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Effects of Cigarette Smoking on Neurocognitive Performance in Dementia Patients

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Effects of Cigarette Smoking on Neurocognitive Performance in Dementia Patients

by

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Each person whose signature appears below certifies that this thesis in his/her opinion is adequate, in scope and quality, as a thesis for the degree Doctor of Philosophy.

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ABBREVIATIONS

AD	Alzheimer's disease
CVLT-II	California Verbal Learning Test – second edition
DKEFS	Delis-Kaplan Executive Function System
DLB	dementia with Lewy bodies
FTD	frontotemporal dementia
LRP	Lewy-related pathology
MCI	mild cognitive impairment
MDD	Major Depressive Disorder
MMSE	Mini-Mental State Examination
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NOS	not otherwise specified
RAVLT	Rey Auditory Verbal Learning
SPMSQ	Short Portable Mental Status Questionnaire
VaD	vascular dementia
WAIS-III	Wechsler Adult Intelligence Scale – third edition

ABSTRACT OF THE DISSERTATION

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Dementia has become a serious problem worldwide due to the rapidly increasing incidence rate and the lack of effective treatments that cure or slow disease progression, and thus. prevention is crucial. Some studies suggests that cigarette smoking may increase the risk of developing dementia, but others suggest that smoking may have a neuroprotective effect. To clarify our understanding of the relationship between cigarette smoking and dementia, this study examined the effects of smoking on multiple cognitive domains via secondary data analysis of a sample consisting of 54% female subjects with an average age of 58±13 years. Measures of executive function, verbal memory, attention, and processing speed were administered to two groups of dementia patients, never smokers and current/former smokers. Hierarchical linear regression analysis was used to test smoking status as a predictor of functioning in each of these four cognitive domains after controlling for potentially confounding factors such as cardiovascular disease, type 2 diabetes, depression, anxiety, and substance use. No relationship was found between smoking, any of the covariates, and cognitive performance in any domain. Future research should utilize a prospective design and administer neuropsychological

batteries to participants in early or middle adulthood who have not been yet diagnosed with dementia.

CHAPTER ONE

INTRODUCTION

Dementia has become a serious worldwide problem, as it is the leading cause of functional limitation among older adults (APA, 2012). In developed countries, the prevalence of dementia ranges from 5% to 10% in individuals over age 65 and affects as many as 50% of the population age 85 and older (Rincon & Wright, 2013). In the United States alone, one in three adults will develop dementia or suffer a stroke in their lifetime. Even more startling is the fact that the prevalence of Alzheimer's disease (AD), an illness characterized by plaques and tangles in the brain, early onset memory impairment, deficits in naming and visuoconstruction abilities, and social withdrawal (Schoenberg & Duff, 2011), doubles every 4.3 years. Additionally, AD is currently the sixth leading cause of death in the U.S. and the fifth leading cause in people over age 65. (Alzheimer's Association, 2012). Perhaps the most disheartening fact concerning dementia is that among the top 10 leading causes of death in the U.S., AD is the only one without a cure, a course of prevention, or even a way to slow its progression (Alzheimer's Association, 2012). Moreover, the current Alzheimer's disease literature posits that the complex pathophysiological process of AD begins years, and perhaps even a decade or more, before the symptoms manifest; therefore, prevention is crucial (Sperling, Karlawish, & Johnson, 2013).

Similarly, the prevalence of vascular dementia (VaD), a disease typified by early deficits in attention, executive function, processing speed, and visuoconstruction skills (Schoenberg & Duff, 2011), doubles every 5.3 years (Rincon & Wright, 2013). Unfortunately, there is a lack of literature on the rate of increase in prevalence of

dementia with Lewy bodies (DLB) or frontotemporal dementia (FTD). Estimates of the prevalence of DLB, an illness notable for abnormal protein aggregates known as Lewy Bodies, motor impairment, fluctuating mental clarity, and vivid visual hallucinations of people or animals (Schoenberg & Duff, 2011), are as high as 5% in the general population and 30.5% of all dementia cases, rendering DLB the second most common type of dementia after AD (Zaccia, McCracken, & Brayne, 2005). Epidemiological data also suggest that FTD, a disease characterized by early onset of executive dysfunction and personality changes and impairments in confrontation naming and verbal fluency (Schoenberg & Duff, 2011), has an incidence and prevalence similar to AD as a common cause of early onset dementia in individuals younger than 65 years of age (Rabinovici & Miller, 2010). These statistics, in conjunction with the prediction that by the year 2030 the portion of the U.S. population over age 65 will double, suggest that health care costs associated with dementia will increase substantially (Hurd et al., 2013). Given that there are no cures for dementia in the foreseeable future, prevention is the key, but it is not possible unless the risk factors of dementia are identified.

A number of factors thought to increase the risk of dementia have been described in the literature. The risk factors most commonly discussed are age, family history, hypertension, high cholesterol, diabetes, depression, cigarette smoking, and alcohol use (Mayo Clinic Staff, 2014). While age and family history cannot be changed, the other factors can be avoided, prevented, or controlled by lifestyle changes, such as improvements in diet and exercise, quitting smoking, and/or adhering to treatment with medication. In particular, cigarettes are probably the most significant source of chemical toxins in humans. They are the leading preventable cause of death in the United States

(U.S. Department of Health and Human Services, 2014) and have been forecasted by the World Health Organization as being the cause of death for approximately nine million people per year globally by the year 2030 (Swan & Lessov-Schlaggar, 2007). Smoking is associated with an increased incidence of cardiovascular disease including cerebrovascular disease, coronary heart disease, and vascular diseases.

Given the association between smoking and cardiovascular disease, and the link between cardiovascular disease and increased risk for dementia (Peters, 2012), it is not surprising that a number of studies have suggested a link between cigarette smoking and AD and VaD (Peters et al., 2008; Rincon & Wright, 2013; Rusanen et al., 2011; Swan & Lessov-Schlaggar, 2007). In contrast, a study examining the potential relationship between cigarette smoking and the risk of neuropathologic changes of Lewy-related pathology (LRP) in the brain (Tsuang et al., 2009) found that smoking was associated with significantly *reduced* relative risk for LRP, which is characteristic of DLB and sometimes found in cases of AD. However, this is only one study, and more investigations into the relationship between smoking and DLB are necessary to determine if tobacco reduces the risk of DLB. In the case of frontotemporal dementia, very little is known about the risk factors associated with this dementia as compared with AD and VaD (Kalkonde et al., 2012). Therefore, we need a better understanding of cigarette smoking as a potential risk factor for the various types of dementia.

