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Emerging risk factors for dementia: associations between clinical infections, PTSD, psychotropic PTSD medication use, and the risk for dementia

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EMERGING RISK FACTORS FOR DEMENTIA: ASSOCIATIONS BETWEEN CLINICAL INFECTIONS, PTSD, PSYCHOTROPIC PTSD MEDICATION USE, AND THE RISK FOR DEMENTIA

by

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CERTIFICATE OF APPROVAL

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PH.D THESIS

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This is to certify that the Ph.D. thesis of

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To my wife, Dr. Oluchi Jane Abosi, and children, Karen, Francis Jr., Adrian and Marie.

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ABSTRACT

Dementia is a major public health problem worldwide. Emerging research indicates that clinical infections and PTSD could be important risk factors for dementia. However, evidence for infections and the risk of dementia primarily examines central nervous system (CNS) infections. Extant epidemiological evidence for systemic bacterial infections and the risk for dementia is limited while that for PTSD and the risk for dementia did not account for psychotropic medications commonly used in management of PTSD and could affect cognitive function. The purpose of this study was to 1) review the evidence for CNS infections as possible causes of Alzheimer's disease (AD) dementia, and 2) using nationwide Veterans Health Administration databases, conduct original retrospective cohort analyses in nationally representative samples of U.S. veterans aged 56 years and older to determine the associations between systemic bacterial infections, PTSD, and psychotropic PTSD medication use with the risk for developing dementia.

Review of the research pertaining to an infectious AD etiology hypothesis including the various mechanisms through which different clinical and subclinical infections could cause or promote the progression of AD, and the concordance between putative infectious agents and the epidemiology of AD showed evidence linking AD to an infectious cause to be largely inconclusive; however, the amount of evidence suggestive of an association is too substantial to ignore.

Analysis of the associations between systemic bacterial infections and the risk for dementia showed a significant association between exposure to any systemic bacterial infection and an increased risk for dementia (hazard ratio [HR] = 1.20; 95% confidence interval [CI] = 1.16-1.24) after adjustment for demographic characteristics, and medical and psychiatric comorbidity. In addition, septicemia (HR=1.39; 95%CI=1.16-1.66), bacteremia (HR=1.22; 95%CI=1.0-1.49), osteomyelitis (HR=1.20; 95%CI=1.06-1.37), pneumonia (HR=1.10; 95%CI=1.02-1.19), UTI (HR=1.13; 95%CI=1.08-1.18), and cellulitis (HR=1.14; 95%CI=1.09-1.20) were independently associated with significantly increased risk of developing dementia after adjustment for potential confounders.

Analysis of the associations between PTSD and psychotropic PTSD medication use with the risk for dementia showed a significant association between PTSD and the risk for dementia (HR=1.35; 95%CI=1.27-1.43) after adjustment for demographic characteristics, medical and psychiatric comorbidity, and health care utilization. Analysis of the impact of psychotropic PTSD medications including selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), benzodiazepines (BZA), novel antidepressants (NA) and atypical antipsychotics (AA) on the association between PTSD and the risk for dementia showed significant interactions between PTSD and use of SSRIs (p<.0001), NAs (p=.0016), and AAs (p<.0001). Multivariate analysis showed a significant association between PTSD and an increased risk for dementia among individuals not using any psychotropic PTSD medications at baseline (HR=1.70; 95%CI=1.58-1.82). PTSD patients using SSRIs (HR=2.10; 95%CI=1.82-2.41), NAs (2.19; 95%CI=1.94-2.48) or AAs (4.56; 95%CI=4.04-5.15) were significantly more likely to develop dementia compared to those without PTSD and not using any psychotropic PTSD medications. PTSD patients using SSRIs (HR=1.24; 95%CI=1.08-1.42), NAs (HR=1.29; 95% CI=1.14-1.46) or AAs (HR=2.69; 95%CI=2.38-3.04) were also significantly more likely to develop dementia compared to those with PTSD and not using any psychotropic PTSD medications. SNRI (HR=1.35; 95%CI=1.26-1.46) and BZA drug use (HR=1.40; 95%CI=1.35-1.45) at baseline was associated with an increased risk for dementia regardless of PTSD diagnosis.

These findings indicate; 1) evidence for an infectious AD etiology hypothesis in inconclusive, 2) both severe (e.g. sepsis), and less severe (e.g. cellulitis) systemic bacterial infections are collectively and independently associated with an increased risk of dementia among older U.S. veterans hence prevention of systemic bacterial infections could positively influence the risk for dementia among older adults, and 3) PTSD and psychotropic medication use are associated with an increased risk for dementia among U.S. veterans.

Further epidemiologic, clinical, and basic science research is required to elucidate the mechanisms and the associations between infections and the risk for

dementia and to determine if the independent and effect modifying impacts of psychotropic PTSD medication use on the risk for dementia are related to differences in PTSD severity, other psychiatric comorbidity, or whether psychotropic PTSD medication use is an independent risk factor for dementia.

PUBLIC ABSTRACT

Emerging research indicates clinical infections and posttraumatic stress disorder (PTSD) could influence the risk for developing dementia. However, extant research on infections and the risk for dementia primarily examined central nervous system (CNS) infections. Evidence for systemic bacterial infections and risk for dementia is limited while previous research on PTSD and risk for dementia did not account for psychotropic medications commonly used in the management of PTSD and could affect cognitive function. Our first aim was to review the evidence for CNS infections as possible causes of Alzheimer's dementia. The second and third aims were to conduct original analyses using nationwide Veterans Health Administration data to determine the associations between systemic bacterial infections, PTSD, and psychotropic PTSD medication use with the risk for developing dementia among veterans aged 56 years and older.

Results showed 1) evidence for CNS infections as possible causes of AD is largely inconclusive but a substantial amount of evidence suggests an association, 2) severe (e.g., sepsis) and less severe (e.g., cellulitis) systemic bacterial infections are collectively and independently associated with an increased risk of dementia, and 3) PTSD is associated with an increased risk of dementia among individuals not using psychotropic medications; however, PTSD patients using certain psychotropic medications are more likely to develop dementia compared to both those with and without PTSD and not using psychotropic PTSD medications. Further epidemiologic, clinical, and basic research is required to elucidate the mechanisms and independent associations between clinical infections, PTSD, and psychotropic medications with the risk for dementia.

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LIST OF ABBREVIATIONS

Aβ	β-amyloid
AA	Atypical antipsychotic
AD	Alzheimer's disease
ApoE4	Apolipoprotein ε4
APP	Amyloid precursor protein
BZA	Benzodiazepines
CDW	Corporate data warehouse
CNS	Central nervous system
CSF	Cerebral spinal fluid
CPRS	Computerized patient record system
DSS	Decision Support System
HSV-1	Herpes simplex virus type 1
ICD-9	International classification of disease, ninth revision, clinical modification
NA	Novel antidepressants
OCF	Outpatient Care Files
PCR	Polymerase chain reaction
PTF	Patient Treatment Files
PTSD	Posttraumatic stress disorder
SSRI	Selective serotonin reuptake inhibitor
SNRI	Serotonin-norepinephrine reuptake inhibitor
UTI	Urinary tract infection
VAMC	Veteran's Affairs Medical Center
VHA	Veterans Health Administration
VistA	Veterans Health Information Systems and Technology Architecture

CHAPTER 1

INTRODUCTION

Dementia is a chronic neurodegenerative disorder that is characterized by progressive global cognitive decline. According to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* a clinical diagnosis of dementia is made based on presence of significant impairment in one or more cognitive domains, which include complex attention, executive functioning, learning and memory, language, perceptual-motor or visuospatial function and social cognition (1). Associated symptoms vary according to disease stage and underlying neuropathology and may include various psychiatric, behavioral and personality disorders as well as motor deficits (2). Definitive diagnosis of dementia requires postmortem examination of the brain.

Public health significance

Dementia is a major public health problem globally, the prevalence of dementia worldwide is currently estimated at 47.5 million people, and it is projected that there are 7.7 million new dementia cases per year worldwide (3). In addition, the global prevalence of dementia is expected to increase to more than 135 million by the year 2050 (3) due to increase in the number of susceptible or older persons in the population.

In the United States (U.S.), the prevalence of dementia is currently estimated at more than 5.3 million people and it is expected to increase almost threefold by the year 2050 (4). Moreover, Alzheimer's dementia alone is the sixth leading cause of all deaths in the U.S. (5), the fifth leading cause of death among individuals aged 65 years and older, and fourth leading cause of death among individuals 85 years and older (6).

Dementia is a leading cause of disability and institutionalization among individuals aged 65 years and older; for example, in a population-based study, involving 1,810 adults aged 75 years and older, the risk for institutionalization attributable to dementia was 61% (7). In addition, in a retrospective cohort study involving 1,440 newly

diagnosed dementia patients aged 65 years and older and 6,988 age- and sex-matched controls, dementia was associated with an increased risk for institutionalization (hazard ratio [HR] = 3.45; 95% confidence interval [CI] = 3.05-3.90) after 5 years of follow-up and adjustment for sex, age, and comorbidity (8). Similarly, in a population-based cohort study involving 1,147 adults aged 66 years and older, dementia was associated with an increased risk for institutionalization after 12 years of follow-up (HR=5.09; 95%CI=2.92-8.84) (9). Institutionalization for dementia has been associated with a higher rate of cognitive decline (10) as well as significant increase in both cost of dementia care (11) and risk of mortality (12, 13).

Dementia significantly increases health care utilization and costs among patients. For example, in a population based study involving 5,666 dementia patients and 5,666 age- and gender-matched non-demented controls, dementia was associated with higher frequency of psychiatric ($p<.001$), non-psychiatric ($p<.001$) and overall ($p<.001$) outpatient clinic visits (14). Dementia is also associated with increased hospitalizations. For example, in a cross-sectional study involving a nationally representative sample of Medicare beneficiaries aged 65 years and older, dementia was associated with increased risk for hospitalizations due to all causes (odds ratio [OR] = 3.68; 95%CI=3.62-3.73) and potentially avoidable causes (OR=2.40; 95%CI=2.35-2.46) after adjustment for age, sex, race, occurrence of death, and comorbidity (15). Several other authors (16-20) reported similar results. Furthermore, dementia has been associated with increased length of hospital stay (20, 21), and emergency room utilization (16, 19). Consequently, these associations contribute to a substantial increase in dementia related health care costs. In the U.S. alone, the annual per person health care costs attributable to dementia ranged from $42,746 to $69,834 in 2010 (22). The increased health care utilization and costs might be due to the disease itself or possibly because of the increased risk for various medical and psychiatric comorbidity associated with dementia, which include diabetes, hypertension, pneumonia, falls, depression, and anxiety (23).

Research has also linked dementia to significant emotional, psychiatric, and economic impacts on patients' families and caregivers. As dementia progresses,

individuals typically lose the ability to perform activities of daily living and require caregiver assistance. In the U.S., 85% of unpaid or informal care to older adults is provided by family members (4) including spouses, relatives, and children and yet the burden of caregiving for a family member with dementia has been associated with decreased immune function (24, 25), and increased risk for various medical and psychiatric disorders including infectious diseases (25), hypertension and cardiovascular diseases (26-29), and sleep, depression and anxiety disorders (25, 26, 28, 30). In addition, the burden of proving care for dementia patients has also been associated with increased health care utilization and costs among caregivers (28), lost wages and income (31), and an increased risk of mortality (32).

Finally, the costs of dementia to society are substantial with global estimates of direct costs estimated at $640 billion per year (33). In the U.S. alone, cost estimates in 2010 ranged from $159 - $215 billion per year (22) and are projected to increase to more than $1 trillion by 2050 (4).

Neuro-pathogenesis of dementia

Several environmental exposures and medical and psychiatric disorders could possibly cause chronic cognitive decline including alcohol abuse, vitamin B12 deficiency, brain tumors, normal pressure hydrocephalus, Creutzfeldt-Jakob disease, Huntington's disease, hypo- and hyper-thyroidism, HIV infection, meningitis, and encephalitis; however, the majority of these conditions are associated with non-neurodegenerative or potentially reversible cognitive impairments (34-36). In contrast, the most commonly diagnosed dementia syndromes are associated with irreversible neurodegenerative pathologies, which include Alzheimer's disease, vascular dementia (cognitive vascular disease), Lewy body dementia, and frontotemporal dementia. Currently, there is no cure for these dementia syndromes.

Alzheimer's disease (AD)

AD is the leading cause of dementia worldwide and accounts for between 60-80% of all dementia cases (4). Clinically, AD is primarily characterized by progressive

memory impairment, which is typically the earliest and predominant cognitive deficit (37, 38).

Neuropathologically AD is characterized by neuronal degeneration, synaptic loss, brain atrophy, and intraneuronal neurofibrillary tangles (NFTs) and neutropil threads (NTs), and extracellular β-amyloid (Aβ) plaques within particular regions of the brain (39-41). NFTs and NTs result from gradual accumulation and subsequent aggregation of hyperphosphorylated tau proteins into insoluble fibrils within nerve cell bodies and dendritic processes, respectively while Aβ plaques stem from the gradual deposition and accumulation of Aβ peptides within extracellular spaces (39, 40). Aβ peptides are derived from the cleavage of integral membrane glycoprotein, amyloid precursor protein (APP) by α- and β-secretase into N- and carboxyl-terminal fragments and subsequent cleavage of the carboxyl terminal fragments by γ-secretase into various length Aβ peptides of which the 40 and 42 amino acid residue long peptides primarily constitute the Aβ plaques (42).

Characteristically, AD neuropathology starts in particular CNS sites primarily, the locus coeruleus and then gradually spreads to involve other subcortical and cortical sites in a specific sequence that has been categorized into six distinct stages. Stage I is characterized by involvement of the transentorhinal region, stage II the entorrhinal and hippocampus, stage III the temporal lobe and basal neocortical regions, stage IV the insular and basal frontal areas, stage V the prefrontal areas and stage VI the premotor as well as the primary motor and sensory cortices (43). Evidence indicates that clinical symptoms of AD correspond with the spread of the neuropathological lesions within the brain.

Vascular dementia/Vascular cognitive impairment

Vascular dementia is the second most common cause of dementia and accounts for approximately 8–15.8% of all dementia cases (44). Clinically, vascular dementia is characterized by dementia symptoms in addition to evidence for cerebral- or systemic-vascular disease (45).

The neuropathological features of vascular dementia include focal strategic infarcts, multifocal infarcts, lacuna infarcts, micro-infarcts, hemorrhages and microbleeds, white matter lesions, hippocampal sclerosis, and mixed cortico-subcortical and diffuse post-ischemic lesions (44, 46). These lesions result from ischemic, hemorrhagic or hypoxic-hypoperfusion events due to systemic, cardiac, or cerebral large and small vessel disease (47).

Lewy body dementia

Lewy body dementia is the third most common cause of dementia that accounts for between 1.2 to 9.7% of all dementia cases (48). It is characterized by dementia symptoms that are associated with recurrent visual hallucinations, spontaneous symptoms of Parkinsonism, and fluctuating cognition with pronounced variations in attention and alertness (49, 50). In contrast to AD, memory impairment might not be the earliest or predominant cognitive deficit instead; attention, executive function, and visuospatial function deficits may predominate (50). In addition, Lewy body dementia is often associated with sleep anomalies, repeated falls, severe autonomic dysfunction, syncope, paranoid delusions, urinary incontinence, and depression (50).

Neuropathologically, Lewy body dementia is characterized by intracytoplasmic inclusions in neurons (Lewy bodies) and neurites (Lewy neurites), glia, and presynaptic terminals (51). Lewy bodies and neurites occur in either the brainstem (classic) and/or cerebral cortex (cortical) and result from the accumulation and aggregation of presynaptic proteins α-synuclein and ubiquitin into insoluble filaments (52).

