pasco JA, Berk M. How cigarette smoking may increase the risk of anxiety symptoms and anxiety disorders: a critical review of biological pathways. Brain Behav 2013;3:302–26.
[245] DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Carmelli D. Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. Arch Neurol 2001;58:643–7.
[246] Ravaglia G, Forti P, Maioli F, et al. Conversion of mild cognitive impairment to dementia: predictive role of mild cognitive impairment subtypes and vascular risk factors. Dement Geriatr Cogn Disord 2006;21:51–8.
[247] Petersen RC. Early diagnosis of Alzheimer's disease: is MCI too late? Curr Alzheimer Res 2009;6:324–30.
[248] Xia CF, Arteaga J, Chen G, Gangadharmath U, Gomez LF, Kasi D. [(18)F]T807, a novel tau positron emission tomography imaging agent for Alzheimer's disease. Alzheimers Dement 2013;9:666–76.
[249] Kaiser LG, Schuff N, Cashdollar N, Weiner MW. Age-related glutamate and glutamine concentration changes in normal human brain: 1H MR spectroscopy study at 4 T. Neurobiol Aging 2005;26:665–72.
[250] Pratico D, Clark CM, Lee VM, Trojanowski JQ, Rokach J, FitzGerald GA. Increased 8,12-iso-iPF2alpha-VI in Alzheimer's disease: correlation of a noninvasive index of lipid peroxidation with disease severity. Ann Neurol 2000;48:809–12.
[251] Handoko M, Grant M, Kuskowski M, Zahs KR, Wallin A, Blennow K, et al. Correlation of specific amyloid-beta oligomers with tau in cerebrospinal fluid from cognitively normal older adults. JAMA Neurol 2013;70:594–9.
[252] Honig LS, Tang MX, Albert S, Costa R, Luchsinger J, Manly J, et al. Stroke and the risk of Alzheimer disease. Arch Neurol 2003;60:1707–12.
[253] Erkinjuntti T, Roman G, Gauthier S, Feldman H, Rockwood K. Emerging therapies for vascular dementia and vascular cognitive impairment. Stroke 2004;35:1010–7.
[254] Konno S, Meyer JS, Terayama Y, Margishvili GM, Mortel KF. Classification, diagnosis and treatment of vascular dementia. Drugs Aging 1997;11:361–73.
[255] Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. Ann Intern Med 2010;152:10–7.
[256] Bernstein SL, Yu S, Post LA, Dziura J, Rigotti NA. Undertreatment of tobacco use relative to other chronic conditions. Am J Public Health 2013;103:e59–65.
[257] Eisenberg MJ, Filion KB, Yavin D, Belisle P, Mottillo S, Joseph L, et al. Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. CMAJ 2008;179:135–44.
[258] Vos SJ, Xiong C, Visser PJ, Jasielec MS, Hassenstab J, Grant EA, et al. Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study. Lancet Neurol 2013;12:957–65.
[259] Chrysohoou C, Panagiotakos DB, Pitsavos C, Zeimbekis A, Zampelas A, Papademetriou L, et al. The associations between smoking, physical activity, dietary habits and plasma homocysteine levels in cardiovascular disease-free people: the 'ATTICA' study. Vasc Med 2004;9:117–23.