Cardiovascular damage is not the only way in which smoking may be connected to the development of a neurodegenerative disorder. Many of the more than 4,700 constituents of cigarette smoke are associated with brain toxicity, such as hydrogen cyanide, arsenic, and vinyl chloride, a chemical thought to be connected with brain

cancer (Fowles & Dybing, 2003). Especially problematic are the heavy metals present in tobacco smoke, such as lead and cadmium, which in recent epidemiological studies have been shown to be a risk factor for AD pathology (i.e., plaques and tangles) via an increase in oxidative stress (Bernhard, Rossmann, & Wick, 2005; Liu et al., 2006). Lifetime exposure to lead is cross-sectionally associated with cognitive decline in executive functioning, verbal memory and learning, visual learning, processing speed, language, and visual construction, as well as decreases in brain volume and increases in the number of white matter lesions (Shih et al., 2006). Cigarettes are also a significant source of oxidative stress through direct exposure, the inflammatory immune response pathway, and glutamate neurotoxicity (Swan & Lessov-Schlaggar, 2007). Oxidative stress refers to cell injury mediated by reactive oxygen and nitrogen species. Oxidative stress is currently thought to play an important part in the neurodegenerative process of AD as the resulting damage has been reported extensively in AD patients (Practicò, 2008, Wang et al., 2013). The reactive species, unavoidable byproducts of normal metabolic reactions, are generally chemically unstable and highly reactive. When an excess of these reactive species are present in a biological system they are capable of oxidizing DNA, RNA, protein, and lipids, resulting in cell damage (Wang et al., 2013).

Given all of the known toxic effects of cigarette smoke on the human body, the relationship between smoking and cognitive decline/dementia would seem to be intuitively obvious, but that is not the case. The literature in this area is mixed, with some studies suggesting an increased risk for dementia and others suggesting that tobacco actually protects against dementia. For example, a number of prospective studies have found a significant association between increased risk of dementia and current cigarette

smoking (Hirayama et al., 1992; Juan et al., 2004; Launer et al., 1999; Merchant et al., 1999; Ott et al., 1998; Reitz et al., 2005). Additional prospective studies have also demonstrated a significant link between smoking and increased risk of cognitive decline that does not meet the DSM-IV criteria for dementia (Aggarwal et al., 2006; Collins et al., 2009; Galanis et al., 1997; Nooyens et al., 2008; Ott et al., 2004; Reitz et al., 2005; Sabia et al., 2008). Finally, another prospective study conducted on women participants found that avoiding cigarette smoking significantly predicted maintenance of cognitive function (Barnes et al., 2007).

While the majority of prospective studies have demonstrated a positive association between smoking and dementia, a prospective study conducted in Taiwan showed that cigarette smoking decreased the risk of cognitive decline (Wang et al., 2010). The results of this study may be due to participant attrition, which was attributed to death or loss to follow-up. The literature suggests that smoking-related mortality may mask the association between Alzheimer's disease and smoking (Chang, Zhao, Lee, & Ganguli, 2012; Kryscio et al., 2013). Two additional prospective studies have suggested that there is no link between smoking and dementia. A prospective analysis from the Canadian Study of Health and Aging found that smoking was not related to the risk of AD (Lindsay et al., 2002). Another prospective study of wine and tobacco consumption suggested that smoking is associated with a decreased risk of decline in attention and visuospatial functioning (Leibovici et al., 1999).

In contrast, a number of case-control studies conducted in the 1980s and early 1990s showed that smoking might *protect* individuals from the onset of AD. Lee (1994) performed a meta-analysis on 13 of these case-control studies and found that there was a

40% reduction in risk of AD among cigarette smokers. Several articles have posited that the seemingly counterintuitive results may be due to biases in study design (Kukull, 2001; Anstey et al., 2007; Cataldo, Prochaska, & Glantz, 2010). Case-control studies can be biased if the way in which cases and controls are identified and enrolled is associated with smoking history. These types of studies can also be biased if smoking history is obtained differently for cases and controls. Recall bias is also a well-known problem of case-control studies. For the smoking case-control studies, recall bias results from discrepancies in the reporting of smoking status by case and control participants (Kukull, 2001). Unsurprisingly, a meta-analysis of the case-control studies conducted by Lee (1994), who was a paid statistical consultant for the tobacco industry (Cataldo, Prochaska, & Glantz, 2010), observed the same trend as the original case-control studies. Regardless of Lee's admonition that "prospective studies are often more scientifically valid than case-control studies," the tobacco industry continued to fund case-control studies. It should also be noted that a meta-analysis performed by Cataldo, Prochaska, and Glantz (2010) found that even after controlling for study design, tobacco industry affiliation was associated with findings of decreased risk of AD in smokers. Given the conflicting current literature and the urgent need to ascertain dementia risk factors, it is important to determine the nature of the relationship between smoking and dementia as well as the cognitive domains that are affected by cigarette smoking.

Studies examining the level of risk of cognitive impairment or decline among former smokers compared to never smokers have also produced equivocal results. One reason for these mixed results is that few of the studies investigating the relationship between smoking and risk of dementia or cognitive decline differentiated between long-

term ex-smokers and recent ex-smokers (Sabia et al., 2012). A number of studies have found that ex-smokers either have similar declines in cognition or slower declines than never smokers due to the ambiguous definition of former smokers (Anstey et al., 2007; Peters et al., 2008; Sabia et al., 2012). The studies that differentiated between the two levels of ex-smokers found that long-term former smokers exhibited similar risk of cognitive impairment as never smokers (Galanis et al., 1997; Sabia et al., 2012). Almeida et al. (2011) found that the cognitive scores of chronic smokers (i.e., smoked a minimum of five cigarettes per day for a continuous period of 12 months or more throughout their lifetime) who quit smoking for a minimum of 18 months were comparable to those of never smokers. In contrast, it is possible that long-term former smokers' risk may be reduced to the level of never smokers' risk, although more research is needed to clarify this. The tobacco literature indicates that many of the body's systems damaged by cigarette smoking return to the condition of a nonsmoker when the smoker has abstained from smoking for a long enough duration (e.g., risk of coronary heart disease is the same as for nonsmokers after 15 years of abstinence; Abrams et al., 2003). Given that the heart and lungs heal, and a number of the studies of the relationship between smoking and cognition found no differences between the cognition of never smokers and long-term ex-smokers (Galanis et al., 1997; Sabia et al., 2012), it is possible that the brain heals as well or that a reduction in cardiovascular risk translates into a reduction in the risk for dementia.

The variability in the procedures utilized for testing cognition is another potential source of inconsistent outcomes in studies on the link between smoking and dementia. A number of studies (Juan et al., 2004; Ott et al., 2004; Wang et al., 2010) measured

cognitive decline using only the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) or the Short Portable Mental Status Questionnaire (SPMSQ; Pfeiffer, 1975). The MMSE and SPMSQ both have good specificity, but limited sensitivity (Lezak, 2004). The MMSE is most effective at distinguishing participants with moderate to severe cognitive deficits from control participants, but less effective at distinguishing control participants from those with mild deficits. Unlike many neuropsychological tests, these screening measures use a cutoff score rather than comparing each participant's score with the scores of other individuals the same age. In the case of the MMSE, a cut-off score of 24 is applied without accounting for potential differences due to the participant's age or level of education, which are factors known to affect measures of cognition. Furthermore, using a cut-off of 24 may lead to incorrectly classifying a participant with subtle or focal cognitive deficits. The lack of sensitivity of these measures and the use of cutoff scores is problematic when studying the possible relationship between smoking and dementia because of the risk of type II errors. Screening measures such as the MMSE are more likely to fail to detect dementia, especially early in the disease process, than a measure with good sensitivity that is normed by age and education level.