Frontotemporal dementia

Frontotemporal dementia results from degeneration and atrophy of the frontal and anterior temporal lobes. Clinically, two major variants are recognized i.e., behavioral variant and primary progressive aphasia. Behavioral variant frontotemporal dementia is characterized by prominent early personality or behavioral changes with executive function deficits, and relative sparing of memory and visuospatial functions (53). In contrast, primary progressive aphasia is characterized by prominent language

deficit and is further categorized into semantic, non-fluent/agrammatic, and logopenic variants which are characterized by anomia and single word comprehension deficits, aggramatism and effortful speech, impaired single-word retrieval and sentence and phrase repetition, respectively (54).

Neuropathology of frontotemporal dementia is characterized macroscopically by frontal and anterior temporal lobe atrophy and microscopically by microvacuolation and neuronal loss (55). Molecular or immune-histochemical features include intra-cytoplasmic inclusions categorized according to the constituent protein aggregates which include microtubule associated protein tau (FTLD-TAU), TAR DNA-binding protein-43 (FTLD-TDP), fused in sarcoma protein (FTLD-FUS), proteins of the ubiquitin proteasome system FTLD-UPS, and FTLD-no inclusions (FTLD-ni) (56).

Causes and risk factors for dementia

In terms of causation, dementia has been broadly classified into genetic (familial) and sporadic subtypes depending on whether the disease is due to an inherited genetic defect or unknown cause, respectively. Genetic dementias are characterized by early onset of clinical symptoms (typically before 60 years of age) and stem from inherited autosomal dominant mutations; for example, familial AD has been linked to autosomal dominant mutations in the amyloid precursor protein (APP), and presenilin 1 and 2 genes. Familial frontotemporal dementia has been associated with autosomal dominant mutations in the microtubule-associated protein tau (MAPT), proguanuline (PGRN) and hexanucleotide repeat expansion of C9ORF72 (57, 58). Similarly, familial vascular dementia or cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is associated with mutations in the Notch homolog 3 (NOTCH3) gene (58, 59). However, genetic dementias are generally rare and account for only 0-5% of all dementia cases.

Most dementia cases are sporadic and the exact causes for majority of these dementias remain largely unknown. This dissertation pertains to sporadic dementias. Existing research has identified modifiable and non-modifiable potential risk factors for

sporadic dementia. Non-modifiable risk factors for dementia include increasing age (60, 61), female gender (62), African-American or Hispanic Race/Ethnicity (62-65) and certain genetic variants most prominently, the apolipoprotein ε4 allele (66-68). Modifiable risk factors for dementia include lack of physical activity (69), traumatic brain injury (70-73), lower education status (74-76), hypertension (77, 78), cardiovascular disease (79, 80), diabetes mellitus (81) alcohol abuse (82, 83), smoking (84), depression (85-87), and bipolar disorder (88). Conversely, protective factors that have been identified include physical activity (89-91), high cognitive activity (76), higher education status (92), low to moderate alcohol use (93), and consumption of a predominantly Mediterranean diet (90, 94).

However, interpreting the evidence for several putative risk factors for dementia remains controversial because some studies report negative or inverse associations. For example, MacKnight et al. (95) found no association between diabetes and the overall risk for dementia, while Chen et al. (96), Becker et al. (97), and Lindsay et al. (98) found no association between depression and the risk for dementia. Similarly, Mehta et al. (99) found no association between head trauma and the risk for dementia while Katz et al. (100) found no significant associations between either race, education status, or gender and the risk for dementia. In addition, Yip et al. (101) and Doll et al. (102) found no associations between smoking and the risk for dementia while Ruitenberg et al. (103) and Wang et al. (104) found hypertension and smoking to be associated with a decreased risk for dementia, respectively. Moreover, evidence indicates that only 20% of all dementias are attributable to apolipoprotein ε4 and other genetic risk factors (105), while the proportion attributable to the potentially modifiable risk factors has been estimated at 28% (106). Taken together, these findings indicate that other factors possibly influence the risk for development of dementia in humans.

Other and emerging risk factors for dementia

Due to controversies in the evidence and the unexplained sources of variability in the literature, attention has turned to other potential risk factors namely, exposure to

central nervous system infections, inflammation due to systemic bacterial infection and posttraumatic stress disorder. Central nervous system infections have been widely studied as possible risk factors for the development of Alzheimer's disease dementia with mixed results and several authors have previously reviewed this evidence (107-110). However, prior reviews did not consider additional evidence or alternative explanations for the putative associations between the various central nervous system infections and the risk for dementia including; 1) compatibility of dementia neuropathology with an infectious cause, 2) evidence that various clinical and subclinical infections indirectly promote AD progression, 3) the possibility that patients with AD might be prone to infectious diseases, and 4) potential correlations between putative infectious agents and the epidemiology of AD. Therefore, a comprehensive review that addresses these limitations is required to examine the possible associations between infections of the central nervous system and the risk for dementia.

In addition, evidence has recently emerged from both animal experiments (111-114) and epidemiological human studies (115-117) that systemic bacterial infections could possibly increase the risk for dementia among older adults. However, the epidemiological evidence for this association is limited. Moreover, these reports have been largely limited to a specific systemic bacterial infection, and did not consider subsequent or multiple infections and psychiatric comorbidity associated with increased risk for both infections and dementia such as posttraumatic stress disorder, depression, and bipolar disorder. Thus, this hypothesis requires further rigorous scientific inquiry.

Emerging research also indicates that PTSD could be a major risk factor for the development of dementia in humans. For example, three recent retrospective cohort studies (118-120) reported an association between PTSD and an increased risk for dementia among U.S. veterans. However, these prior studies did not account for psychotropic medications commonly used in management of PTSD despite evidence to indicate that these treatments might affect cognitive functioning and possibly, the risk for developing dementia.

Goals and objectives

The goal of this research is to examine the emerging risk factors for dementia. This is a "three paper" thesis. The first paper (published) reviews the literature on the associations between direct central nervous system infections with various organisms and the risk for dementia (121). The next two papers contain original analyses of data from various Veterans Health Administration national databases and examine the potential associations between common clinical bacterial infections, PTSD, psychotropic PTSD medication use with the risk for developing dementia.

Specific aims

Aim 1

Review the existing evidence for infections as possible causes of AD. Specifically, to 1) examine whether AD neuropathology is compatible with an infectious cause, 2) systematically review the evidence associating certain infectious agents with AD in humans, 3) evaluate the evidence suggesting that various clinical and subclinical infections indirectly promote AD progression, including the possibility that patients with AD could be prone to infectious diseases, 4) evaluate correlations between putative infectious agents and the epidemiology of AD, and 5) suggest epidemiologic and basic science studies that might improve on current understanding of the associations between infections and AD and possibly uncover ways to control this prevalent and debilitating disease.

Aim2

Conduct a comprehensive assessment of the associations between several different severity levels of systemic bacterial infections specifically, septicemia, bacteremia, pneumonia, osteomyelitis, septic arthritis, cellulitis, and urinary tract infections, with risk of developing dementia in a nationally representative sample of U.S. veterans aged 56 years and older using a retrospective cohort study design.

Aim 3

Determine the association between PTSD and the risk for developing dementia in a nationally representative sample of U.S. veterans 56 years of age and older and the impact of psychotropic PTSD medication use on this association using a retrospective cohort study design.

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CHAPTER 2

CAN INFECTIONS CAUSE ALZHEIMER'S DISEASE?

(Mawanda F, Wallace RB. *Epidemiol Rev*. 2013;35:161-80.)

ABSTRACT

Late-onset Alzheimer's disease (AD) is the most prevalent cause of dementia among older adults, yet more than a century of research has not determined why this disease develops. One prevailing hypothesis is that late-onset AD is caused by infectious pathogens, an idea widely studied in both humans and experimental animal models. This review examines the infectious AD etiology hypothesis and summarizes existing evidence associating infectious agents with AD in humans. The various mechanisms through which different clinical and subclinical infections could cause or promote the progression of AD are considered, as is the concordance between putative infectious agents and the epidemiology of AD. We searched the PubMed, Web of Science, and EBSCO databases for research articles pertaining to infections and AD and systematically reviewed the evidence linking specific infectious pathogens to AD. The evidence compiled from the literature linking AD to an infectious cause is inconclusive, but the amount of evidence suggestive of an association is too substantial to ignore. Epidemiologic, clinical, and basic science studies that could improve on current understanding of the associations between AD and infections and possibly uncover ways to control this highly prevalent and debilitating disease are suggested.

INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder and the leading cause of dementia among individuals aged 65 years or older. Clinically, AD manifests as progressively deteriorating cognitive function, and a diagnosis is made according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (1) and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders working group (2); this diagnosis is also applied for research purposes. Definitive diagnosis, however, necessitates the histopathologic examination of either biopsy or postmortem brain tissue. In most cases, gradually degenerating memory is the

earliest and predominant cognitive deficit (2, 3), but other cognitive deficits as well behavioral disorders, personality changes, and motor and sensory deficits can become manifest, especially in advanced stages of the disease (4). Typically, symptoms gradually worsen; ultimately, the ability to communicate and perform the activities of daily living is severely impaired, resulting in the loss of independence (4).

AD is categorized into early- and late-onset subtypes depending on whether the onset of clinical symptoms occurs before or after the age of 65 years, respectively. Early-onset AD is uncommon, accounting for less than 1% of all AD cases, and is caused primarily by autosomal dominant mutations in either the amyloid precursor protein (APP) or the presenilin (presenilin-1 or presenilin-2) genes (5-9). In contrast, the exact cause of late-onset AD remains largely unknown. Some risk factors for late-onset AD have been identified and include increasing age (10, 11), lesser educational attainment (12, 13), head trauma (14–16), cardiometabolic disorders such as midlife hypertension (17, 18) and diabetes mellitus (19, 20), and certain genetic variants, most prominently, the apolipoprotein ε4 (ApoE4) allele (21–28). Few other environmental factors have been consistently associated with AD in humans (29, 30).

Infectious agents have been known to cause chronic progressive central nervous system (CNS) diseases and syndromes for well over a century. Several of these agents, such as herpes simplex virus type 1 (HSV-1), *Helicobacter pylori*, *Chlamydophila pneumoniae*, and *Borrelia burgdorferi*, are associated with neurocognitive decrements either in humans or in experimental animal models and have been implicated as possible causes of AD in humans (31-38). These pathogens might induce AD directly through CNS infection and resulting neuroinflammation or indirectly via the various effects of systemic inflammation on the brain. Alternatively, infectious pathogens might induce an autoimmune response that targets the brain, resulting in neuroinflammation and possibly AD (39). Although such possibilities have been suggested, no specific pathogen has been linked conclusively to the causation of late-onset AD in humans.

The present review examines the existing evidence for infections as possible causes of AD. Specifically, our review intended to 1) examine whether AD neuropathology is compatible with an infectious cause; 2) systematically review the evidence associating certain infectious agents with AD in humans; 3) evaluate the evidence suggesting that various clinical and subclinical infections indirectly promote AD progression, including the possibility that patients with AD could be prone to infectious diseases; 4) evaluate correlations between putative infectious agents and the epidemiology of AD; and 5) suggest epidemiologic and basic science studies that might improve on current understanding of the associations between infections and AD and possibly uncover ways to control this prevalent and debilitating disease.

MATERIALS AND METHODS

Search strategy

We searched the PubMed, Web of Science, and EBSCO electronic databases from inception through 2012 for research articles pertaining to infections and AD using the following key words: "Alzheimer's disease" OR “dementia” AND "infection", "Alzheimer's disease" OR “dementia” AND "bacteria", "Alzheimer's disease" OR “dementia” AND "virus", "Alzheimer's disease" OR “dementia” AND "Herpes simplex", "Alzheimer's disease" OR “dementia” AND "Chlamydia", "Alzheimer's disease" OR “dementia” AND "Chlamydophila", "Alzheimer's disease" OR “dementia” AND "Helicobacter pylori", "Alzheimer's disease" OR “dementia” AND "Borrelia burgdorferi", "Alzheimer's disease" OR “dementia” AND "varicella zoster", "Alzheimer's disease" OR “dementia” AND "cytomegalovirus", "Alzheimer's disease" OR “dementia” AND "Treponema", "Alzheimer's disease" OR “dementia” AND "prions", and "amyloid-beta" AND "infection". In addition, we searched the reference lists of all relevant articles and previous reviews found. We limited our searches to original research articles, and research letters. We did not search other literature sources and no attempts were made to contact study authors for additional information.

For the systematic review of the evidence associating certain infectious agents with AD in humans, we proceeded to apply predetermined inclusion and exclusion criteria and conduct systematic data extraction.

Inclusion criteria

We included all studies found which, 1) were original research articles, 2) were conducted in humans 3) studied late onset Alzheimer's disease, 4) were published in English, 5) described the method for AD diagnosis, and 6) described the methods for diagnosis of the infection.

Exclusion criteria

We excluded articles which, 1) studied familial or early onset Alzheimer's disease, 2) studied only dementia other than AD, 3) were conducted in animals, 4) were published in languages other than English and no English translation was available, and 5) were previous reviews or comments.

Data extraction

Data were extracted from full text articles by one reviewer. Extracted items included authors, publication year, study location, study design, sample size, methods for diagnosis of the infection, methods for AD diagnosis, mean age of the study participants, effect measure and main findings.

Study quality and risk of bias assessment

Study quality and risk of bias was assessed for the case control studies examining the associations between Herpes simplex virus 1 and the risk of AD using the Newcastle-Ottawa quality assessment scale for case control studies (40, 41), which was modified slightly for the purpose of this study. Studies received 1 point each for adequate case definition, representativeness of cases, selection of controls, adequate control definition, method of exposure assessment, and using similar method to ascertain exposure status among both cases and controls. In addition, studies could receive up to

3 points for controlling for potential confounders including age, APOE4 allele or other factors. Results showed that the majority of studies were low quality with scores ranging from 3-6 points out of a possible total of 9 points.

RESULTS

The initial database search yielded 6,017 articles, of which 2,960 were duplicates; these were excluded, leaving 3,057 articles. We reviewed some of these abstracts and selected key, representative papers to include in the review. For the systematic review of the 4 major pathogens associated with AD, the initial database search yielded 664 articles; these were categorized by pathogen and arranged according to author and title, and duplicates and irrelevant articles were excluded (Figure 2.1). All the relevant publications were included in the systematic review.

Compatibility of central nervous system Alzheimer's disease pathology with infections

AD neurohistopathology is characterized by the simultaneous presence of neuronal degeneration, intraneuronal neurofibrillary tangles and neuropil threads, and extracellular β-amyloid (Aβ) plaques within particular regions of the brain. Neurofibrillary tangles and neuropil threads reside inside nerve cell bodies and dendritic processes, respectively, and arise as the result of tau hyperphosphorylation, which causes tau to accumulate and aggregate into insoluble fibrils (42-45). Aβ plaques, on the other hand, accumulate in extracellular spaces as the result of gradual deposition and accumulation of specific Aβ peptides (46). Plaque-forming Aβ peptides are derived from the stepwise cleavage of APP, an integral membrane glycoprotein. APP is first cleaved by α- and β-secretase into N- and carboxyl terminal fragments (46, 47). Next, the carboxyl terminal fragments are cleaved by γ-secretase into 39 to 42 amino acid residue long Aβ peptides, of which the 42 (Aβ1–42) and 40 (Aβ1–40) amino acid residue long peptides primarily constitute the AD Aβ plaques (45).

Despite being the histopathologic hallmarks of AD, Aβ plaques, neurofibrillary tangles, and neuropil threads are not unique to AD; they occur in a variety of other CNS conditions, including chronic infections. Neurofibrillary tangles and neuropil threads, for

example, have been observed in cases of measles virus-induced subacute sclerosing pan-encephalitis (48, 49) and in general paresis of tertiary syphilis (50), whereas amyloid plaques are present in the majority of cases of some prion protein diseases such as Kuru and Creutzfeldt-Jakob disease (51-53). In addition, amyloidopathy—a condition characterized by elevated levels of serum amyloid and by amyloid deposition and aggregation in tissues—is a frequent occurrence in several acute and chronic systemic inflammatory conditions, especially chronic infections like tuberculosis and leprosy (53–60). Furthermore, emerging evidence indicates that Aβ has an antimicrobial property (61), which further supports the possibility that Aβ production and deposition in AD might be induced by infectious pathogens.

AD neuropathology characteristically starts in particular CNS sites, primarily the locus coeruleus, and gradually spreads to other subcortical and cortical sites in a specific sequence (62, 63). In addition, AD neuropathology spreads within anatomically connected CNS sites, from affected sites to only those regions that receive neuronal input from the affected sites (64), yet neurotropic infectious pathogens (e.g., varicella zoster virus and herpes simplex virus types 1 and 2) infect and spread within the nervous system via trans-synaptic and intra-axonal anterograde and retrograde transport (65-68). These findings have led some to suggest that sequential spread of AD neuropathology reflects dissemination of infectious pathogens within the CNS (69-72). Still, sequentially spreading neuropathology is not limited to AD but is also observed in noninfectious pathogen-related disorders—for example, Lewy-body-associated disorders such as Parkinson's disease and dementia with Lewy bodies (73). Moreover, trans-synaptic spread of tau pathology in the absence of infectious organisms has been described in the transgenic mouse model (74).

AD neuropathology is accompanied by a significant inflammatory component in the form of activated microglia and reactive astrocytes within the neuritic plaques, as well as elevated levels of various CNS and systemic inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α (75-78). Although inflammation is not triggered only by infectious pathogens, it is typical of most infectious diseases;

hence, AD neuropathology could be a manifestation of an infection. Evidence from animal models supports this hypothesis: For example, the injection of a bacterially derived endotoxin, lipolysaccharide, into the mouse hippocampus has been found to trigger a neuroinflammatory response characterized by activation of microglia, infiltration by macrophages and T cells, and hyperphosphorylation and aggregation of tau proteins (79). Intraperitoneal injection of lipolysaccharide in mice also resulted in significantly elevated levels of proinflammatory cytokines and Aβ1-42 (80) in the mouse hippocampus; however, interpretation of these experiments is complicated by the observation that microglia can detect and be activated by Aβ deposition and tau aggregation in the absence of infection (81). An alternative hypothesis is that neuroinflammation in AD reflects an autoimmune response, in which epitopes from an infectious pathogen trigger production of autoantibodies that attack the brain. In support of this hypothesis, autoantibodies have been found in patients with AD (82-85), and mounting evidence indicates that a significant aspect of the disease is immune deregulation (86-89). Nevertheless, no specific pathogen has been linked to the autoantibodies in AD.

Infectious agents that could be associated with Alzheimer's disease

Several researchers have posited that certain specific infectious pathogens cause AD in humans. The following section systematically reviews the evidence associating Herpes simplex virus type-1, *C. pneumoniae*, *B. burgdorferi*, *H. pylori*, prions, and other specific infectious pathogens with the pathogenesis of AD.

Herpes simplex virus type 1

HSV-1 is a is highly neurotropic double-stranded DNA virus that is transmitted from person to person, mainly through direct contact with discharging vesicles or infected bodily fluids such as saliva (90). Shortly after initial infection, HSV-1 infects and remains latent within neural tissues, primarily the trigeminal ganglia (91). HSV-1 infection is characterized by prolonged latent periods and episodic recrudescence. In humans, HSV-1 is mainly associated with herpes labialis, but HSV-1 is also known to

cause genital herpes and is the leading cause of sporadic encephalitis in the United States (92).

HSV-1 also has been implicated in the possible causation of AD. The seroprevalence of HSV-1 increases with age and is highest among those aged 60 years and older (90, 93). Similarly, the prevalence of AD increases with age and is highest among those aged 65 years and older (94). In addition, genes that influence immune responses to HSV-1 infection also influence the risk of developing AD (95), and HSV-1 proteins that regulate host cell infectivity and viral replication interact with the products of many AD susceptibility genes, such as ApoE4, presenlin 1, presenlin 2, and APP (96). Furthermore, the combination of ApoE4 genotype and HSV-1 infection is associated with an increased risk of AD: Using polymerase chain reaction (PCR), Lin et al. (97) examined postmortem brain tissue samples from 36 patients with AD and 36 age-matched normal controls and found a significantly higher frequency of the ApoE4 genotype in the HSV-1-positive AD samples (table 2.1). A similar study by Itzhaki et al. (98) also found the combination of infection with HSV-1 and ApoE4 genotype to be associated with a significantly higher risk of AD, but neither HSV-1 infection nor ApoE4 genotype was independently associated with AD risk. Moreover, Beffert et al. (99) found no association at all between AD risk and the combination of HSV infection and ApoE4 genotype.

Serologic analysis, however, has also linked HSV-1 to increased AD risk. In a population-based cohort study, Letenneur et al. (32) followed 512 initially dementia-free older individuals for 14 years and found, after controlling for age, gender, educational level, and ApoE4 status, that anti-HSV-1 immunoglobulin M antibody seropositivity was associated with a significantly increased risk of developing AD. In addition, high serum anti-HSV-1 immunoglobulin M antibody levels are associated with lower levels of plasma Aβ1-42 and Aβ1-40 (100)—a biomarker for AD.

HSV-1 also has been detected in postmortem brain tissue from AD cases (31, 101-103) (Table 1). Notably, in situ hybridization of postmortem brain tissue samples

from 21 patients with AD and 19 controls detected HSV-1 DNA in a significantly higher proportion of AD samples (81%) than controls (47.4%) (101). Similarly, using PCR, Jamieson et al. (31) detected HSV-1 thymidine kinase gene sequences in a higher proportion of brain tissue samples from AD cases (14/21) than controls (9/15); in addition, among all HSV-1-positive samples, HSV-1 was detectable only at CNS sites primarily affected in AD, such as the temporal cortex and hippocampus. Furthermore, using in situ PCR to detect HSV-1 DNA and immunohistochemistry to detect amyloid plaques in AD postmortem brain tissue samples, Wozniak et al. (104) found that 90% of Aβ plaques contained HSV-1 DNA.

Evidence also directly links HSV-1 infection to abnormal APP metabolism and elevated CNS Aβ peptide production. APP is a major component of the HSV-1 viral envelope (65). Moreover, the HSV-1 viral envelope contains glycoprotein B, which possesses an internal sequence that is homologous to the carboxyl-terminal region of AD Aβ peptides and is capable of self-assembling into insoluble fibrils ultrastructurally indistinguishable from AD Aβ plaques (105). In addition, in vitro evidence indicates that HSV-1 interferes with normal intraneuronal APP transportation and distribution (106) and inhibits Aβ peptide degradation and secretion by preventing the fusion of Aβ peptide autophagosomes with lysosomes (107). Furthermore, human neuroblastoma cells inoculated with HSV-1 showed marked reduction in intracellular APP levels, elevated levels of C-terminal APP fragments, and significantly increased levels of both Aβ1-40 and Aβ1-42 peptides (65, 108, 109).

Tau pathology and neurodegeneration also have been linked directly to HSV-1 infection. Mouse neuronal cultures infected with HSV-1 displayed abnormal microtubule dynamics, tau hyperphosphorylation, and significant neurite damage ultimately resulting in apoptosis (110). Similar tauopathies were observed in HSV-1-infected human neuroblastoma cell cultures (111). Moreover, Wozniak et al. (112) found that, in vitro, HSV-1 infection induced glycogen synthase kinase 3 beta and protein kinase A to phosphorylate tau at sites phosphorylated in AD samples (i.e., serine 202, threonine 212, serine 214, serine 396, and serine 404).

Nevertheless, the role of HSV-1 in the causation of AD remains questionable. Several studies of postmortem brain tissues found no evidence linking HSV-1 to AD (113-119). For example, Taylor et al. (114) used in situ hybridization to analyze postmortem brain samples (55 from 8 patients with AD and 57 from 9 non-neurologic control patients), as well as samples from HSV-1-infected mice; with this technique, none of the samples revealed detectable levels HSV-1 DNA. In another in situ hybridization study, Roberts et al. (115) examined postmortem brain specimens from 25 patients with AD and 32 controls, but none hybridized to HSV-1 DNA probes. Similarly, HSV-1 DNA was not detected by Southern blotting in any postmortem brain tissue samples or peripheral blood cells obtained from 5 patients with AD and 5 normal controls (118). These negative findings, however, could be due in part to differences in methodology because in situ hybridization and Southern blotting are less sensitive than PCR in detecting DNA. Consistently, the majority of studies reporting positive findings used PCR. Nevertheless, most PCR-based studies show no significant difference in the frequency of AD versus control brain tissue samples that contain HSV-1 DNA (99, 104, 120-125).

Several serology-based studies also found no evidence to link HSV-1 infection to AD (85, 126, 127). For example, Renvoize et al. (126) analyzed serum from 33 patients with a clinical diagnosis of AD and 28 controls suffering from psychiatric disorders but without evidence of comorbid dementia. They found that serum from the 2 groups did not differ significantly in the levels of antibody titers to various viral pathogens, including HSV-1, but this result is not surprising given the high prevalence of HSV-1 among older adults. Moreover, Ounanian et al. (85) found that controls, rather than patients with AD, showed higher levels of anti-HSV-1 antibody titers. Thus, lack of consistency leaves studies linking HSV-1 to the causation of AD inconclusive.

C. pneumoniae

C. pneumoniae is an obligate intracellular bacterium that is spread from person to person mainly through droplet inhalation. *C. pneumoniae* is associated primarily with

lower-respiratory-tract disease such as pneumonia and bronchitis, but increasing evidence implicates *C. pneumoniae* in several other acute and chronic human diseases, such as atherosclerosis (128-130). Evidence also suggests that *C. pneumoniae* could be involved in the pathogenesis of AD.

C. pneumoniae has been detected, both directly and indirectly, in postmortem AD brain tissue (Table 2.2). For example, Balin et al. (33) used various methods, including PCR, electron and immunoelectron microscopy, culture, reverse-transcription PCR, and immunohistochemistry, to test postmortem brain tissue samples from 19 cases with AD and 19 controls without AD for *C. pneumoniae*. Evidence of *C. pneumoniae* was found in 17 of 19 AD samples but only 1 of 19 control samples. In addition, among the positive AD samples, *C. pneumoniae* was detected only within areas affected by AD neuropathology. A case-control study by Gerard et al. (34) reported similar findings: With PCR alone, postmortem brain tissue samples from 27 AD cases and 27 non-AD controls were analyzed for evidence of *C. pneumoniae* DNA. *C. pneumoniae* Cpn1046 and Cpn0695 genes were present in 20 of 27 AD specimens, compared with only 3 of the 27 controls. Moreover, *C. pneumoniae* DNA in the AD brain tissue samples was detected only within the astrocytes, microglia, and neurons in close proximity to Aβ plaques and neurofibrillary tangles.

Similarly, Paradowski et al. (35) used PCR to analyze cerebral spinal fluid (CSF) samples from 57 patients with AD, 21 patients with vascular dementia, and 47 normal controls. They detected *C. pneumoniae* DNA in a significantly higher proportion of patients with AD (43.9%) than controls (10.6%). The presence of *C. pneumoniae* DNA in CSF also was associated strongly with the risk of AD (odds ratio = 7.21), but there was no association between *C. pneumoniae* in CSF and CSF levels of either hyperphosphorylated tau protein or Aβ peptides.

A serology-based study by Hammond et al. (131) also reported positive findings. With immunohistochemistry, 5 AD and 5 non-AD postmortem brain tissue samples were tested for evidence of *C. pneumoniae*. *C. pneumoniae* antigens were detected

intracellularly, within neurons, neuroglia, endothelial cells, and peri-endothelial cells, and in extracellular spaces in the frontal and temporal cortices in all 5 AD samples but only 2 of the non-AD samples. Furthermore, immunoreactivity was confined to CNS regions with Aβ deposition.

Studies in animals as well as in vitro also allude to a possible association between AD and *C. pneumoniae*. *C. pneumoniae* expresses a kinase that phosphorylates secreted structural proteins in vitro, specifically at motifs similar to those hyperphosphorylated in AD (132). In addition, mice intranasally infected with *C. pneumoniae* isolated from a postmortem AD brain developed amyloid deposits similar to AD Aβ plaques (133). Moreover, the density, size, and number of these deposits increased significantly, as the infection progressed. Similarly, Boelen et al. (134) found extracellular Aβ immunoreactivity in mouse brains at 1 and 3 months after intranasal infection with *C. pneumoniae*. These findings, however, were inconclusive because Aβ immunoreactivity also was detected in brains of mock-infected mice, as well as in brains of mice that were neither *C. pneumoniae* nor mock infected. Still, these studies merit particular attention in light of Koch's postulates, which suggest, as one of the criteria for establishing a causal association, that putative microorganisms isolated from affected tissue should cause the disease when inoculated into a susceptible host (135).

Furthermore, eradication of *C. pneumoniae* in infected patients with AD results in significant clinical improvement. In a randomized clinical trial, Loeb et al. (136) randomly assigned 101 patients with probable or mild to moderate AD to receive either placebo or daily doses of oral doxycycline (200 mg) plus rifampin (300 mg). Although the treatment and control groups showed similar rates of *C. pneumoniae* infection, after 3 months of therapy, the rates of cognitive decline and dysfunctional behavior in the treatment group were significantly less than in the placebo group.

Again, however, several studies found no evidence to suggest an association between *C. pneumoniae* infection and AD pathogenesis (137-145). For example, Nochlin et al. (137) examined paraffin-embedded tissue sections of autopsy brain samples from

12 patients with AD and 13 controls without AD but failed to detect *C. pneumoniae* DNA in any of the AD or control samples using both immunocytochemistry and PCR. Similarly, Gieffers et al. (138) analyzed paraffin-embedded AD brain tissue samples using nested PCR as well immunocytochemistry but detected neither *C. pneumoniae* DNA nor antigens in either case or control samples. Ring and Lyons (139) also used nested PCR and, in addition, attempted to culture *C. pneumoniae* from postmortem samples of various regions of the brain, including those typically affected by AD, from 15 patients with AD and 15 normal controls. All cultures, however, tested negative for growth, and *C. pneumoniae* DNA was not detected in any AD or control samples. Wozniak et al. (140) also found no evidence of *C. pneumoniae* DNA in any of 4 AD, 19 vascular dementia, or 16 control brain specimens tested, and Taylor et al. (141) found no evidence of *C. pneumoniae* in any of 19 AD or 2 control brain specimens tested with PCR.

Finally, Bruunsgaard et al. (142) found no association of serum anti-*C. pneumoniae* antibody titers with either dementia or cardiovascular disease. Again, ambiguous study findings leave the exact role of *C. pneumoniae* in the pathogenesis of AD unclear.

B. burgdorferi

Another infectious pathogen that has been evaluated extensively for a possible etiologic link to AD is *B. burgdorferi*. *B. burgdorferi* is a spirochete bacterium that is transmitted from vertebrate hosts to humans through the bite of an infected tick of the Ixodes family, mainly I. scapularis and I. pacificus in the United States (146). Although the primary host reservoir is the white-footed mouse (Peromyscus leucopus), *B. burgdorferi* has been isolated from several other vertebrate species (146). *B. burgdorferi* is the etiologic agent of Lyme borreliosis, a disease characterized by erythema chronicum migrans at the site of the tick bite immediately after initial infection, as well as by various neurologic and cardiac symptoms and by monoarticular large-joint arthritis in advanced stages (147). *B. burgdorferi* also has been directly detected and isolated

from postmortem AD brain tissue samples, which suggests a possible etiologic association.

MacDonald (148) was the first to report direct visualization and culture of *B. burgdorferi* spirochetes from the postmortem brain tissue of 2 AD cases. Subsequently, MacDonald found 2 more AD cases in which *B. burgdorferi* spirochetes were directly visualized as well as cultured from postmortem brain tissue samples (149, 150). Several other researchers have reported similar findings (Table 2.3). For example, Meer-Scherrer et al. (151) detected *B. burgdorferi* DNA in association with AD neuropathology in the postmortem brain tissue of an 83-year-old female patient who had been treated unsuccessfully for Lyme disease and who later developed progressive dementia. In addition, in a case-control study, Miklossy (38) detected *B. burgdorferi* spirochetes in blood, CSF, and brain tissue of 3 of 14 histopathologically confirmed AD cases but in none of the 13 age-matched controls. A subsequent follow-up study involving 3 of the *B. burgdorferi*-positive AD cases found that *B. burgdorferi* antigens and genes were localized within Aβ deposits (152). Furthermore, a pooled analysis of studies investigating the association between *B. burgdorferi* and AD found that *B. burgdorferi* was 13 times more frequent in the brains of patients with AD than in brains of controls (153).