As with most brief screening instruments, the MMSE and SPMSQ are affected by age (Lezak, 2004). For example, in a sample of community-dwelling participants, the average number of correct items on the SPMSQ dropped from 7.8 among participants ages 65 to 69 to 6.05 among participants ages 85 to 89 (Scherr et al., 1988). Given that cognition declines with age even in healthy individuals, the scores for ages 70 to 97 are likely to be lower than those for ages 18 to 69 (Soubelet & Salthouse, 2011) on a measure

such as the MMSE, regardless of health and lifestyle factors. These age effects may make it difficult to detect differences in cognitive functioning due to smoking because a study with an age range of 55 to 70 is likely to produce different results compared to a study with an age range of 65 to 80, regardless of whether participants are current smokers. Another problem with studies using single, gross measures of cognitive functioning such as the MMSE is that cognitive impairment is a multifaceted phenomenon and cannot be accurately determined from the results of a single test (Lezak, 2004).

Another limitation of existing studies on the relationship between dementia and smoking is that they have used computerized neuropsychological tests (Paul et al., 2006), which have the advantage of being administered to all participants in exactly the same way, as well as not requiring trained neuropsychologists for administration. However, given the absence of a qualified neuropsychologist and that the participants are limited to pushing keys to register their answers on a computer test, potential cognitive deficits are determined solely through quantitative methods. Subtle or focal deficits are often missed without the observations of trained evaluators (Lezak, 2004). In addition, within a group of elderly participants there are apt to be a number of participants who have little or no computer experience; their unfamiliarity and potential discomfort with the technology may affect their test scores. Therefore, the lack of significant differences between current smokers and never or former smokers in these studies may be due to participants in both groups lacking familiarity with computers or experiencing computer related anxiety (Lezak, 2004). Given the limitations of using brief screening instruments and computerized testing to measure cognitive impairment in smokers, it is important that future studies use more sensitive and comprehensive testing batteries.

The majority of studies on the relationship between smoking and dementia were not able to ascertain the specific cognitive functions affected by cigarette smoking due to their use of brief screening measures. The investigations that utilized more comprehensive batteries to determine participant eligibility did not describe the cognitive deficits associated with smoking. Therefore, a brief search of the literature on the relationship between smoking and cognitive function was conducted to determine which areas of cognitive function might be most impaired due to smoking. These studies have demonstrated an association between current smoking and cognitive decline in four cognitive domains: executive function, verbal memory, attention, and information processing speed (Arntzen et al., 2011; Dregan, Stewart, & Gulliford, 2012; Sabia et al., 2009; Starr et al., 2007). For example, Dregan, Steward, and Gulliford (2012) investigated the relationship between cardiovascular risk factors, including smoking, blood pressure, cholesterol levels, and BMI, and cognitive decline in individuals age 50 and older who participated in the English Longitudinal Study of Aging. Cognition was measured in terms of verbal memory, and executive function was measured in terms of verbal fluency. Smokers were divided into two groups: never smokers or ex-smokers and current smokers. The study found that cigarette smoking was the most consistent vascular risk predictor for cognitive decline across all outcomes. An earlier longitudinal study (Whitehall II Study; Sabia et al., 2009) examined the association between health behaviors such as smoking, alcohol consumption, physical activity, and diet, and cognition in late midlife. The cognitive domains evaluated were again verbal memory and executive function; however, this study measured abstract reasoning as well as verbal fluency. The results suggested that the greater the exposure to smoking across midlife,

the higher the odds that the verbal memory and executive function of participants was poor. While it is important to determine whether or not an association exists between smoking and cognitive function, future studies need to utilize multiple measures and assess the effects of smoking across all cognitive domains in order to gain a greater understanding of the ways in which cigarette smoke affects the human brain.

In addition to increasing the breadth and sensitivity of measures of cognitive function, it is important for future studies on the relationship between cigarette smoking and dementia to control for potential confounding variables. There are several likely candidates, including cardiovascular disease, type 2 diabetes, substance use, depression, and anxiety. Cardiovascular disease and diabetes are well-known risk factors for vascular dementia, Alzheimer's disease, and cognitive decline (Blom, Emmelot-Vonk, & Koek, 2013; Ng, Turek, & Hakim, 2013; Luchsinger, 2012). Epidemiologic studies have also shown that cigarette smoking increases the incidence of myocardial infarction and coronary artery disease (Ambrose & Barua, 2004). Research indicates that type 2 diabetes is also associated with both cognitive decline and cigarette smoking. Specifically, a number of studies have reported an association between type 2 diabetes and dementia, including AD and VaD (Roberts et al., 2013). A longitudinal cohort study of 800 older participants found that the participants diagnosed with type 2 diabetes had a 65% higher risk of incidence than those who were not diagnosed with diabetes (Arvanitakis et al., 2004). Additionally, a large number of studies have found an association between active cigarette smoking and increased incidence of type 2 diabetes (Willi et al., 2007).

Depression and anxiety are also associated with both cognitive decline and cigarette smoking (Brady, Haynes, Hartwell, & Killeen, 2013; Holma et al., 2013). In

older adults, mild depression appears to be associated with subtle weaknesses in visual memory and nonverbal aspects of general intelligence. However, older adults with moderate to severe depression demonstrate mild weaknesses in information processing speed and executive skills (Boone et al., 1995). Depression is not the only disorder commonly diagnosed in older adults; anxiety is also fairly prevalent in this population especially individuals with mild cognitive impairment (MCI). An increasing body of research has shown an association between anxiety and declines in cognitive function in older adults. This research suggests that older adults with clinical levels of anxiety have poorer global cognitive function, episodic memory, and aspects of executive function such as set shifting as compared to non-anxious age-matched controls (Pietrzack et al., 2012).

According to the literature on the association between nicotine dependence and psychiatric disorders, approximately 50% of daily smokers have a history of a psychiatric disorder and they smoke a disproportionately large percentage of the overall number of cigarettes consumed (Grover, Goodwin, & Zvolensky, 2012). Moreover, individuals who successfully quit smoking have fewer lifetime depression diagnoses and depressive symptoms than those who are unsuccessful quitters and current smokers (Jamal, Van der Does, Cuijpers, & Penninx, 2012). Current smokers with a diagnosis of Major Depressive Disorder (MDD) have more difficulty quitting than smokers who do not meet the criteria for MDD and are more likely to be heavy smokers. Furthermore, the severity of depressive symptoms is associated with the number of days smoked and the number of cigarettes smoked per day. There also appears to be a bi-directional relationship between nicotine dependence and anxiety disorders, as the research has found that smoking may

result in increased anxiety, and individuals experiencing increased levels of anxiety are more likely to smoke (Moylan, Jacka, Pasco, & Berk, 2013). In fact, nicotine dependent individuals are more than twice as likely to develop an anxiety disorder than any other psychiatric disorder. Additionally, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) found that the 12-month prevalence rates of nicotine dependence were elevated in individuals with panic disorder (Brady, Haynes, Hartwell, & Killeen, 2013).