B. burgdorferi also has been found to induce AD-like neuropathology in vitro. Mammalian glial and neuronal cells exposed to *B. burgdorferi* and lipolysaccharide showed morphologic changes analogous to Aβ deposits and demonstrated increased levels of APP and hyperphosphorylated tau protein 2–8 weeks after exposure (154).

Nevertheless, several rigorous studies found no evidence to suggest that *B. burgdorferi* is causally linked to AD (155-160). For example, Pappolla et al. (155) tested postmortem brain tissue samples from 6 histopathologically confirmed AD cases and 4 non-AD controls by culturing samples for *B. burgdorferi*, but all were negative for growth. Despite electron microscopy of the culture supernatant, direct immunofluorescence and acridine orange fluorescence, indirect immunofluorescence

and enzyme-linked immunosorbent assay of CSF, as well as direct immunofluorescence of imprint preparations of brain tissues, none of the AD or control samples showed evidence of *B. burgdorferi*. In a similar, multipronged approach, Gutacker et al. (156) found no evidence of *B. burgdorferi* in any of 10 postmortem AD brain tissue samples tested with both standard and nested PCR, as well as enzyme-linked immunosorbent assay and Western blotting for anti-*B. burgdorferi* antibodies. Marques et al. (157) also used PCR but found no evidence of *B. burgdorferi* in any of the postmortem brain tissue samples from 15 patients with AD and 15 age- and sex-matched controls, and McLaughlin et al. (158) tested for *B. burgdorferi* spirochetes in peripheral blood and fresh postmortem brain specimens of 22 patients with AD and 6 controls, but only 1 tested positive. Another large case-control study by Galbussera et al. (159) found no conclusive evidence of *B. burgdorferi* in any of the serum samples from 50 patients with AD, 23 controls without AD, or 25 healthy caregivers of the patients with AD using enzyme-linked fluorescent assay. Because of these mixed findings, the role of *B. burgdorferi* in the etiology of AD remains unresolved.

H. pylori

H. pylori are spiral-shaped, Gram-negative bacteria associated mainly with upper gastrointestinal disorders such as chronic gastritis, peptic ulcer disease, and gastric cancer. Recently, *H. pylori* was implicated in the pathogenesis of several extra-digestive diseases, including atherosclerosis (161, 162), chronic respiratory disease (163), and idiopathic thrombocytopenic purpura (164-166). Evidence implicating *H. pylori* in AD pathogenesis also has emerged (Table 2.4). For example, Kountouras et al. (36) used enzyme-linked immunosorbent assay to analyze serum and CSF of 27 patients with AD and 27 age-matched cognitively normal controls and found significantly higher mean concentrations of anti-*H. pylori* immunoglobulin G antibodies in patients with AD. Malaguarnera et al. reported similar findings (37); they analyzed serum levels of anti-*H. pylori* antibodies in 30 patients with AD, 30 patients with vascular dementia, and 30 nondemented controls matched by age, educational level, and nutritional and socioeconomic status and found significantly higher levels of both anti-*H. pylori*

immunoglobulin G and immunoglobulin A antibodies in patients with AD than in controls. Furthermore, using histology, Kountouras et al. (167) found the prevalence of *H. pylori* in gastric mucosal biopsies to be significantly higher among patients with AD than among control patients without AD who had iron deficiency anemia.

H. pylori is also linked to increased severity of cognitive impairments in AD. Patients with AD and with *H. pylori* infection performed significantly worse than noninfected patients on the Mini-Mental State Examination (36, 168). In addition, anti-*H. pylori* immunoglobulin G antibody concentrations in CSF correlated with the severity of cognitive impairments among patients with AD (36), and CSF tau levels were significantly elevated among *H. pylori*-infected patients with AD (168). Moreover, successful eradication of *H. pylori* in patients with AD with the use of triple therapy led to significant improvements in both cognitive and functional status symptoms even 2 years after treatment (169) and resulted in a significantly higher 5-year survival rate (170).

There is also evidence of an association between *H. pylori* infection and mild cognitive impairment, which now is known to precede AD in the majority of cases. *H. pylori* seroprevalence rates were found to be significantly higher in patients with mild cognitive impairment than in normal controls (171), and serum anti-*H. pylori* immunoglobulin G concentrations correlated with the level of cognitive functioning.

Still, as with the other pathogens discussed, a causal link between *H. pylori* and AD remains uncertain. The body of evidence is limited, and the exact mechanisms through which *H. pylori* might contribute to the genesis of AD remain undetermined. Because *H. pylori* is not known to be neurotropic, it is unlikely to induce neuroinflammatory effects directly. Nevertheless, *H. pylori* might cause CNS endothelial damage, neuroinflammation, neurodegeneration, and possibly AD through various systemic effects that have been observed in other *H. pylori*-associated conditions, such as enhanced platelet and platelet-leukocyte aggregation, release of inflammatory and vasoactive substances, development of cross-reactivity with host antigens, production

of reactive oxygen metabolites, and increased homocysteine (172). It remains to be determined whether these mechanisms operate in AD, but evidence from a study by Ge and Sun (173) indicates that the cytoplasmic protein Hpn, produced by *H. pylori*, aggregates into amyloid-like fibrils in vitro.

To our knowledge, so far, only 1 study has reported negative findings with regard to the association between *H. pylori* and AD. Shiota et al. (174) measured urinary levels of anti-*H. pylori* antibodies in 385 patients with AD and 97 controls and found no significant difference.

Evidence linking *H. pylori* to AD is still limited, but these preliminary studies suggest that patients with AD and patients with mild cognitive impairment might benefit from rigorous *H. pylori* treatment and eradication. Given the potential implications of these findings for the prognosis and quality of life of patients with AD, further research is required to verify these findings.

Prions

The possibility that AD could be instigated through a prion-like mechanism also has been explored. Prions are implicated in the etiology of several chronic neurodegenerative disorders in humans, including Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and kuru, as well bovine spongiform encephalitis in cattle and scrapie in sheep and goats (175). The infectious agent of prion diseases is an abnormally folded isoform of the prion protein, which via seeding or nucleation induces the templated misfolding of normal prion protein molecules (175, 176).

Several pathologic correlates exist between prion diseases and AD. These include the presence of misfolded protein aggregates consisting of highly ordered polymeric isoforms with cross-β-sheet-rich structures, neurodegeneration, and progressively and sequentially spreading neuropathology (177-179). In addition, as noted previously, AD-like neuropathology in the form of Aβ deposits is present in most cases of Creutzfeldt-Jakob disease and kuru. Evidence also suggests that prion-like seeding contributes to AD

neuropathology. For example, several studies found inoculation of either human or mouse AD brain extracts containing aggregated Aβ peptides to induce Aβ deposition in the brains of recipient APP transgenic mice (180-183). Similarly, several studies found injection of either human or mouse AD brain extracts containing tau aggregates to trigger the formation of sequentially spreading tau aggregates in the brains of recipient transgenic mice (184, 185). Seeding studies using synthetic Aβ fibrils, however, generated mixed results: For example, whereas Stöhr et al. (186) found that synthetic Aβ aggregates induce Aβ deposition and propagation in mice, in a study by Meyer-Luehmann et al. (181), synthetic Aβ40 and Aβ42 aggregates, or a mixture of both, failed to induce seeding of Aβ deposition in vivo. Nevertheless, synthetic Aβ aggregates demonstrate lower specific bioactivity than that of brain-derived aggregates (186), which might explain the inconsistent results.

Studies also have suggested a link between prion disease susceptibility genes and AD, but this evidence is highly controversial. Whereas some studies claimed an association between polymorphisms of the human prion protein (PRNP) gene and AD risk, (187-191), other studies found no such evidence (192-196). Studies investigating the association between AD susceptibility genes, such as ApoE4, and the risk of prion disease also generated mixed results, with some finding an association (197, 198) and others finding no evidence of an association (199). Finally, known prion diseases are generally rare, which is not compatible with the incidence and prevalence rates of AD.

O*ther infectious agents*

Several other infectious pathogens, although not widely studied, have been explored for possible associations with AD. For example, Friedland et al. (200) tested CSF and serum specimens from patients with AD, patients with Down's syndrome (which is associated with early-onset AD), patients with non-AD dementia, and normal controls for antibodies to human immunodeficiency virus type-1, caprine arthritis encephalitis virus, and equine infectious anemia virus but failed to detect antibodies against any of these lentiviruses in any of the specimens. Studies also investigated whether

herpesviruses other than HSV-1, including HSV-2, human herpesvirus 6, Epstein-Barr virus, varicella zoster virus, and cytomegalovirus, are associated with AD. Like HSV-1, these viruses are highly prevalent in the general population and cause chronic infections with prolonged latent periods and episodic recrudescence. Moreover, HSV-2 and varicella zoster virus are highly neurotropic, infecting and remaining latent in neural tissues. Nevertheless, most studies so far have found no association between any of these herpesviruses and AD. For example, using PCR, Lin et al. (97) failed to detect varicella zoster virus in any of the postmortem brain tissue samples from either patients with AD or normal controls. Using Southern blotting, Kittur et al. (118) did not detect HSV-1, HSV-2, Epstein-Barr virus, or cytomegalovirus in peripheral blood cells and postmortem brain tissue from patients with AD and normal controls. Moreover, Renvoize et al. (126) analyzed serum from 33 patients with AD and 28 controls but found no statistically significant differences in titers against the herpesviruses HSV and cytomegalovirus; against the non-herpesviruses adenovirus, influenza A, influenza B, measles; or against bacteria, including *Chlamydia* group B, *Coxiella burnettii*, or *Mycoplasma pneumoniae*. Although Strandberg et al. (201) found herpesvirus seropositivity to be associated with a significantly increased risk of cognitive impairments among older adults; their study did not ascertain whether any of the herpesviruses tested for (including cytomegalovirus, HSV-1, and HSV-2) were independently associated with the increased risk of cognitive impairment. Of the herpesviruses other than HSV-1, only human herpesvirus 6 has been remotely associated with AD. Using PCR, Lin et al. (202) detected human herpesvirus 6 DNA sequences in a higher proportion of postmortem AD brain tissue samples than samples from age-matched normal controls; however, in a similar study, Hemling et al. (203) found no significant difference in the frequency of occurrence of human herpesvirus 6, cytomegalovirus, or varicella zoster virus between AD cases and controls.

Studies also have investigated several other bacterial pathogens for possible associations with AD. As noted previously, Renvoize et al. (126) found no statistically significant correlations between serum antibody titers to *Chlamydia* group B, *Coxiella*

burnettii, or *Mycoplasma pneumoniae* and AD. On the other hand, Riviere et al. (160) found oral *Treponema, including T. denticola, T. pectinovorum, T. vincentii, T. amylovorum, T. maltophilum, T. medium, and T. socranskii* in a significantly higher proportion of postmortem brain specimens from AD cases than controls. These results have, however, not been replicated.

The possible role of systemic infections in Alzheimer's disease and other dementias

In addition to the possibility that neurotropic agents might directly infect the brain and cause later-life neurologic sequellae, another mechanism by which infections could promote the genesis of AD is through the varied effects of systemic infections on the brain. Among children, for example, studies show that those with recurrent systemic infections demonstrate significant cognitive impairments in later childhood or adult life (204-206), and those surviving severe sepsis demonstrate significantly worse cognitive function than the general population (207).

Sepsis is associated with decreased brain metabolism (208), impaired microcirculation (209), and oxidative stress (210, 211), which could result in neuronal dysfunction and neurodegeneration. Sepsis also is associated with increased levels of circulating inflammatory chemokines, cytokines, and nitric oxide, all of which have neurotoxic properties (212-215). In addition, evidence shows that cytokines that are generated by inflammatory events outside the CNS reach macrophages in the brain, trigger the conversion to the microglia phenotype, and increase interleukin-1beta expression and axonal injury (216). Taken together, these findings suggest that severe, recurrent, or chronic systemic infections, of various types, can damage the CNS permanently, ultimately manifesting as cognitive impairments or dementia. Indeed, this hypothesis is supported by experiments in a rat model in which lipopolysaccharide-induced sepsis resulted in neurodegeneration in the hippocampus and prefrontal cortex, as well as significant memory deficits up to 3 months after recovery from the sepsis (217). An example evocative of this process in humans has recently been pointed out: Iwashyna et al. (218) found that survivors of severe sepsis have a significantly higher risk

of developing moderate to severe cognitive impairments even up to 8 years after the event. Moreover, the risk of cognitive impairments increased significantly over time.

There is also evidence to suggest that individuals with AD experience significantly higher rates of various systemic infections, which further supports the hypothesis that systemic infections could play a role in the causation or promotion of AD. For example, nursing home residents with AD were found to have higher rates of hospitalization for infections, including pneumonia, gastroenteritis, and urinary tract infections (219). In addition, over a 4-year period, Perls and Herget (220) found that rates of upper respiratory infections were significantly and consistently higher in an AD special care unit than in traditional nursing home units. Similar results were found among community-dwelling persons with AD. For example, Heun et al. (221) found significantly higher rates of hospitalization for infectious diseases such as pneumonia and urinary tract infections among community-dwelling elderly patients. Natalwala et al. (222) reported similar findings, and Albert et al. (223) found the rates of pneumonia and other infectious diseases, at discharge diagnoses, to be significantly higher among patients with AD than among controls.

One must be cautious when interpreting these data as evidence that systemic infections cause AD and other dementia. Patients with AD might be more susceptible to infectious disease because of the cognitive and motor deficits associated with AD. Nevertheless, there is evidence to suggest that individuals with AD could be more susceptible to infections well before AD onset. For example, the ApoE4 genotype, a well-established risk factor for late-onset AD, is also strongly associated with increased susceptibility to and severity of infections in adulthood, even though it appears to exert a protective effect during early childhood (224). Evidence indicates that ApoE4 enhances the attachment and entry into host cells by various infectious pathogens, including human immunodeficiency virus type-1, HSV-1, and *C. pneumoniae* (225-227). ApoE4 also is associated with increased recurrence of genital herpes (228) and an enhanced immune response to infections and sepsis (229). These findings suggest the increased

risk of late-onset AD that is associated with ApoE4 could result in part from a greater susceptibility to infection.

Compatibility of an infectious etiology with the epidemiology of other Alzheimer's disease risk factors

Many potential risk factors have been implicated in the complex epidemiology of AD and related dementias; not all are widely accepted. For example, claims that cigarette smoking is linked to AD remain controversial (30). Nonetheless, for any risk factor generally associated with AD, questions can be raised as to whether the factor is compatible with the infectious etiology for AD and related dementias. Although an exhaustive review of such correlates is not presented out here, a brief consideration of 2 groups of risk factors is offered. The first is a set of AD risk factors associated with infant and childhood characteristics, including lower socioeconomic status and poverty, minority status (African-American and Hispanic ethnicity in the United States), and lower educational attainment and poorer educational performance (230, 231). This set of risk factors and the economic gradient it represents are also associated with an increased risk of several categories of early-acquired infections, such as tuberculosis, sexually transmitted infections (including herpesvirus), and *H. pylori* (232, 233). Although this "compatibility" is noted, these childhood social and ethnic gradients also might be associated with putative noninfectious causes of AD, such as head trauma (232).

Another often-suspected group of AD risk factors is cardiometabolic disorders, such as midlife hypertension, diabetes mellitus, obesity, and their incumbent vascular diseases (232, 234). Not only might obesity directly affect metabolism in ways that affect brain function (235), but obesity also might have other connections. Like childhood infections, obesity inversely correlates with socioeconomic status (236). Also, obesity is associated with increased risk of several types of infectious outcomes in adults, including surgical-site and nosocomial infections, periodontitis, and skin infections (237), some of which could become chronic. Of interest, seroprevalence

studies suggest that some infections (e.g., HSV-1, cytomegalovirus) are linked to central adiposity, which has been reported to be an AD risk factor in women but not in men (238). More generally, obesity seems to impair immune function in both humans and animal models, which likely increases the risk for several community-acquired infections, including *H. pylori* (239). These findings support the idea that cardiometabolic disorders are associated with AD and are also linked to infections, which supports the infectious AD-etiology hypothesis.

Infections as promoters of Alzheimer's disease

Another interpretation of the data associating infections with AD might be that infections are not the primary cause of AD, but rather, they exacerbate nascent CNS pathology already present at the time of infection. The fact that various infectious pathogens have been detected in the postmortem AD brain, particularly in areas showing AD neuropathology, might suggest that neuropathologic changes in the AD brain render affected areas susceptible to infections. To support this hypothesis, Wojtowicz et al. (240) found evidence that synthetic Aβ fibrils promoted the infection of target cells by enveloped viruses such as HSV-1. In addition, there is evidence to suggest that AD neuropathology impairs blood-brain barrier function, which could potentially increase the risk of CNS infections. Studies on this question however, yielded controversial results; some found evidence of blood-brain barrier disruption in AD (241-244), whereas others did not (245-247).

DISCUSSION AND CONCLUSIONS

Our review of the literature suggests that infections possibly play a role in the pathogenesis of AD. Multiple studies directly and indirectly detected various infectious pathogens in AD brain tissues; moreover, pathogens were detected primarily in or near brain areas showing AD neuropathology. Additionally, studies have shown that certain infectious agents, such as HSV-1 and *C. pneumoniae*, can induce AD neuropathologic changes in vitro and in vivo. Finally, it is important to note that the infectious AD hypothesis is compatible with the epidemiology of some of the well-established risk

factors for AD and with other suggested hypotheses, such as oxidative stress and neuroinflammation.

Still, the evidence linking AD to an infectious cause is incomplete. To date, no single infectious agent has been consistently and conclusively associated with the etiology of AD. Studies investigating specific viral, bacterial, or prion-like pathogens produced mixed results, whereas associations between other pathogens such as human herpesvirus 6, cytomegalovirus, and *H. pylori* have not yet been exhaustively studied. Additionally, none of the human studies provided evidence that primary CNS infection or secondary spread of infection to the CNS preceded the onset of AD neuropathologic changes. Notably, most studies examined only small sample sizes, precluding any meaningful statistical analysis. Moreover, in some studies, pathogen detection relied on indirect methods such as serology, which does not demonstrate conclusive evidence of the presence or absence of an infectious pathogen or, by implication, an association with AD. Furthermore, the majority of the important work on the association between AD and particular infectious pathogens has been conducted by a few investigative groups. Also, from an epidemiologic perspective, publication bias is a strong potential limitation. It is possible that some of the studies with negative findings have not been published. In fact, some of the negative studies we found were published only as research letters. Nevertheless, we included these studies in our review.

Previous reviews on the issue have drawn differing conclusions. For example, whereas Miklossy et al. (143) identified *B. burgdorferi* as the most probable cause of AD on the basis of both Koch's postulates and Bradford Hill criteria for causation, Honjo et al. (248) identified *C. pneumoniae* as the most likely cause of AD on the basis of the Bradford Hill criteria. Nevertheless, evidence shows that HSV-1, *B. burgdorferi*, and *C. pneumoniae* each fulfill many but not all of both the revised Koch's postulates (249) and the Bradford Hill criteria (250). For example, although nucleic acids belonging to each of these organisms have been detected in the AD brain, particularly in areas affected by AD neuropathology, these nucleic acids also have been detected in normal brain tissue samples.

Although no single infectious agent has been linked conclusively to the causation of AD, several different infectious pathogens have been detected directly in AD brain tissue, which raises other possibilities for interpretation. For instance, various neurotropic agents might have a causal or promoting role, depending on the circumstances of exposure and possibly host factors (e.g., genetic constitution). Alternatively, viral and bacterial pathogens might be found more often in AD brain tissue because AD neuropathology increases the susceptibility of affected areas to infections. Moreover, systemic infections might play a role in AD pathogenesis, but issues surrounding any role for systemic infections are complex. Indeed, research addressing whether late-life cognitive decline can be linked to adulthood chronic infections bacterial or otherwise, is limited. This is an important direction for future epidemiologic inquiry.

Regardless of whether certain infectious agents play a role in the genesis of AD, further work should examine the empirical findings that suggest antibiotic therapy can control AD symptoms or disease progression. For example, more research is needed to determine whether the impact of antibiotics on AD is due to effects on CNS pathogens, other systemic infections, or other AD-related pathologies. Indeed, patients with AD might benefit from prompt diagnosis and treatment of infections.

In conclusion, the particular role infections play in the pathogenesis of AD remains undetermined, but substantial evidence suggests an association. Further research is needed to 1) establish whether CNS infection precedes onset of AD neuropathology or vice versa, 2) determine whether systemic infections put patients at greater risk for AD, 3) define the role of infections in AD progression and prognosis, and 4) examine whether treating patients with AD for various systemic and CNS infections improves their quality of life and survival rate.

Figure 2.1 Systematic review of the major infectious pathogens associated with AD

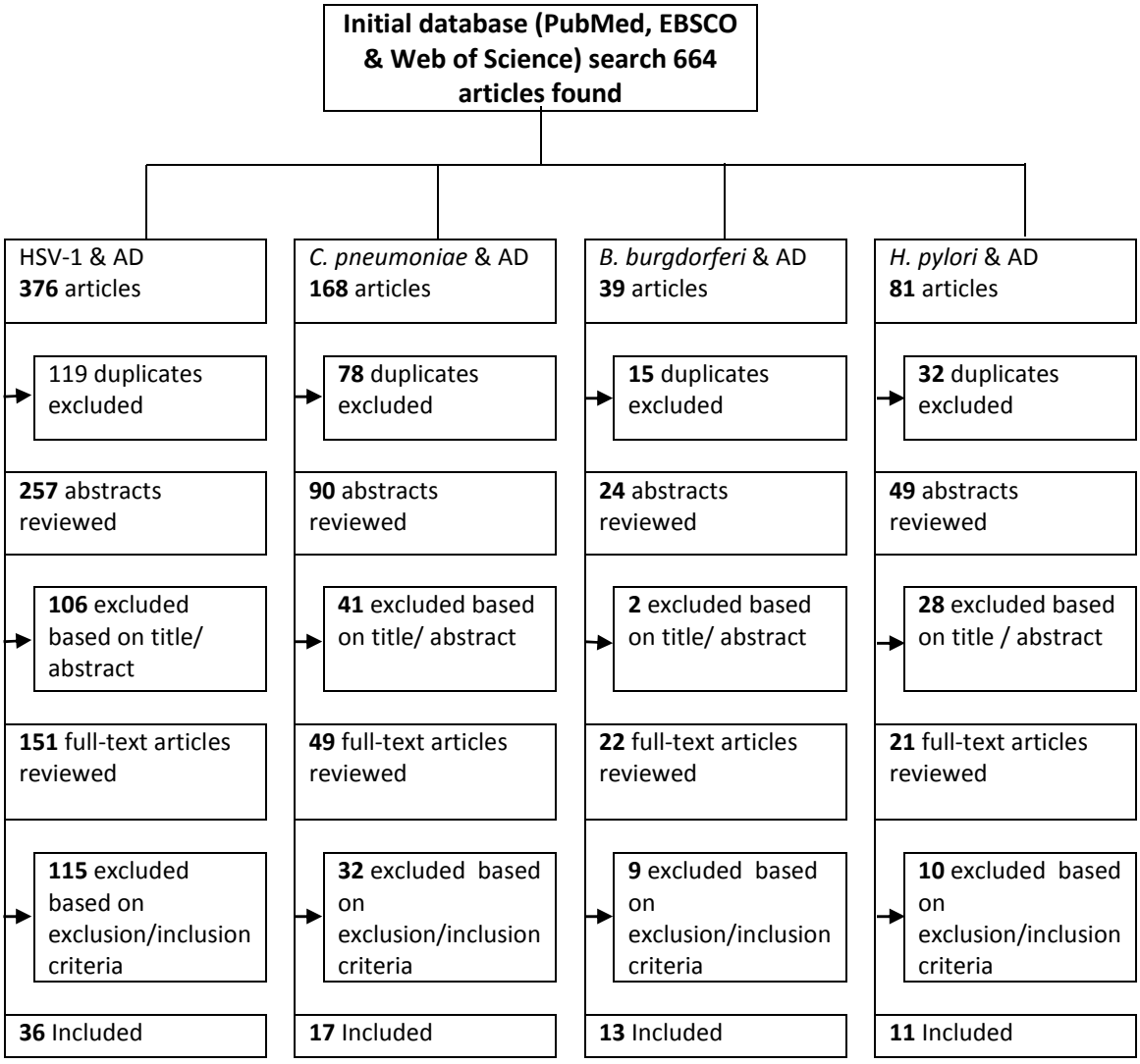

Table 2.1 Epidemiological studies on the association between HSV-1 and AD

Author	Study design	N		Specimen	Method	HSV-1 +ve n (%)		OR(95%CI)
		AD	CTRL			AD	CTRL	
Sequiera et al. (1979) (102)	Case series	3		PM brain	*In situ* hybridization	2		
Middleton et al. (1980) (113)	Case series	3		PM brain	*In situ* hybridization	0		
Mann et al. (1983) (119)	Case control	13	7	PM brain	Immuno-peroxidase staining	1	1	0.5† (0.03-9.46)
Taylor et al. (1984) (114)	Case control	8	9	PM brain	*In situ* hybridization	0	0	
Roberts et al. (1986) (115)	Case control	25	32	PM brain	Immunohisto-chemistry	0	0	
Pogo et al. (1987) (116)	Case control	18	5	PM brain	*In situ* hybridization, Southern blotting	0	0	
Walker et al (1989) (117)	Case control	4	2	PM brain	*In situ* hybridization	0	0	
Ounanian et al. (1990) (85)	Case control	19	21	Serum	ELISA	16(84)	19(90.5)	0.56† (1.08-3.79)
Deatly et al. (1990) (101)	Case control	21	19	PM brain	In situ hybridization	17(81)	9(47.4)	4.72† (1.15-19.4)
Jamieson et al. (1991) (120)	Case control	8	6	PM brain	PCR	8(100)	6(100)	

Table 2.1 Continued

Jamieson et al. (1991) (121)	Case control	8	5	PM brain	PCR	8(100)	5(100)	
Jamieson et al. (1992) (31)	Case control	21	15	PM brain	PCR	14(67)	9(60)	1.33† (0.34-5.27)
Kittur et al. (1992) (118)	Case control	5	5	Blood PM brain	Southern blotting	0	0	
Lin et al. (1996) (97)	Case control	36	36	PM brain	PCR	28(78)	23(64)	1.98† (0.7-5.59)
Itzhaki et al. (1997) (98)	Case control	46	44	PM brain	PCR	36(78)	28(64)	2.06† (0.81-5.22)
Itabashi et al. (1997) (123)	Case control	46	23	PM brain	PCR	14(30.4)	5(21.7)	1.57† (0.48-5.09)
Beffert et al. (1998) (99)	Case control	73	33	PM brain	PCR	54(74)	24(73)	1.07† (0.42-2.69)
Cheon et al. (2001) (124)	Case control	8	10	PM brain	PCR	8(100)	10(100)	
Lin et al. (1998) (125)	Case control	15	4	PM brain	PCR	9(60)	2(50)	1.5† (0.16-13.7)
Mori et al. (2004) (103)	Case control	5	6	PM brain	PCR	5(100)	1(16.7)	
Wozniack et al. (2005) (127)	Case control	27	13	CSF	ELISA	14(52)	9(69)	0.48† (0.12-1.94)
Wozniack et al. (2009) (104)	Case control	6	5	PM brain	PCR	6(100)	5(100)	

AD, Alzheimer's disease; CI, confidence interval; CSF, cerebral spinal fluid; CTRL, controls; ELISA, Enzyme Linked Immunosorbent Assay; OR, odds ratio; PCR, polymerase chain reaction; PM postmortem

†not reported

Table 2.2 Epidemiological studies on the association between *C. pneumoniae* and AD

Author	Study Design	N		Method	Specimen	*C. Pneumoniae* +ve n (%)		OR(95%CI)
		AD	CTRL			AD	CTRL	
Balin et al. (1998) (33)	Case Control	19	19	PCR Electronmicroscopy Immunohisto-chemistry Culture	PM brain	17(89.5)	1(5.3)	153† (13-1846)
Nochlin et al. (1999) (137)	Case Control	12	13	PCR Immunohisto-chemistry	PM brain	0	0	
Gieffers et al. (2000) (138)	Case series	20		PCR	PM brain	0	0	
Ring et al. (2000) (139)	Case Control	15	15	PCR	PM brain	0	0	
Taylor et al. (2000) (141)	Case control	9	2	PCR Immunohisto-chemistry	PM brain	0	0	
Wozniack et al. (2003) (140)	Case control	4	16	PCR	PM brain	0	0	
Yamamoto et al. (2005) (143)	Case control	61	32	ELISA	Serum	22(36)	8(25)	1.69† (0.65-4.4)
Gerard et al. (2006) (34)	Case Control	27	27	PCR In situ hybridization Culture	PM brain	20(74.1)	3(11.1)	22.86† (5.22-100)
Paradowski et al. (2007) (35)		57	47	PCR	CSF	25(43.9)	5(10.6)	6.56† (2.26-19)
Dreses-Werringloer et al. (2009) (144)	Case series	2		Culture PCR	PM brain	2(100)		
Ecemis et al. (2010) (145)	Case control	54	50	EIA	Serum	25(46.3)	22(44)	1.09† (0.51-2.38)
Hammond et al. (2010) (131)	Case Control	5	5	Immunohisto-chemistry	PM brain	5(100)	2(40)	

AD, Alzheimer's disease; CI, confidence interval; CSF, cerebral spinal fluid; CTRL, controls; ELISA, Enzyme Linked Immunosorbent Assay; OR, odds ratio; PCR, polymerase chain reaction; PM postmortem

†not reported

Table 2.3 Epidemiological studies on the association between *B. burgdorferi* and AD

Author	Study design	N		Method	Specimen	*B. burgdorferi* +ve n (%)		OR(95%CI)
		AD	CTRL			AD	CTRL	
McDonald (1986) (148)	Case series	2		Microscopy IFA	PM brain	2		
McDonald et al. (1987) (149)	Case study	1		Culture Microscopy	PM brain	1		
McDonald (1988) (150)	Case study	1		Culture Immunocyto-chemistry	PM brain	1		
Papolla et al. (1989) (155)	Case control	6	4	Culture Immunoblotting IFA ELISA	PM brain CSF	0	0	
Miklossy et al. (1993) (38)	Case control	14	13	Culture	Peripheral-blood CSF PM brain	3(21.4)	0	
Gutacker et al. (1998) (156)	Case series	10		PCR ELISA Western blotting	PM brain CSF	0		
Mclaughlin et al. (1999) (158)	Case control	22	6	Direct microscopy Culture	PM brain	0	0	
Marques et al. (2000) (157)	Case control	15	15	PCR	PM brain	0	0	
Reviere et al. (2002) (160)	Case control	16	18	PCR Immunohisto-chemistry	PM brain	5(31.3)	1(5.6)	7.73 (0.79-75)
Meer Scherer et al. (2006) (151)	Case study	1		PCR	PM brain	1		
Galbusera et al. (2008) (159)	Case control	50	53	ELFA	Serum	0	0	
Miklossy et al. (2011) (153)	Pooled analysis	75	52	PM brain		19(25)	1(1.9)	17.3 (2.2-134)

AD, Alzheimer's disease; CSF, cerebral spinal fluid; CTRL, controls; ELISA, enzyme-linked immunosorbent assay; OR, odds ratio; PCR, polymerase chain reaction; PM postmortem

Table 2.4 Epidemiological studies of the association between H. pylori and AD

Author	Study design	N		Specimen	Method	*H. pylori* +ve n(%)		*H. pylori* IgG titers mean(SD)		OR	P
		AD	Control			AD	Control	AD	Control		
Malaguarnera et al. (2004) (37)	Case control	30	30	Plasma	ELISA			14.6(3.6)	21.3(6.3)		<.0001
Kountouras et al. (2006) (167)	Case control	50	30	Gastric biopsy	Histology	44(88)	14(46.7)			8.4	0.0002
Kountouras et al. (2009) (36)	Case control	27	27	CSF	ELISA			10.5(12.5)	8.6(8.0)		0.047
				Serum	ELISA			30.4(33.9)	16.2(5.8)		0.041
Shiota et al. (2011) (174)	Case control	385	97	Urine	Immuno-chromatography	239(62.0)	58(59.7)			1.1	0.679
Roubaud-Baldraun et al. (2011) (168)	Case series	53		Serum	ELISA Immunoblot	20(38)					

AD, Alzheimer's disease; ELISA, Enzyme Linked Immunosorbent Assay; OR, odds ratio; SD, standard deviation

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CHAPTER 3

SYSTEMIC BACTERIAL INFECTIONS AND THE RISK OF DEMENTIA AMONG U.S. VETERANS: A RETROSPECTIVE COHORT STUDY

ABSTRACT

Background: Emerging evidence indicates associations between severe systemic bacterial infections and the risk for dementia. However, data are lacking on the exposures to less severe systemic bacterial infections and adjustment for psychiatric comorbidity.