Chronic substance use has also been shown to be associated with cognitive impairment and is highly comorbid with tobacco use. While the research focused on determining the existence of a relationship between chronic substance abuse and an increased risk of dementia is not yet conclusive, there have been a number of studies that demonstrated cognitive impairments in chronic substance users. A recent meta-analysis suggested that chronic exposure to opiates results in cognitive impairment across a range of different neuropsychological domains, especially verbal working memory, and cognitive flexibility in the context of verbal fluency (Baldacchino et al., 2012). For chronic methamphetamine users, cognitive impairments are most likely seen in attention/working memory, information processing speed, learning and memory, executive function, and motor skills (Weber et al., 2012). Repeated ketamine users demonstrate impairments in spatial working memory, planning, visual recognition, and semantic memory (Liang et al., 2013).

The research on the association between alcohol consumption and the risk of dementia or cognitive impairment is more complicated than that for the drugs mentioned above. As might be expected, heavy chronic alcohol consumption without comorbidities

and nutritional deficits appears to result in cognitive impairment, specifically involving memory and executive function (Sinforiani et al., 2011). In contrast, a number of studies suggest that light-to-moderate alcohol consumption (i.e., no more than two drinks per day) has a protective effect on cognition similar to the protective effect on the cardiovascular system (Anstey, Mack, and Cherbuin, 2009; Sinforiani et al. 2011). While the majority of the cardiovascular protective effects seem to be attributed to the flavenoids in red wine with antioxidant properties, these protective effects have been noted for white wine, beer, and distilled spirits as well. According to the literature, the degree of cognitive impairment has been associated with sex (Mancinelli, Vitali, & Ceccanti, 2009), duration of abuse, the amount of alcohol consumed, and possibly the age of abuse onset (Sinforiani et al., 2011).

As was mentioned earlier, tobacco use is highly comorbid with the use of alcohol and illicit drugs. More than 75% of alcohol and drug dependent individuals early in the recovery process smoke cigarettes and are often characterized as heavy, highly nicotine-dependent smokers (Kalman, Morrisette, & George, 2005). Approximately 80% of cocaine users and opioid dependent individuals also smoke cigarettes. The Harvard College Alcohol Study, a survey of over 14,000 randomly chosen college students, found that students were significantly more likely to smoke cigarettes if they used alcohol and marijuana (Tullis et al., 2003).

Given that cigarette smoke contains over 4700 neurotoxic compounds; is associated with increased risk of hypertension and diabetes; and is comorbid with substance use, depression, and anxiety, all of which are risk factors for dementia, it is reasonable to hypothesize that cigarette smoking is related to cognitive decline and

dementia. Therefore, the goal of the current study was to evaluate the effects of cigarette smoking on cognitive function in four key domains identified in the literature: executive function, verbal memory, attention, and information processing speed in participants diagnosed with dementia, after controlling for covariates that have been shown to be related to both cigarette smoking and dementia in the scientific literature (cardiovascular disease, type 2 diabetes, substance use, depression, and anxiety). We posited that cigarette smoking would negatively affect neuropsychological performance in patients with a dementia diagnosis. In other words, dementia patients who are current smokers would perform worse on neuropsychological measures of executive function, verbal memory, attention, and information processing speed than dementia patients who are long-term ex-smokers or never smokers. In terms of the covariates, the supposition was that the more cigarettes smoked later in life, the more cognitive impairment would be noted in domains affected by these factors. Specifically, smoking along with the presence of cardiovascular disease, depression, or anxiety would be associated with impairments in executive function and attention/working memory, substance abuse would result primarily in executive function dysfunction, and type 2 diabetes would be associated with attention and information processing speed impairments.

CHAPTER TWO

METHOD

Participants

Participants were patients referred to Harbor UCLA Medical Center for neuropsychological testing between 1991 and 2011 who were diagnosed with AD, VaD, mixed dementia (VaD and AD), DLB, FTD, or dementia not otherwise specified (NOS). The sample consisted of 45.6% males (N = 52) and 54.4% females (N = 62). The ages ranged from 24 to 85 (M = 58.16, SD = 12.85). The racial/ethnic composition of the sample was 35.2% African American, 30.6% Caucasian, 14.8% Hispanic, 13.8% Asian, 0.9% Middle Eastern, and 4.6% other. The average level of education was 12.35 years (SD = 3.04), and ranged from 3 to 18 years. In terms of dementia diagnosis, the sample comprised 52.1% patients diagnosed with dementia NOS, 24.5% with VaD, 12.3% with AD, 3.7% DLB, 3.7% with FTD, 2.5% with mixed dementia, and 1.2% dementia due to substance abuse (Table 1). Average participant cognitive performance is shown in Table 2.

Table 1

Participant Demographics

	M	*SD*	N(%)	
Age (years)	58.16	12.85		
Education (years)	12.35	3.04		
Gender				
Female			62(54.4)	
Male			52(45.6)	
Ethnicity:				
African American			38(35.2)	
Caucasian			33(30.6)	
Hispanic			16(14.8)	
Asian			15(13.9)	
Middle Eastern			1(0.9)	
Other			5(4.6)	
Dementia Type:				
Dementia NOS			85(52.1)	
Vascular Dementia			40(24.5)	
Alzheimer's Disease			20(12.3)	
Lewy Body Dementia			6(3.7)	
Frontal Temporal Dementia			6(3.7)	
Mixed Dementia			4(2.5)	
Dementia due to Substance Abuse			2(1.2)	
Chronic History:			No	Yes
Hypertension			38(40.4)	56(59.6)
Diabetes			67(72.8)	25(27.2)
Depression			63(61.8)	39(38.2)
Anxiety			93(90.3)	10(9.7)
Substance Use			72(72.7)	27(27.2)
Tobacco Use			51(62.6)	31(37.8)

Table 2

Participant Cognitive Performance

Neuropsychological Measures	*N*	*M*	*SD*
WAIS-III Digit Span	111	6.70	2.66
WAIS-III Digit Symbol Coding	80	6.84	14.83
DKEFS Phonemic Fluency	105	16.69	10.67
RAVLT	60	1.33	1.79

Measures

Participants were referred for a one-day neuropsychological assessment, evaluating performance in all cognitive domains: general intellectual functioning, attention/working memory, language, visuospatial skills, verbal memory, non-verbal memory, executive functioning, information processing speed, and motor skills. These assessments typically lasted approximately eight hours. The evaluations involved a battery of approximately 21 primarily paper and pencil tests, though the composition of the battery varied somewhat over time. The current study examined participant performance in the four cognitive domains that research indicates are most affected by chronic cigarette smoking: executive function, verbal memory, attention/working memory, and information processing speed. In each domain, one test was selected that had good internal consistency reliability, had been used in other studies of smoking and cognitive decline, and had been administered to the majority of participants.