Aim: Conduct a comprehensive assessment of the associations between several different severity levels of systemic (i.e., affecting organ systems other than the central nervous system) bacterial infections including septicemia, bacteremia, pneumonia, osteomyelitis, septic arthritis, cellulitis, and urinary tract infections (UTI) with risk of developing dementia.

Methods: Retrospective cohort study using national Veterans Health Administration patient care databases involving 417,172 veterans aged ≥56 years during fiscal year (FY) 2003. Eligibility required no *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9) codes for dementia or mild cognitive impairment at baseline (FY02-03) and ≥1 visit every 2 years during follow-up (FY04-12).

Measures included demographic characteristics, and ICD 9 codes for systemic bacterial infections, dementia and medical and psychiatric comorbidity. Cox proportional hazard models determined the combined and independent associations between systemic bacterial infections occurring > 2years prior to dementia diagnosis and the risk for dementia.

Results: Average age at baseline was 68.0±8.1 and 97.3% were male. After adjustment for demographic characteristics, and medical and psychiatric comorbidity exposure to any systemic bacterial infection was associated with an increased risk for dementia (hazard ratio [HR] = 1.20; 95% confidence interval [CI] = 1.16-1.24). In addition, septicemia (HR=1.39; 95%CI=1.16-1.66), bacteremia (HR=1.22; 95%CI=1.00-1.49),

osteomyelitis (HR=1.20; 95%CI=1.06-1.37), pneumonia (HR=1.10; 95%CI=1.02-1.19), UTI (HR=1.13; 95%CI=1.08-1.18), and cellulitis (HR=1.14; 95%CI=1.09-1.20) were independently associated with a significantly increased risk for dementia after adjustment for potential confounders.

Conclusion: Severe (e.g., septicemia) and less severe (e.g., cellulitis) systemic bacterial infections are collectively and independently associated with an increased risk for dementia. Prevention of bacterial infections could positively impact the risk for dementia among older adults. Further basic and epidemiologic research in veterans and other populations is required to elucidate the mechanisms and the associations between systemic bacterial infections and the risk for dementia.

INTRODUCTION

Dementia is a chronic degenerative disorder that is characterized by progressive global cognitive dysfunction. The prevalence of dementia worldwide is currently estimated at 47.5 million and it is expected to increase to more than 135 million by the year 2050 (1). In addition, dementia is a leading cause of mortality (2, 3), disability (4, 5), and institutionalization (6) among persons aged 65 years and older. Dementia is also associated with increased health care utilization and costs for both patients (7, 8) and their caregivers (9).

The leading neuropathological causes of dementia include Alzheimer's disease, vascular, Lewy body and frontotemporal dementias. Potential risk factors for these dementia syndromes include modifiable and non-modifiable factors. Non-modifiable risk factors for dementia include increasing age (10, 11), and apolipoprotein ε4 allele (12-14), while potentially modifiable risk factors include lack of physical activity (15), traumatic brain injury (16-20), lower education status (21-24), hypertension (25, 26) and other cardiovascular disorders (27, 28), diabetes mellitus (29-31), alcohol abuse (32-35), smoking (26, 34, 36), depression (37-39), and bipolar disorder (40). However, the proportion of dementia cases that is attributable to the modifiable risk factors has been estimated at 28% (41) and to apolipoprotein ε4 allele, estimated at 20-25% (42, 43). This

leaves possibility that other factors influence the risk for the development of dementia in humans.

Emerging evidence from animal models indicates that systemic inflammation might play a significant role in the neuropathogenesis of dementia syndromes. For example, systemic inflammation – induced by peripheral injection of bacterial lipopolysaccharide – has been found to induce, potentiate, and exacerbate the development and propagation of dementia neuropathology in the brain of transgenic mice (44-47). Results from animal experiments also indicate that peripherally induced systemic inflammation can induce various cognitive decrements including impaired memory (48, 49) and, attention and executive functioning, (50-52). Taken together, these findings indicate that conditions associated with significant systemic inflammation such as systemic bacterial infections could trigger, exacerbate and potentiate the development and spread of dementia neuropathology, cause cognitive impairments and possibly increase the risk for dementia among humans.

Indeed, epidemiological research has linked severe systemic bacterial infection or sepsis with an increased risk of developing long-term cognitive dysfunction and dementia in humans. For example, in a prospective cohort study involving 1,194 adults, severe sepsis was associated with a significantly increased risk for long term, moderate to severe cognitive impairments up to 8 years after the infection (53). In addition, in a retrospective cohort study involving 25,368 intensive care recipients, sepsis was associated with a significantly increased risk for dementia after discharge (Hazard ratio [HR] = 1.40; 95% confidence interval [CI] = 1.28-1.53) (54).

Epidemiological studies also report significant associations between other severe or non-sepsis systemic bacterial infections and an increased risk for dementia in humans. For example, in a case control study involving 9,954 dementia cases and 9,374 non-dementia controls a previous history of two or more systemic bacterial infections was associated with a significantly increased risk of dementia among individuals 84 years of age or older (55). In addition, in a cohort study involving 5,888 adults aged 65

years and older, hospitalization for pneumonia was associated with a significantly increased risk for subsequent dementia (HR=2.24; 95%CI=1.62-3.11) (56). Similarly, in a cohort study involving 3,069 healthy community volunteers at baseline, hospitalization with pneumonia was associated with a significantly increased risk for dementia (HR= 1.9; p <.0001) after adjustment for age, sex, race, study site, education, and baseline cognitive status (57). Moreover, results from this study also showed that collectively, previous hospitalization for either cellulitis, urinary tract infections, septicemia, or bacteremia was associated with a significantly increased risk for dementia (HR=2.1; p<.0001). Furthermore, in a retrospective cohort study involving 17,238 patients newly diagnosed with chronic osteomyelitis, and 68,944 age- and gender-matched controls, chronic osteomyelitis was associated with a significantly increased risk of developing dementia (relative risk=1.6; 95%CI=1.4-1.83) (58).

Nevertheless, the epidemiological evidence for the potential associations between systemic bacterial infections during adulthood and subsequent risk of developing dementia is still very limited. Moreover, existing research examined particular severe or chronic systemic bacterial infections, and the independent impacts of less severe systemic bacterial infections such as cellulitis, and urinary tract infections on the risk for dementia remains undetermined. In addition, research has not considered outpatient infections and lacked adjustment for psychiatric comorbidity such as posttraumatic stress disorder, depression, and bipolar disorder, which have been associated with increased risk for both infections (59-61) and dementia (37-40, 62-64). Thus, the purpose of this study was to conduct a comprehensive assessment of the associations between several different severity levels of systemic bacterial infections i.e., septicemia, bacteremia, pneumonia, osteomyelitis, septic arthritis, cellulitis, and urinary tract infections (UTI), with risk of developing dementia in a large, nationally representative sample of U.S. veterans aged 56 years and older.

METHODS

Study design and population

We utilized a retrospective cohort study design. The study population was comprised of 3,139,780 U.S. veterans aged 56 years and older during fiscal year 2003 who were enrolled and receiving care at Veteran's Affairs Medical Centers (VAMCs). From this cohort, we excluded: 1) veterans who died or had clinical encounters containing *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) diagnosis codes for dementia or mild cognitive impairment during the baseline observation period (i.e., from October 01, 2002 through September 31, 2004), 2) veterans who did not have at least one VAMC visit every two years during the follow-up period (i.e., from October 1, 2004 through September 31, 2012), and 3) veterans with clinical encounters containing ICD-9 codes for other neurodegenerative disorders, or conditions associated with potentially reversible or non-neurodegenerative cognitive impairments (Table A.1, Appendix A). Furthermore, we excluded veterans with clinical encounters containing ICD-9 diagnosis codes for chronic inflammatory disorders or malignancies (Table A.1, Appendix A) at any time during the study period since these conditions are also associated with systemic inflammation and possibly, use of anti-inflammatory or immunosuppressive medications, which could impact our assessment of the association between systemic bacterial infections and the risk of developing dementia. Thus, the final sample consisted of 417,172 veterans with complete information on all variables of interest. The institutional review board of the University of Iowa and the Research and Development Committee of the Iowa City VAMC reviewed and approved this study.

Data resource

The Veterans Health Administration (VHA) is one of the largest integrated health care systems in the U.S. and includes more than 150 medical centers and more than 1,400 community-based outpatient clinics, community living centers, Vet Centers and domiciliaries in all 50 states and Puerto Rico. Data were derived from the VHA national

repository of databases. These data are derived from a decentralized hospital computer program known as the Veterans Health Information Systems and Technology Architecture (VistA), which comprises more than 100 applications that clinicians access via the nationwide Computerized Patient Record System (CPRS) to review and update a patient's electronic medical record for various services including medications, special procedures, x-rays, patient care nursing orders, diets, laboratory tests, and consults (65). VistA data from all local VHA facilities are extracted and aggregated into VHA's National Patient Care Database system based at the Corporate Data Warehouse (CDW) (65).

Datasets from the CDW that were utilized for this study include 1) the Patient Treatment File (PTF) Bed Section Files, and 2) the Outpatient Care Files (OCF). The PTF Bed Section Files identifies all VHA inpatient admissions and includes data elements such as demographic characteristics, principal and up to 12 secondary diagnoses, and procedures (as defined by ICD-9 codes) from the time of admission until discharge, admission and discharge dates, and vital status. The OCF database contains data including demographic characteristics and principal and up to 12 secondary diagnoses and procedures (as defined by ICD-9 codes) visit dates and information on the number and types of clinic stops made by the patient for each outpatient encounter at all VHA facilities. We linked these databases using unique patient identifiers (i.e., scrambled social security numbers) to create a comprehensive longitudinal medical record for each participant.

Diagnosis of systemic bacterial infections

The systemic bacterial infections (i.e., infections of organ systems other than the central nervous system) of interest included septicemia (presence of bacteria or bacterial toxins in the blood), bacteremia (presence of bacteria in the blood), pneumonia (infection of the lungs), osteomyelitis (infection of bone), septic arthritis (joint infection), UTI (infection of the urethra, urinary bladder, ureters or kidneys), and cellulitis (infection of the skin and subcutaneous tissues) and were diagnosed using ICD-

9 diagnosis codes (53, 66-69) (Table A.2, Appendix A) in the PTF Bed Section Files and OCF. All participants with ICD-9 diagnosis codes for the systemic bacterial infections of interest as a primary or secondary diagnosis during the follow-up period were classified as having a systemic bacterial infection. To account for preclinical dementia and associations between dementia and increased risk of certain bacterial infections only infections occurring more than two years prior to the date of dementia diagnosis were considered among participants diagnosed with dementia. Participants in the study cohort, who did not have a diagnosis of a systemic bacterial infection during the study period, were used as the controls.

Follow-up and censoring

Participants were followed through the medical records until when they either developed dementia or were censored. Participants were considered censored if they: 1) ceased to have contact with a VAMC during the study period, 2) died during the observation period, or 3) were not diagnosed with dementia by the end of the 9-year follow up period.

Dementia diagnosis

The diagnosis of dementia was determined from the PTF Bed Section Files and OCF using ICD-9 diagnosis codes for dementias as defined by previous studies in this population (63,64) and included; 290.0x, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3x, and 331.2 (senile dementias), 290.40, 290.41, 290.42, 290.43 (vascular dementia), 294.10, 294.11, 294.8x (dementia-not-otherwise specified), 331.0 (Alzheimer disease), 331.11, 331.19 (frontotemporal dementia), and 331.82 (Lewy Body dementia).

Measurement of other covariates and potential confounders

Potential confounders or effect modifiers were selected based on review of the existing literature and included; demographic characteristics (i.e., age, gender, race/ethnicity and annual income), medical comorbidity (i.e., traumatic brain injury, hypertension, ischemic heart disease, cerebrovascular disease, atherosclerosis, diabetes

mellitus, hyperlipidemia, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, and peptic ulcer disease/gastritis), and psychiatric comorbidity (i.e., major depression, bipolar disorder, and alcohol, tobacco and illicit substance abuse). Data on the participants' demographic characteristics, and medical and psychiatric comorbidity were abstracted from the PTF Bed Section Files and OCF at baseline. Medical and psychiatric comorbidity were diagnosed using ICD-9 codes (Table A.3, Appendix A).

Statistical analysis

Data were analyzed quantitatively using SAS software *version 9.3* and an alpha level of less than 0.05 was considered significant. We used a Mann-Whitney U test or a chi-square test to determine whether participants with systemic bacterial infections and the controls differed in terms of the baseline continuous or categorical characteristics, respectively.

Cox proportional hazards models with age as the time scale and systemic bacterial infections as time-dependent covariates were used to determine whether the systemic bacterial infections of interest were associated with the risk of developing dementia. The analysis was conducted in several steps. First, we assessed for potential collinearity among the medical and psychiatric covariates using Pearson correlation coefficients and excluded one covariate based on relevance in extant literature and/or clinical experience, from each pair of strongly correlated covariates. Thus the medical and psychiatric covariates included in our adjustments included traumatic brain injury, hypertension, ischemic heart disease, cerebrovascular disease, atherosclerosis, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, peptic ulcer disease/gastritis, bipolar disorder, posttraumatic stress disorder, and alcohol abuse.

Second, we determined the overall association between any systemic bacterial infection and the risk for dementia in unadjusted as well as models adjusted for demographic characteristics, and medical and psychiatric comorbidity.

Third, we considered each systemic bacterial infection of interest as an independent risk factor for dementia. Thus, each individual systemic bacterial infection of interest was assessed for association with the risk for dementia in unadjusted and models including adjustments for demographic characteristics, and medical and psychiatric comorbidity. The Cox proportional hazards assumption was assessed for all variables in all the models using log-log survival curves and weighted Schoenfeld residuals.

RESULTS

The average age of the participants at baseline was 67.7 (±8.1) years and mean follow-up duration for all participants was 9.03 (±1.1) years. The majority of participants (97.9%) were male and 82% were White.

Of the 417,172 veterans in the final sample, 87,400 (21%) veterans had a diagnosis of at least one systemic bacterial infection during the study period. Table 3.1 provides a summary of baseline characteristics of the veterans with and without systemic bacterial infections. The most commonly diagnosed infection was UTI while septic arthritis was least frequent (Table 3.2). Overall, compared to the controls, participants with a systemic bacterial infection were significantly younger (mean age 66 vs 68, p<.0001), and more likely to have diagnoses of most of the medical and psychiatric comorbidity known to be associated with the risk for dementia at baseline including hypertension (p<.0001), diabetes mellitus (p<.0001), cerebral vascular disease (p<.0001), atherosclerosis (p<.0001), chronic obstructive pulmonary disease (p<.0001), peptic ulcer disease (p<.0001), depression (p<.0001), bipolar disorder (p<.0001), alcohol abuse (p<.0001), tobacco use (p<.0001), and illicit drug abuse (p<.0001).

By our surveillance methods, 25,639 veterans developed dementia during the follow up period. In unadjusted cox proportional hazard model, a diagnosis of at least one systemic bacterial infection was associated with a significantly increased risk for dementia (HR=1.50; 95%CI=1.45-1.55), which remained significant after adjustment for

demographic characteristics, and medical and psychiatric comorbidity (HR=1.20; 95%CI=1.16-1.24) (Table 3.3).

In-unadjusted analyses, all systemic bacterial infections of interest were each individually associated with an increased risk for dementia (Table 3.3). However, after adjustment for demographic characteristics, and medical and psychiatric comorbidity, septicemia (HR=1.39; 95%CI=1.16-1.66), bacteremia (HR=1.22; 95%CI=1.0-1.49), pneumonia (HR=1.10; 95%CI=1.02-1.19), osteomyelitis (HR=1.20; 95%CI=1.06-1.37), UTI (HR=1.13; 95%CI=1.08-1.18) and cellulitis (HR=1.14; 95%CI=1.09-1.20) were found to be independently associated with statistically significant increased risk for dementia (Table 3.4). Although septic-arthritis was associated with an increased risk for dementia, this result was not statistically significant at .05 alpha level (HR=1.04; 95%CI=0.78-1.39).

DISCUSSION AND LIMITATIONS

The purpose of this study was to determine the associations between several different severity levels of systemic bacterial infections i.e., septicemia, bacteremia, pneumonia, osteomyelitis, septic arthritis, cellulitis, and urinary tract infections (UTI) with risk of developing dementia in a large nationally representative sample of U.S. veterans aged 56 years and older. Results showed statistically significant associations between any systemic bacterial infection, septicemia, bacteremia, pneumonia, osteomyelitis, cellulitis, and UTI, with the risk for developing dementia after adjusting for demographic characteristics, and medical and psychiatric comorbidity. These results were consistent with prior studies. For example, Shah et al. (56) and Tate et al. (57) found a significant association between hospitalization for pneumonia and an increased risk for subsequent dementia while Tseng et al. (58) found a significant association between a diagnosis of chronic osteomyelitis and an increased risk for dementia. To our knowledge, our study is the first study to assess the independent impacts of UTI, cellulitis, and septic arthritis and on the risk for dementia.

Mechanisms of the association between infections and the risk for dementia

The association between severe bacterial infections or sepsis and acute cognitive dysfunction (i.e., sepsis associated encephalopathy or delirium) is well established. However, sepsis has been associated with various detrimental central nervous system effects including decreased metabolism (70), oxidative stress (71), and impaired microcirculation (72) all of which are capable of causing permanent neuronal dysfunction and degeneration that might manifest as chronic cognitive deficits or dementia. Indeed, sepsis has been previously associated with an increased risk of long-term cognitive dysfunction (53) and dementia (54). Our results examining the associations between sepsis and the risk for dementia were consistent with prior research.

In addition, sepsis and other less severe systemic bacterial infections might be associated with dementia neuropathogenesis because of the effects of systemic inflammation on the central nervous system (CNS). Systemic bacterial infections have been associated with significant systemic inflammation (73) and significantly increased levels of circulating pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (73, 74). Evidence indicates that circulating systemically generated cytokines can activate CNS astrocytes and microglia (75, 76) which in turn can cause neuronal death and injury through various mechanisms including release of nitric oxide and reactive oxygen species, activation of the complement cascade and neglect of essential neuro-protective roles (77-80). In addition, circulating systemically generated pro-inflammatory cytokines have been linked to blood-brain barrier disruption (81, 82), which can cause neuronal injury, and apoptosis (83) and dementia (84). Furthermore, both the activated CNS microglia and astrocytes, and damaged or necrotic neurons release various chemokines and cytokines directly into the CNS, which cause further neuronal injury, and recruitment and activation of additional astrocytes and microglia (85, 86) thus exacerbating the systemic-inflammation induced neurotoxicity. These findings indicate that systemic bacterial infections could possibly result in a self-sustaining cycle of progressive neurodegeneration or dementia (87).

Evidence also indicates that systemic bacterial infections can directly induce neuronal destruction and apoptosis in the absence of inflammatory cytokine mediated effects. For example, Murray et al. (88) found peripherally injected bacterial liposaccharide directly stimulated CNS endothelium and primed microglia despite effective blockage of systemic cytokine synthesis. Thus, systemic bacterial infections – either directly or indirectly through effects of systemic inflammation on the brain and blood brain barrier – could possibly cause permanent and progressive neuronal dysfunction and degeneration that might manifest as chronic cognitive dysfunction or dementia.

However, because dementia neuropathology possibly develops over several decades (89, 90), an alternative mechanism for the associations between systemic bacterial infections and the risk for dementia could be that infections during late adulthood exacerbate the development and spread of underlying CNS neuropathology due to infections earlier in life or other causes. Evidence from animal models indicates minimal activation of CNS astrocytes and microglia following initial stimulation by systemic inflammatory events (91); however, subsequent stimulation of previously exposed or primed astrocytes and microglia results in a markedly exaggerated inflammatory response (91, 92). Moreover, Njie et al. (93) found microglia derived from aged animals secrete significantly greater amounts of pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α in response to stimulation compared to those from young animals. Henry et al. (94) also reported exaggerated cytokine production in aged microglia while Damani et al. (95) found aged microglia to be associated with a more sustained inflammatory responses. Indeed, systemic inflammation has been found to exacerbate and potentiate the propagation of underlying dementia neuropathology in the brains of transgenic mice (44-47).

Our results showed significant combined and independent associations between both severe (e.g., septicemia) and less severe (e.g., cellulitis) systemic bacterial infections and an increased risk for dementia. Moreover, the association between systemic bacterial infections and the risk for dementia was stronger for severe

infections compared to less severe infections, which suggests a dose-response type of association. However, further studies are required to elucidate the exact mechanisms for the associations between systemic bacterial infections and dementia pathogenesis.

Strengths and limitations

Our study has several limitations. First, potential confounders such as apolipoprotein ε4 allele status were not accounted for in the analysis, which could result in residual confounding. In addition, we did not adjust for non-bacterial systemic infections such as viral and fungal infections, which might also result in systemic inflammation. Nevertheless, bacterial infections have been found to induce a more robust systemic inflammatory response as evidenced by significantly higher serum concentrations of cytokines including IL-1Ra, IL-2, IL-6, and TNF- α compared to viral infections (73) and we adjusted for many potential confounders and effect modifiers including psychiatric comorbidity not accounted for in previous analyses.

Second, because we used ICD-9 codes for diagnosis of the primary exposures, outcomes, and medical and psychiatric comorbidity, this could result in possible misclassification bias in our analyses. However, the agreement between inpatient diagnoses abstracted from the VA administrative files using ICD-9 codes and written medical records for various medical conditions (including most of our variables of interest) has been estimated at more than 98.3% (96). Positive predictive values associated with ICD-9 codes in detecting clinical bacterial infections in the VHA database range from 70% for pneumonia and cellulitis, to 95% for osteomyelitis (66).

Third, because veterans can elect to use services other than the VHA for primary health care and the fact that our sample was restricted largely to regular users of the VA, our findings might not be generalizable to all military veterans or non-military populations. In addition, it is possible that certain infections were diagnosed outside the VA and not included in our analysis. Nevertheless, our sample was largely restricted to regular VHA system users and included both in and outpatient data in order to capture majority of infections in the sample.

Strengths of this study include the retrospective cohort study design, very large sample size, adjustment for multiple potential confounders, and time dependent analysis for the effect of infections. In addition, because the VHA maintains electronic records on veterans across the country, our study is largely representative of the study population.

In conclusion, several different severity levels of systemic bacterial infections are collectively and independently associated with an increased risk of developing dementia among older U.S. veterans. Thus, prevention of systemic bacterial infections could positively impact the risk for developing dementia among older adults. Further basic and epidemiological research in different populations is recommended to elucidate the mechanisms and associations between systemic bacterial infections and the risk for dementia.

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Table 3.1 Comparison of the baseline characteristics of participants with and without systemic bacterial infections

Variable	No infections (n=329,772) Mean (SD) or n (%)	Infection (n=87,400) Mean (SD) or n (%)	P-value
Demographic characteristics			
Age	68.12(8.00)	66.12(8.27)	<0.0001
Gender			
Male	323,851 (98.20)	84,685(96.89)	<0.0001
Race			<0.0001
White	277,803(84.24)	64,610(73.92)	
Black	30,312(9.19)	14,663(16.78)	
Other	21,675(6.75)	8,127(9.30)	
Income (percentile)			<0.0001
25th	91,005(27.60)	13,304(15.22)	
50th	74,213(22.50)	30,065(34.40)	
75th	77,001(23.35)	27,293(31.23)	
>75th	78,553(26.55)	16,738(19.15)	
Medical comorbidities			
Traumatic brain injury	659(0.20)	447(0.51)	<0.0001
Hypertension	228220 (69.21)	65,476(74.92)	<0.0001
Ischemic heart disease	99,549(30.19)	26,377(30.18)	0.9654
Cerebrovascular disease	22,010(6.67)	8,370(9.58)	<0.0001
Atherosclerosis	3,778(1.15)	2,470(2.83)	<0.0001
Hyperlipidemia	166,347(50.44)	41,896(47.94)	<0.0001
Diabetes	85,024 (25.78)	32,687(37.40)	<0.0001
Chronic obstructive pulmonary disease	6,282(1.90)	3,691(4.22)	<0.0001
Kidney Disease	5,960(1.81)	3,101(3.55)	<0.0001
Liver Disease	111(0.03)	37(0.04)	0.2260
Gastric/peptic ulcer disease	9,441(2.86)	3,566(4.08)	<0.0001
Psychiatric comorbidities			
Posttraumatic stress disorder	15,724(4.7)	6,950(7.95)	<0.0001
Depression	32,417(9.83)	13,056(14.94)	<0.0001
Bipolar disorder	2,920(0.89)	1,571(1.80)	<0.0001
Substance abuse			
Tobacco use	30,132(9.14)	13,579(15.54)	<0.0001
Alcohol abuse	36,605(11.10)	16,893(19.33)	<0.0001
Drug abuse	2,736(0.83)	2,207 (2.53)	<0.0001

SD, standard deviation

Table 3.2 Prevalence of systemic bacterial infections

Systemic bacterial Infection	**N**	**%**
Septicemia	3,484	0.84
Bacteremia	2,368	0.57
Pneumonia	15,613	3.74
Osteomyelitis	5,005	1.20
Septic arthritis	1,000	0.24
Urinary tract infection	40,186	9.63
Cellulitis	45,346	10.87

Table 3.3 Unadjusted Cox proportional hazard ratios for systemic bacterial infections vs no infection and the risk for dementia

Infection	Hazard ratio (95%CI)	P-value
Any infection	1.50 (1.45-1.55)	<.0001
Septicemia	2.09 (1.75-2.49)	<.0001
Bacteremia	1.88 (1.54-2.29)	<.0001
Pneumonia	1.54 (1.43-1.67)	<.0001
Osteomyelitis	1.73 (1.52-1.97)	<.0001
Septic arthritis	1.43 (1.07-1.90)	0.0144
Urinary tract infection	1.44 (1.38-1.51)	<.0001
Cellulitis	1.49 (1.42-1.56)	<.0001

Table 3.4 Adjusted Cox proportional hazard ratios for systemic bacterial infection vs no infection and the risk for dementia

Infection	Hazard ratio (95%CI)*	P-value
Any infection	1.20 (1.16-1.24)	<.0001
Septicemia	1.39 (1.16-1.66)	.0003
Bacteremia	1.22 (1.00-1.49)	.0463
Pneumonia	1.10 (1.02-1.19)	.0126
Osteomyelitis	1.20 (1.06-1.37)	.0055
Septic arthritis	1.04 (0.78-1.39)	.7721
Urinary tract infections	1.13 (1.08-1.18)	<.0001
Cellulitis	1.14 (1.09-1.20)	<.0001

* Adjusted for demographics characteristics and medical and psychiatric comorbidity

APPENDIX A

SUPPLEMENTARY TABLES FOR SYSTEMIC BACTERIAL INFECTIONS AND THE RISK OF DEMENTIA AMONG U.S. VETERANS: A RETROSPECTIVE COHORT STUDY

Table A. 1 Exclusion criteria ICD-9 diagnosis codes

Exclusion criteria	**ICD-9 diagnosis codes**
Other neurodegenerative disorders	332 Parkinson's disease 331.11 Pick's disease 340 Multiple sclerosis 335.20 Amyotrophic lateral sclerosis 333.4 Huntington's chorea 331.3-331.5 Hydrocephalus
Chronic inflammatory disease	579 Celiac disease 555 Crohn's, disease 556 Ulcerative colitis 710 Diffuse diseases of the connective tissues 714 Rheumatoid arthritis and other inflammatory polyarthropathies 720 Ankylosing spondylitis and other inflammatory spondylopathies 696 Psoriasis and related disorders
Cancer	140-239 Neoplasms
Vitamin b12 deficiency	266.2 Other vitamin b complex deficiency 266.9 Vitamin b12 deficiency not otherwise specified 281.0 Pernicious anemia 281.1 Other vitamin b12 deficiency anemia
Hypo and hyper-thyroidism	242.9 Hyperthyroidism 243-244 Hypothyroidism
HIV infection	042 HIV infection

Table A.1 continued

Central nervous system infections	046.1 Creutzfeldt-Jakob disease 094 Neurosyphilis 320 Bacterial meningitis 062 Mosquito-borne viral encephalitis 064 Viral encephalitis transmitted by other and unspecified arthropods 323.0 Encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere 321.0 Cryptococcal meningitis

Table A. 2 ICD-9 codes for diagnosis of systemic bacterial infections

Systemic bacterial infection	ICD-9 diagnosis codes
Pneumonia	481 Pneumococcal pneumonia 482 Other bacterial pneumonia 483 Pneumonia due to other specified organism 484 Pneumonia in infectious diseases classified elsewhere 485 Bronchopneumonia, organism unspecified 486 Pneumonia, organism unspecified 011 Pulmonary tuberculosis 003.22 Salmonella pneumonia 020.3 Primary pneumonic plague 020.5 Pneumonic plague 021.2 Pulmonary tularemia 022.1 Pulmonary anthrax 031.0 Pulmonary, other mycobacteria 513.0 lung abscess
Septicemia	038.x Septicemia 785.52 Septic shock 995.91 Sepsis 995.92 Severe sepsis 998.02 Postoperative septic shock 003.1 Salmonella septicemia 098.89 Gonococcal septicemia 022.3 Anthrax septicemia 027.0 Listeria septicemia
Bacteremia	790.7 Bacteremia 003.9
Urinary tract infection	599.0 urinary tract infection 590.x pyelonephritis 595 Cystitis 597.0 Urethral abscess 597.80 Urethritis, unspecified 098.0 Acute gonococcal lower UTI 098.1 Acute gonococcal upper UTI 098.2 Chronic gonococcal lower UTI 098.3 Chronic gonococcal upper UTI 099.41 Non gonococcal urethritis 099.53 Chlamydia, lower UTI