Executive Function

The majority of studies measure executive function using variations of verbal fluency tasks. Verbal fluency is a cognitive function that facilitates information retrieval from memory using frontal systems abilities such as selective attention and mental set shifting. The typical verbal fluency test comprises two tasks, a phonemic fluency task that involves the generation of as many words as possible that begin with a specified letter within one minute (e.g., FAS) and a semantic fluency task that requires the participant to list as many items as s/he can in a specified category (e.g., animals) within the same time period. For the current study, we chose the Delis-Kaplan Executive Function System Verbal Fluency Test (DKEFS Verbal Fluency, Delis, Kaplan, &

Kramer, 2001), with the letters F, A, S for the phonemic fluency subtest, and the category of animals for the semantic fluency subtest, because the test has good internal consistency and validity. The internal consistency of the phonemic fluency subtest ranges from .77 to .90 for ages 20 – 89. While the internal consistency for the semantic fluency subtest is lower than that of the phonemic fluency subtest (.61 to .76 for the same age range), the reliability coefficients are comparable to those published for a number of other commonly used neuropsychological tests, including the Wisconsin Card Sorting Test (Delis, Kramer, Kaplan, & Holdnack, 2004).

Verbal Memory

The measures used in the literature to evaluate verbal memory take the form of list learning tasks that involve a list of unrelated words that are presented verbally with immediate and delayed recall trials (e.g., Rey Auditory Verbal Learning [RAVLT], California Verbal Learning Test – second edition [CVLT-II]). The RAVLT was utilized in the current study due to a high internal reliability score (approximately .90; van den Burg & Kingma, 1999), the measure's high sensitivity to neurological impairments and memory deficits in patients with a variety of disorders (Powell et al., 1991), and the fact that it correlates moderately well with other measures of learning and memory such as the Wechsler Memory Scale Logical Memory subtest (Johnstone et al., 2000). The RAVLT requires the examinee to learn a list of 15 words over five trials. Following the five trials, the examinee is presented with a distractor list and then asked to recall the list of words. After a 30-minute delay, the examinee is again asked to recall the list of words, and then

presented with another list of words comprising words from the initial list and words that were not on the initial list and asked if s/he recognizes each word as being on the first list.

Attention/Working Memory

The current study utilized the Wechsler Adult Intelligence Scale – third edition (WAIS-III) Digit Span subtest as a measure of simple attention/working memory. Digit span is composed of two parts: Digit Span forward and Digit Span backwards. In Digit Span forward, the examinee is presented with an increasingly longer auditory sequence of digits comprising the numbers zero through nine and asked to repeat the sequence in the exact order in which it was presented. In contrast, in Digit Span backwards the examinee is presented a sequence of digits similar to those in the forward portion of the task and asked to verbally respond with the digit sequence in reverse order. The internal consistency for WAIS-III Digit Span ranges from .85 to .99, depending on the age group (for age ranges 30-54, 55-74, & 75-89; Iverson, 2001).

Information Processing Speed

Given that the WAIS-III Digit Symbol Coding subtest was utilized in a number of investigations into the relationship between smoking and changes in cognitive function (Arntzen et al., 2011, Starr et al., 2007), it was a logical choice for the current study. Patients are presented a key that contains digits one through nine and the symbol that corresponds to each digit. They are given rows of boxes where the top box contains a digit and the bottom box is empty then asked to fill the bottom boxes with the symbols corresponding with the digits in the top box as fast as they can. The digit-symbol coding

score is the number of correct symbols completed in 120 seconds. As with the majority of neuropsychological measures, the Digit Symbol subtest assesses more than one cognitive domain. Tests of information processing speed such as Digit Symbol Coding require intact attention, and cognitive flexibility as well as processing speed to be successfully completed (Baudouin et al., 2009; Ziegler, 2010). Specifically, Digit Symbol Coding requires the participant to attend to (attention) and process the stimuli as quickly as possible (information processing speed), while switching back and forth between symbols and numbers (cognitive flexibility). According to the WAIS-III technical manual, the Digit Symbol Coding subtest has an average reliability of .82 (The Psychological Corporation, 1997).

Tobacco Use

The tobacco data were collected by asking each participant the question "do you have a history of tobacco use". The tobacco item required a response of "yes" or "no".

Covariates

Medical data were collected by asking each participant, "do you have a history of chronic hypertension," and "do you have a history of diabetes." The medical items all required "yes" or "no" answers. In addition, participants were asked, "do you have a history of chronic depression," "do you have a history of chronic anxiety," "do you have a history of chronic alcohol use," "do you have a history of chronic cocaine use," "do you have a history of chronic amphetamine use," and "list any other chronic substances used." The definition of "chronic" for the current study was substance use of more than

one year. The psychiatric/substance use items all required "yes" or "no" answers. For the present study, participants' responses on all substance use questions were combined into one substance use variable, indicating whether they had a chronic history of any type of substance use (yes or no).

Procedures

Patients were primarily referred for testing by the Psychiatry, Neurology, and Neurosurgery departments at Harbor-UCLA Medical Center. Additionally, patient referrals were received from other hospitals and mental health clinics in the surrounding community. Patients were referred for neuropsychological evaluation in order to characterize their current cognitive abilities in the context of complaints of memory decline. The assessment process began with a brief explanation of neuropsychological assessment and the purpose of the evaluation. Patient confidentiality was discussed and informed consent was obtained for each participant. A clinical interview, which lasted approximately one hour, was conducted. Each patient was administered a thorough test battery that utilized multiple tests to evaluate each cognitive domain (i.e., general intellectual function, attention/information processing speed, language, visuospatial ability, verbal and nonverbal memory, and executive function), as well as mood and motor ability. The tests were all paper and pencil tests administered by a trained clinical neuropsychologist.

CHAPTER THREE

RESULTS

Four separate hierarchical multiple linear regression analyses were conducted to determine if tobacco use is associated with poorer performance on neuropsychological measures of executive function, attention, information processing speed, and verbal memory after controlling for cardiovascular disease, diabetes, depression, anxiety, and substance use. Prior to analysis, the data were evaluated for outliers and multicollinearity, as well as to determine if the data violated the assumptions of homoscedasticity, independence of residuals, and normality of residuals. The data violated the normality assumption. One outlier was removed from the data for each of the four cognitive measures and an additional outlier was removed from the WAIS-III Digit Span data. Based on the evaluation of normal probability plots, a logarithmic transformation was used to normalize the data because they still violated the normality assumption after the removal of outliers.

To increase statistical power, we simplified the full regression models predicting WAIS-III Digit Span, WAIS-III Digit Symbol Coding, and the DKEFS phonemic fluency by only including the independent variables with effect sizes (sr^2) greater than .01. The regression model predicting scores on the RAVLT (Table 8) was not simplified or interpreted, as the data for the modified model violated the normality assumption for all of the mathematical transformations attempted. A square root transformation was used instead of the logarithmic transformation to normalize the data for the simplified models, based on evaluations of normal probability plots. . The results of independent *t*-tests conducted indicated no significant differences in cognitive performance between

participants with and without a history of hypertension, diabetes, depression, anxiety, substance use, or tobacco use, with one exception (Table 3). Individuals with diabetes performed significantly better on WAIS-III Digit Span than individuals without diabetes, $t(89) = -2.26$, $p < .05$. Correlations among the variables used in the regression models demonstrated positive relationships between hypertension and diabetes, hypertension and depression, diabetes and attention/working memory performance, executive function performance and attention/working memory performance, as well as tobacco use and other substance use (Table 4).

Table 3

Group Differences for Cognitive Test Performance

DV	IV	Yes (*SD*)	No (*SD*)	*t*	*df*	*p*	Cohen's *d*
Digit Span	Hypertension	6.68 (2.12)	6.73 (2.89)	.10	91	.92	-.021
	Diabetes	7.56 (2.29)	6.30 (2.39)	-2.26	89	.03	**.539**
	Depression	6.62 (2.086)	6.37 (2.70)	-.50	98	.62	.101
	Anxiety	6.90 (2.47)	6.45 (2.50)	-.54	99	.59	-.300
	Substance Use	6.26 (2.41)	6.56 (2.55)	.52	95	.60	-.121
	Tobacco Hx	6.26 (2.18)	6.39 (2.39)	.25	78	.81	-.057
Digit Symbol							
	Hypertension	4.44 (3.45)	4.40 (2.45)	-.05	66	.96	.014
	Diabetes	4.42 (2.27)	4.57 (3.38)	.18	66	.86	-.049
	Depression	3.84 (1.73)	7.14 (14.48)	1.26	72	.21	-.301
	Anxiety	4.50 (2.07)	5.88 (11.71)	.33	73	.74	-.125
	Substance Use	4.55 (3.94)	6.17 (12.84)	.58	74	.56	-.148
	Tobacco Hx	4.12 (2.21)	4.06 (2.70)	-.08	56	.94	.024
FAS							
	Hypertension	17.23 (10.73)	14.78 (8.79)	-1.13	87	.26	.258
	Diabetes	16.29 (10.67)	15.71 (9.73)	-.24	85	.81	.059
	Depression	16.35 (10.03)	15.67 (9.78)	-.33	92	.74	.070
	Anxiety	21.22 (9.59)	15.49 (9.74)	-1.68	93	.10	**.595**
	Substance Use	15.67 (8.83)	15.75 (10.43)	.03	89	.97	-.008
	Tobacco Hx	15.07 (7.71)	15.16 (10.21)	.04	73	.97	-.010
RAVLT							
	Hypertension	1.60 (2.05)	1.00 (1.41)	-1.11	51	.27	.370
	Diabetes	1.80 (1.82)	1.31 (1.87)	-.87	52	.39	.269
	Depression	1.18 (1.65)	1.50 (1.90)	.65	56	.52	-.174
	Anxiety	1.20 (2.17)	1.37 (1.78)	.20	57	.84	-.096
	Substance Use	.94 (1.20)	1.52 (1.98)	1.38	48.02	.17	-.329
	Tobacco Hx	1.21 (1.65)	1.60 (2.06)	.68	42	.50	-.211

Note. Bold values of Cohen's *d* indicate effect sizes exceeding the recommended minimum effect size of .41

Table 4

Intercorrelations among Covariates and Cognitive Test Performance

Measure	1	2	3	4	5	6	7	8	9	10
1. History of Hypertension	--									
2. History of Diabetes	**.277**	--								
3. History of Depression	**.237**	.072	--							
4. History of Anxiety	-.036	-.012	.148	--						
5. History of Tobacco Use	.146	.033	-.020	.128	--					
6. History of Substance Use	-.093	-.064	-.116	.055	**.393**	--				
7. WAIS-III Digit Span	-.033	**.217**	.072	.047	-.046	-.064	--			
8. WAIS-III Digit Symbol Coding	.007	-.022	-.147	-.039	.011	-.067	-.202	--		
9. DKEFS Phonemic Fluency	.084	.008	.094	.145	.016	.025	**.512**	-.054	--	
10. Rey Auditory Verbal Learning	.154	.120	-.086	-.027	-.104	-.148	-.174	.245	.162	--

Note. Bold correlation values are significant at $p < .05$.

The author hypothesized that within a sample of dementia patients those who were current smokers would perform worse on select neuropsychological measures of executive function, verbal memory, attention, and information processing speed than those who are nonsmokers. Hierarchical regressions predicting cognitive performance from tobacco use history after controlling for history of hypertension, diabetes, depression, anxiety, and substance use were conducted to test this prediction. Results of the full, originally hypothesized regression models can be found in Tables 5 – 8, and results of the simplified regression models can be found in Tables 9 – 11. Contrary to the hypothesis, smoking did not significantly affect performance on measures of executive function, verbal memory, attention, or information processing speed in patients diagnosed with dementia, $p > .05$. In addition, none of the covariates significantly predicted cognitive performance in any domain, in either the full or simplified regression models, $p > .05$.

Table 5

Results of a Multiple Linear Regression Analysis Predicting WAIS-III Digit Span Performance (Full Model, Logarithmic Transformation)

Step	Predictor Variable	*B*	*SE*	*β*	95% Cl [Lower, Upper]	*p*	sr^2
1	Hypertension	-.015	.041	-.047	[-.097, .067]	.723	.00194
	Diabetes	.087	.046	.245	[-.004, .179]	.060	.05476
	Depression	.047	.042	.143	[-.036, .131]	.260	.01932
	Anxiety	.008	.067	.014	[-.127, .134]	.908	.00020
	Substance Use	-.014	.044	-.040	[-.102, .073]	.746	.00160
2	Hypertension	-.024	.042	-.075	[-.108, .060]	.575	.00476
	Diabetes	.087	.046	.243	[-.004, .178]	.062	.05382
	Depression	.051	.042	.155	[-.033, .135]	.227	.02220
	Anxiety	-.007	.069	-.013	[-.145, .131]	.919	.00014
	Substance Use	-.030	.046	-.083	[-.122, .063]	.523	.00608
	Tobacco History	.045	.043	.139	[-.042, .131]	.307	.01588

Table 6

Results of a Multiple Linear Regression Analysis Predicting WAIS-III Digit Symbol Coding Performance (Full Model, Logarithmic Transformation)

Step	Predictor Variable	*B*	*SE*	*β*	95% Cl [Lower, Upper]	*p*	sr^2
1	Hypertension	.011	.086	.021	[-.163, .185]	.897	.00036
	Diabetes	-.084	.093	-.142	[-.272, .105]	.376	.01742
	Depression	.003	.081	.006	[-.161, .167]	.969	.00004
	Anxiety	-.007	.120	-.009	[-.248, .234]	.953	.00008
	Substance Use	-.086	.086	-.148	[-.259, .088]	.325	.02161
2	Hypertension	.008	.088	.014	[-.170, .185]	.931	.00017
	Diabetes	-.088	.095	-.149	[-.280, .105]	.363	.01877
	Depression	.009	.084	.016	[-.161, .178]	.920	.00023
	Anxiety	-.016	.124	-.020	[-.266, .235]	.900	.00036
	Substance Use	-.094	.091	-.163	[-.278, .090]	.309	.02371
	Tobacco History	.026	.087	.049	[-.150, .201]	.768	.00194

Table 7

Results of a Multiple Linear Regression Analysis Predicting DKEFS Phonemic Fluency Performance (Full Model, Logarithmic Transformation)

Step	Predictor Variable	*B*	*SE*	*β*	95% Cl [Lower, Upper]	*p*	sr^2
1	Hypertension	-.011	.133	-.011	[-.278, .256]	.934	.00012
	Diabetes	.030	.149	.027	[-.268, .327]	.842	.00068
	Depression	.185	.134	.183	[-.085, .454]	.175	.03098
	Anxiety	.133	.232	.074	[-.332, .597]	.570	.00533
	Substance Use	.071	.143	.065	[-.215, .358]	.620	.00410
2	Hypertension	-.032	.135	-.033	[-.302, .238]	.816	.00090
	Diabetes	.015	.149	.014	[-.284, .314]	.919	.00017
	Depression	.195	.135	.194	[-.075, .466]	.153	.03460
	Anxiety	.070	.241	.039	[-.413, .552]	.773	.00137
	Substance Use	.011	.155	.010	[-.300, .323]	.942	.00008
	Tobacco History	.145	.147	.146	[-.149, .439]	.328	.01588

Table 8

Results of a Multiple Linear Regression Analysis Predicting RAVLT Long Delay Performance (Full Model, Logarithmic Transformation)

Step	Predictor Variable	*B*	*SE*	*β*	95% Cl [Lower, Upper]	*p*	sr^2
1	Hypertension	.139	.277	.091	[-.432, .701]	.619	.00689
	Diabetes	.251	.303	.144	[-.365, .867]	.414	.01877
	Depression	-.145	.271	-.093	[-.695, .406]	.597	.00792
	Anxiety	-.178	.462	-.064	[-1.116, .761]	.703	.00410
	Substance Use	-.214	.259	-.138	[-.741, .313]	.414	.01877
2	Hypertension	.154	.287	.100	[-.431, .739]	.597	.00810
	Diabetes	.250	.308	.143	[-.376, .876]	.422	.01877
	Depression	-.150	.276	-.096	[-.710, .411]	.591	.00828
	Anxiety	-.183	.469	-.066	[-1.137, .771]	.699	.00436
	Substance Use	-.185	.291	-.119	[-.778, .408]	.530	.01145
	Tobacco History	-.067	.283	-.045	[-.643, .510]	.815	.00160

Table 9

Results of a Multiple Linear Regression Analysis Predicting WAIS-III Digit Span Performance (Simplified Model, Square Root Transformation)

Step	Predictor Variable	*B*	*SE*	*β*	95% Cl [Lower, Upper]	*p*	sr^2
1	Diabetes	203	.113	.214	[-.021, .428]	.076	.04537
	Depression	.048	.106	.053	[-.164, .259]	.653	.00281
2	Diabetes	.201	.113	.211	[-.025, .427]	.080	.04452
	Depression	.048	.106	.054	[-.164, .260]	.652	.00292
	Tobacco History	.080	.102	.093	[-.124, .283]	.437	.00865

Table 10

Results of a Multiple Linear Regression Analysis Predicting WAIS-III Digit Symbol Coding Performance (Simplified Model, Square Root Transformation)

Step	Predictor Variable	*B*	*SE*	*β*	95% Cl [Lower, Upper]	*p*	sr^2
1	Diabetes	-.061	.176	-.043	[-.411, .290]	.731	.00185
	Substance Use	-.044	.173	-.032	[-.389, .301]	.801	.00102

Table 11

Results of a Multiple Linear Regression Analysis Predicting DKEFS Phonemic Fluency Performance (Simplified Model, Square Root Transformation)

Step	Predictor Variable	*B*	*SE*	*β*	95% Cl [Lower, Upper]	*p*	sr^2
1	Depression	.306	.323	.111	[-.338, .950]	.347	.01232
2	Depression	.308	.324	.112	[-.339, .954]	.346	.01254
	Tobacco History	.232	.324	.084	[-.414, .878]	.477	.00706

CHAPTER FOUR

DISCUSSION

Results of regression models predicting performance in select cognitive domains did not confirm the primary hypothesis that participants diagnosed with dementia who are current smokers would perform worse on measures of executive function, attention/working memory, verbal memory, and information processing speed than those who are current nonsmokers. Although the sample sizes for the RAVLT and WAIS-III Digit Symbol Coding tests were small, the null results are unlikely to be due to low statistical power because the effect sizes for the majority of the independent variables in the regression models were less than .001. This means that most of the independent variables account for less than .1% of the variance in the performance on the neuropsychological measures investigated, which would not be clinically significant even if it were statistically significant. Furthermore, simplifying the models to increase statistical power did not yield any significant results and the effect sizes were still very small (less than .01).

The only potential statistical issue encountered in the current study was the odd finding that participants with diabetes performed significantly better on a measure of simple auditory attention/working memory than participants without diabetes. The literature does not support this finding. In fact, studies typically show that individuals with diabetes perform more poorly on tests of cognitive function (e.g., Mehrabian et al. 2011). This questionable outcome may be due to Type 1 error as a result of the large number of *t*-tests (24) performed on the data. If we apply the Bonferroni correction for Type I error to the number of *t*-tests that were conducted (corrected alpha = .05/24), then

the cutoff for significance becomes .002, which renders the effect of diabetes on digit span performance no longer significant.

Given that the null results are most likely not due to statistical problems, one explanation for the current findings may simply be that cigarette smoking does not affect cognitive functioning. However, there are enough studies that have suggested a relationship between cigarette smoking and cognitive decline that the null findings of the current study are more likely to be attributable to methodological limitations. One methodological limitation was our inability to separate the participants into two groups, long-term ex-smokers and never smokers, and current smokers and recent ex-smokers, because the data were archival. As such, the data did not include the information necessary to split smokers into these groups. A number of studies have found that ex-smokers either have similar declines in cognition or slower declines than never smokers due to the ambiguous definition of former smokers (Anstey et al., 2007; Peters et al., 2008; Sabia et al., 2012). The studies that differentiated between the two levels of ex-smokers found that long-term former smokers exhibited similar risk of cognitive impairment as never smokers (Galanis et al., 1997; Sabia et al., 2012). Almeida et al. (2011) found that the cognitive scores of chronic smokers (i.e., smoked a minimum of five cigarettes per day for a continuous period of 12 months or more throughout their lifetime) who quit smoking for a minimum of 18 months were comparable to those of never smokers. In fact, it is possible that long-term former smokers' risk may be reduced to the level of never smokers' risk, although more research is needed to confirm this.

The tobacco literature indicates that many of the body's systems damaged by cigarette smoking return to the condition of a nonsmoker when the smoker has abstained

from smoking for a long enough duration (e.g., risk of coronary heart disease is the same as for nonsmokers after 15 years of abstinence; Abrams et al., 2003). Given that the heart and lungs heal, and a number of the studies of the relationship between smoking and cognition found no differences between the cognition of never smokers and long-term ex-smokers (Galanis et al., 1997; Sabia et al., 2012), it is possible that the brain heals as well or that a reduction in cardiovascular risk translates into a reduction in the risk for dementia. Therefore, future studies should categorize ex-smokers as either recent or long-term ex-smokers to account for the body's ability to heal itself. Similar temporal arguments may also apply to several of the other independent variables. Factors that may cause neurological damage, such as hypertension, diabetes, or substance use, likely cause cognitive deficits to a degree that depends on the severity, duration, and recency of the insult.

Another issue that may have affected the primary outcome of the study was that smoking may be more likely to be associated with certain types of dementia than others, but we had to combine patients with different dementia diagnoses into one large group because there were not enough patients diagnosed with the different types of dementia to examine them separately. The most common types of dementias stem from different changes in brain pathology such as the amyloid beta plaques and tau tangles that characterize AD (Hashimoto, Rockenstein, Crews, & Masliah, 2003); the abnormal accumulation of α-synuclein in neuronal cell bodies, axons, and synapses found in DLB (Hashimoto, Rockenstein, Crews, & Masliah, 2003); and the hemorrhagic, ischemic, or hypoperfusive lesions that are the hallmark of VaD (Roman & Benavente, 2003). Therefore, it is not unreasonable to posit that smoking may affect each of these disease

processes differently. In fact, a study by Reitz et al. (2007) found an association between current smoking and increased risk of AD but not of VaD, which suggests that the relationship between smoking and risk of a neurodegenerative disease may not be the same for the different types of dementias. Future work needs to be conducted to determine if there are differences in the association between smoking and increased risk of different types of dementia, as well as whether or not smoking exacerbates or changes the symptomatology of the different dementias.

The results of Rusanen et al.'s investigation (2011) not only indicated that the relationship between current smoking and increased risk of dementia was stronger for VaD than AD, they also suggested that the association was dose dependent. These associations were only seen in participants who currently smoked more than two packs per day. The increased risk of VaD in participants who currently smoked one to two packs per day was trending toward statistical significance, while the risk of AD in participants who currently smoked one to two packs per day was not significant. Neither the increased risk of VaD or AD was significant for participants who currently smoked less than one pack per day. In the current study's sample, the majority of participants who currently smoked reported that they smoked one pack of cigarettes or less per day (M = .41, SD = .54). If the outcome is dose dependent, as suggested by Rusanen et al. (2011), then participants in the current study may not have smoked enough cigarettes to influence the development of dementia or to differentially affect their cognitive performance (i.e., more than 2 packs per day).

In addition, the smoking history data were collected by self-report, which is potentially problematic given this sample. According to the test scores for several verbal

memory measures, the majority of the participants are likely to be amnestic, and therefore the accuracy of their reported cigarette consumption may be questionable. Future work should check the accuracy of the information collected from participants using biochemical verification of smoking status (to the extent possible) and brief interviews with non-amnestic friends or family members.

The complex nature of the sample analyzed for the current study gave us the opportunity to conduct this investigation using a diverse sample that is more reflective of real life, rather than one that is primarily Caucasian and homogenous in terms of diagnosis. Unfortunately, the complexity may have also obscured any clear-cut relationships among the variables due to decreased internal validity. There were many uncontrolled factors that may have influenced cognitive performance, such as varying levels of SES, various cultural backgrounds, or histories of homelessness, domestic violence, or other trauma. For example, several studies on the effects of homelessness on neuropsychological functioning have found deficits in information processing speed (Seidman et al., 1997) and executive functioning (Gonzalez, Dieter, Natale, & Tanner).

Another factor that may explain the null results of the current study was the use of a cross-sectional design. Unlike a prospective study, the participants in a cross-sectional study are only assessed at one point in time, and thus there is only one opportunity to observe an effect. Utilizing a prospective study design would have enabled us to observe changes in cognitive performance over time, particularly in relation to changes in smoking habits. Future work should recruit smokers and non-smokers in early or middle adulthood, and assess their smoking behavior and cognitive performance over time.

In the case of the current study, it is probable that participants were at different points in the neurodegenerative disease process, which may have affected study outcomes. For example, we may be more likely to see an association between smoking and poorer performance on select neuropsychological tests early in the disease process, because later on individuals' cognition is more likely to be severely impaired across multiple domains. Thus, future studies should include participants who are identified as early as possible in the disease process. However, the only way to determine that participants are at an optimal point in their disease for detecting differences is if they undergo neuropsychological testing, which would make recruiting participants difficult.

Although the use of a prospective design would have been more methodologically robust, we would still have encountered the problem that statistical modeling of the effect of smoking on AD patients is complicated by the existence of competing risk due to mortality (Chang, Zhao, Lee, & Ganguli, 2012). Given that smokers tend to die at an earlier age than non-smokers, the older smokers in our sample are likely to be the healthiest smokers for a given age group, which suggests that we may be comparing cognitive performance between nonsmokers and the healthiest smokers. The differences in the cognitive skills between these groups may be much smaller than in a comparison with unhealthier smokers who are either deceased or have more urgent health issues to deal with than cognitive decline. Similar arguments apply to the other variables that could affect mortality, including hypertension, diabetes, substance use, and even depression. For example, individuals with severe hypertension or uncontrolled hypertension may not live long enough to develop dementia or experience a decline in cognition, and therefore samples of older participants with hypertension may comprise

healthier hypertensive individuals that are more likely to have milder cognitive deficits than individuals with more severe hypertension who survived to the same age.

A more likely reason for the null results is that the cognition of participants at the time of testing was so impaired that the predicted small effect of smoking or any of the other independent variables on cognitive performance was obscured due to a ceiling effect. Examination of the scores for the measure of verbal memory (RAVLT) showed that the average participant was able to recall only one word and more than half of the participants could not recall any of the words, which suggests that the participants were predominantly amnestic and fairly advanced in the disease process. Further evidence of the level of participant memory impairment is that the average participant scored in the impaired range for another test of verbal memory with the same duration of delay, WMS-III Logical Memory II.

Possible directions for future research include better separation of subjects into groups based on the amount and recency of their tobacco consumption, and use of techniques other than self-report to confirm smoking history and status. More research needs to be conducted that focuses on potential associations between cigarette smoking and the risk of different types of dementias, given the differences in pathology and mechanisms of neurodegeneration. Most importantly, future investigations should use a prospective design to study changes in cognition over time. Utilizing a prospective design that begins in early or middle adulthood and involves administering repeated neuropsychological batteries over time may help resolve the problems caused by recall bias, differential mortality, and evaluation of participants at different stages in the neurodegenerative process.

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