Table A.2 continued

Cellulitis	681 Cellulitis/abscess of finger and toe 682 Other cellulitis and abscess 686 Other local skin infection
Septic arthritis	711.xx Pyogenic arthritis 098.5x Gonococcal arthritis 003.23 Salmonella arthritis 015.1x Tuberculosis of hip joint 015.2x Tuberculosis of knee joint 015.8x Tuberculosis, other specified joint 040.89 Bacterial arthritis
Osteomyelitis	730.0x Acute osteomyelitis 730.1x Chronic osteomyelitis 730.2x Unspecified osteomyelitis 730.9x Unspecified infection of bone 003.24 Salmonella osteomyelitis 015.5x Tuberculosis, limb bone 015.7x Tuberculosis, unspecified bone 731.8 Osteomyelitis, diabetes

Table A. 3 ICD-9 diagnosis codes for identifying potential confounders and effect modifiers

Potential confounder	ICD-9 diagnosis codes
Medical comorbidity	
Hypertension	401 - 405 Hypertensive disease
Ischemic heart disease	410 - 414 Ischemic heart disease
Cerebrovascular disease	430 - 438 Cerebrovascular disease
Atherosclerosis	440 Atherosclerosis
Diabetes mellitus	250 Diabetes mellitus
Traumatic brain injury	800 - 804 Fracture of the skull 850 Concussion 851 Cerebral laceration and contusion 854.0 Intracranial injury of other and unspecified site 959.01 Head injury, unspecified
Chronic obstructive lung disease	490 Bronchitis 491 Chronic bronchitis 492 Emphysema 494 Bronchiectasis 496 Chronic obstructive airway, not specified
Hyperlipidemia	272.4 Other and unspecified hyperlipidemia
Chronic kidney disease	585 Chronic kidney disease V420 Kidney transplant V451.1x Renal dialysis V56. X Encounter for dialysis
Chronic liver disease	571.x chronic liver disease and cirrhosis
Gastric/peptic ulcer disease	535 Gastritis and duodenitis 531 Gastric Ulcer 532 Duodenal Ulcer 533 Peptic ulcer, site unspecified

Table A.3 continued

Psychiatric comorbidity	
Depression	296.2 major depressive disorder, single episode 296.3 Major depressive disorder, recurrent episode 311 Depressive disorder, not elsewhere classified
Bipolar disorder	296.0x Bipolar disorder, single manic episode 296.1x Manic disorder recurrent episode 296.4x Bipolar disorder, current episode, manic 296.5x Bipolar disorder, current episode, depressed 296.6x Bipolar disorder, current episode, mixed 296.7x Bipolar disorder, current episode, unspecified 296.8x Other and unspecified bipolar disorder
Posttraumatic stress disorder	309.81 Posttraumatic stress disorder
Anxiety disorder	300.00 Anxiety state 300.02 Generalized anxiety disorder 300.09 Other anxiety
Alcohol abuse	305 Nondependent alcohol abuse 303 Alcohol dependence syndrome
Tobacco abuse	305.1 Tobacco use disorder
Illicit drug abuse	304.xx Drug dependence 305.xx Nondependent drug abuse 292.0 drug withdrawal 292.1x Drug induced psychotic disorder 292.8x Other drug induced mental disorders, specified 292.9 Other drug induced mental disorder, unspecified

CHAPTER 4

PTSD, PSYCHOTROPIC PTSD MEDICATION USE, AND THE RISK OF DEMENTIA AMONG U.S. VETERANS: A RETROSPECTIVE COHORT STUDY

ABSTRACT

Background: Posttraumatic stress disorder (PTSD) could be a major risk factor for the development of dementia among older adults. However, existing epidemiological studies have not accounted for psychotropic medications commonly used in management of PTSD despite evidence that these treatments might affect cognitive functioning and possibly, the risk for dementia.

Objective: To determine the association between PTSD and the risk of developing dementia and the impact of psychotropic PTSD medication use on this association.

Methods: Retrospective cohort study using national Veterans Health Administration patient care databases involving 417,172 veterans aged ≥56 years during fiscal year (FY) 2003. Eligibility required no *International Classification of Disease, Ninth Clinical Modification* (ICD-9) codes for dementia or mild cognitive impairment at baseline (FY02-03) and ≥1 visit every 2 years during follow-up (FY04-12). Measures included demographic characteristics, ICD-9 codes for PTSD, dementia, and medical and psychiatric comorbidity, and prescription for psychotropic PTSD medications i.e., selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), Novel antidepressants (NA), benzodiazepines (BZA), and atypical antipsychotics (AA). Associations between PTSD, psychotropic PTSD medication use, and the risk for dementia were determined using Cox proportional hazards models.

Results: Average age at baseline was 68.0±8.1 and 97.3% were male. After adjustment for demographic characteristics, medical and psychiatric comorbidity, and number of primary and mental health clinic visits, PTSD was associated with an increased risk for developing dementia (hazard ratio [HR] = 1.35; 95% confidence interval [CI] = 1.27-1.43). Analysis for impact of psychotropic PTSD medication use on the association between PTSD and the risk for dementia showed significant interactions between PTSD and use

of SSRIs (p<.0001), NAs (p=.0016), and AAs (p<.0001). Multivariate analysis showed a significant association between PTSD and an increased risk for dementia among individuals not using any psychotropic PTSD medications at baseline (HR=1.70, 95%CI=1.58-1.82). PTSD patients using SSRIs (HR=2.10; 95%CI=1.82-2.41), NAs (HR=2.19; 95%CI=1.94-2.48) or AAs (HR=4.56; 95%CI=4.04-5.15) were significantly more likely to develop dementia compared to those without PTSD and not using any psychotropic PTSD medications. PTSD patients using SSRIs (HR=1.24; 95%CI=1.08-1.42), NAs (HR=1.29; 95%CI=1.14-1.46), or AAs (HR=2.69; 95%CI=2.38-3.04) were also significantly more likely to develop dementia compared to those with PTSD and not using any psychotropic PTSD medications. Participants using SNRIs (HR=1.35; 95%CI=1.26-1.46) or BZAs (HR=1.40; 95%CI=1.35-1.45) at baseline were more likely to develop dementia regardless of PTSD diagnosis.

Implications: After adjusting for potential confounders, PTSD is associated with an increased risk of dementia among individuals not using psychotropic medications; however, PTSD patients using SSRIs, NAs and AAs are significantly more likely to develop dementia compared to both those with and without PTSD but not using any psychotropic PTSD medications while patients using BZAs or SNRIs are significantly more likely to develop dementia regardless of PTSD diagnosis. Further research is required to determine if the independent and effect modifying impacts of psychotropic PTSD medication use on the risk for dementia are related to differences in PTSD severity, other psychiatric comorbidity, or whether psychotropic PTSD medication use is an independent risk factor for dementia.

INTRODUCTION

Dementia is a chronic neurodegenerative disorder that affects approximately 45.7 million people worldwide (1) and it is a leading cause of morbidity, mortality, disability, and institutionalization among individuals 65 years of age and older (2-8). Clinically, dementia is characterized by progressive global cognitive dysfunction and the most commonly diagnosed dementia syndromes include Alzheimer's disease, vascular, Lewy body and frontotemporal dementias (9). Potential risk factors for these and other

dementia syndromes include increasing age (10, 11), lack of physical activity (12), apolipoprotein ε4 allele (13-15), traumatic brain injury (16-19), lower education status (20-23), cardiovascular disease (24, 25), major depressive disorder (26-28) and bipolar disorder (29). However, research has recently emerged to indicate that posttraumatic stress disorder (PTSD) could also be a major risk factor for the development of dementia among older adults.

PTSD is a neuropsychiatric syndrome that develops in certain individuals upon exposure to one or more traumatic events. PTSD affects approximately 7-8% of the general U.S. population (30) and between 4.7 to 19.9%, 1.9 to 24.0%, and 8.5 to 19.3% of U.S. veterans deployed to Operation Iraqi Freedom and Operation Enduring Freedom, Persian Gulf War and Vietnam War, respectively (31). Clinically, four symptom clusters i.e., re-experiencing phenomena, avoidance behaviors, negative cognitions and mood, and hyperarousal, best characterize PTSD. These symptoms have recently been linked to structural and functional abnormalities within certain anatomical brain sites, particularly the mesolimbic system (i.e., hippocampus, amygdala, and hypothalamus) and prefrontal cortex (32-34).

PTSD has been associated with several medical and psychiatric comorbid conditions including depression (35), bipolar and anxiety disorders (35, 36), alcohol and substance abuse (36, 37), and cardiovascular disease (38-40). In addition, evidence has recently emerged that PTSD also significantly increases the risk for developing dementia syndromes among older adults. For example, in a retrospective cohort study involving 181,093 U.S. veterans, PTSD was found to be associated with a significantly higher 7-year cumulative incidence rate of dementia and an increased risk of developing dementia (hazard ratio [HR] = 1.77; 95% confidence interval [CI] = 1.70-1.85) (41). Similarly, in a retrospective cohort study involving 10,480 U.S. veterans, PTSD significantly increased the risk of developing dementia among veterans without a Purple Heart (as a measure of combat related injuries) (odds ratio=2.2; 95%CI=1.8-2.6) after adjustment for demographics, comorbid illnesses, and number of primary care and mental health clinic visits (42). Correspondingly, in a retrospective cohort study

involving 182,879 U.S. veterans aged 55 years and older, after adjustment for demographics, medical and psychiatric comorbidities, and competing risk of death, PTSD alone or in combination with prisoner of war status significantly increased the risk of dementia (HR=1.52; 95%CI=1.41–1.64) and (HR=2.39; 95%CI= 1.84-3.11), respectively (43).

However, previous research on the associations between PTSD and the risk of developing dementia among U.S. veterans has not considered the potential impact of psychotropic medication use despite evidence that a significant proportion of U.S. veterans with PTSD receive prescriptions for psychotropic medications (44). Moreover, FDA approved and Department of Veterans Affairs recommended pharmacotherapies for PTSD, i.e., selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been associated with long-term cognitive effects. For example, SSRI and SNRI use has been associated with improved cognitive functioning among patients with PTSD (45), depression (46), stroke (47), and mild cognitive impairment (48). Still, other studies have linked SSRI and SNRI use to impaired cognitive functioning e.g., impaired sustained attention (49-52) and memory (53, 54), and impaired hippocampal long-term potentiation (55, 56), which could result in impaired memory consolidation and learning. Furthermore, SSRI use has been associated with an increased risk for developing mild cognitive impairment (57), which often precedes clinical dementia. In addition, purchase of at least one prescription for either SSRI, SNRIs, novel or older antidepressants has been associated with an increased risk for developing dementia (58).

Other psychotropic medications with cognitive effects and commonly prescribed to U.S. veterans with PTSD include benzodiazepines and atypical antipsychotics (44). Several studies have examined the association between long-term benzodiazepine (BZA) use and the risk of cognitive decline with mixed results; for example, while some studies (59-64) reported no association between BZA use and the risk of cognitive decline, others (65, 66) reported a positive association between long-term BZA use the risk for cognitive decline. Moreover, in a meta-analysis of 13 studies Barker et al. (67) found

long-term BZA use was consistently associated with significant impairments across all cognitive domains including verbal memory, working memory, attention and visual-spatial orientation. In addition, long-term BZA use has been directly associated with a significantly increased risk for developing Alzheimer's disease (68) and several studies (69-73) have reported an association between long-term BZA use and an increased risk for developing dementia in general.

In contrast to BZAs, atypical antipsychotic (AA) drug use has been mainly associated with improved cognitive function; however, these effects have been observed predominantly among patients with schizophrenia (74-77). Although the associations between AA drug use and cognitive function among PTSD patients and AA drug use and risk for dementia have not previously determined, AA drug use has been reported to exacerbate the severity and rate of cognitive decline among dementia patients (78-80).

Taken together, findings from prior studies indicate that psychotropic PTSD medication use could affect cognitive function, and possibly the risk of developing dementia syndromes among PTSD patients. Thus, we hypothesized that psychotropic medication use among PTSD patients could be a significant effect modifier or potential confounder of the association between PTSD and the risk for dementia. Therefore, the purpose of this study was to determine the impact of the various psychotropic PTSD medications on the association between PTSD and the risk for dementia among U.S. veterans 56 years of age and older.

METHODS

Study design and setting

We utilized a retrospective cohort study design. The study population was comprised of 3,139,780 U.S. veterans aged 56 years and older during fiscal year 2003 who were enrolled and receiving health care at Veteran's Affairs Medical Centers (VAMCs). From this cohort, we excluded: 1) veterans who died or had clinical encounters containing ICD-9 diagnosis codes for dementia or MCI during the baseline

observation period (i.e., from October 01, 2002 through September 31, 2004), 2) veterans with less than one VAMC visit every two years during the follow-up period (i.e., from October 1, 2004 through September 31, 2012), and 3) veterans with ICD-9 codes for other neurodegenerative disorders, cancer, chronic inflammatory diseases, or conditions associated with potentially reversible or non-neurodegenerative cognitive impairments (Table B.1, Appendix B). Thus, the final sample consisted of 417,172 veterans with complete information on all variables of interest. The institutional review board of the University of Iowa and the Research and Development Committee of the Iowa City VAMC reviewed and approved this study.

Data resource

The Veterans Health Administration (VHA) is one of the largest integrated health care systems in the U.S. and includes more than 150 medical centers and more than 1,400 community-based outpatient clinics, community living centers, Vet Centers and domiciliaries in all 50 states and Puerto Rico. Data were derived from the VHA national repository of databases. These data are derived from a decentralized hospital computer program known as the Veterans Health Information Systems and Technology Architecture (VistA), which comprises more than 100 applications that clinicians access via the nationwide Computerized Patient Record System (CPRS) to review and update a patient's electronic medical record for various services including medications, special procedures, x-rays, patient care nursing orders, diets, laboratory tests, and consults (81). VistA data from all local VHA facilities are extracted and aggregated into VHA's National Patient Care Database system based at the Corporate Data Warehouse (81).

Datasets from the CDW that were utilized for this study include 1) the Patient Treatment File (PTF) Bed Section Files, 2) the Outpatient Care Files (OCF), and 3) Decision Support System (DSS) – National Data Extract national pharmacy database. The PTF Bed Section Files identifies all VHA inpatient admissions and includes data elements such as demographic characteristics, principal and up to 12 secondary diagnoses, and procedures (as defined by ICD-9 codes) from the time of admission until discharge,

admission and discharge dates, and vital status. The OCF database contains data including demographic characteristics and principal and up to 12 secondary diagnoses and procedures (as defined by ICD-9 codes) visit dates and information on the number and types of clinic stops made by the patient for each outpatient encounter at all VHA facilities. The DSS contains drug names, dosages and dates of prescription fill. We linked these databases using unique patient identifiers (i.e., scrambled social security numbers) to create a comprehensive longitudinal medical record for each participants' health and health care utilization.

PTSD diagnosis

The diagnosis of PTSD was determined at baseline using ICD-9 diagnosis code 309.81 for PTSD as either primary or secondary diagnosis, in at least one clinical encounter in the medical record. We used the participants without an ICD-9 diagnosis code for PTSD as controls.

Follow-up and censoring

We collected data from the participants' medical records until when they either developed dementia or were censored. Participants were considered censored if they; 1) did not develop dementia by the end of the 8-year follow-up period, 2) ceased to have any contact with a VAMC during the follow-up period or 3) died during the follow-up period.

Assessment of psychotropic PTSD medication use

Psychotropic PTSD medication use was determined at baseline from receipt of a prescription in the DSS after PTSD diagnosis but before dementia diagnosis. Psychotropic PTSD medication classes identified included; 1) SSRIs, 2) SNRIs, 3) Mixed class or novel antidepressants (NA), 4) benzodiazepines (BZA), and 5) atypical antipsychotics (AA). Table B.2 (Appendix B) provides a complete list of medications included in each drug class.

Dementia diagnosis

The diagnosis of dementia was determined from the PTF Bed Section Files and OCF using ICD-9 diagnosis codes for dementias based on previous studies (41, 42) and included; 290.0x, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3x, and 331.2 (senile dementias), 290.40, 290.41, 290.42, 290.43 (vascular dementia), 294.10, 294.11, 294.8x (dementia-not-otherwise specified), 331.0 (Alzheimer disease), 331.11, 331.19 (frontotemporal dementia), and 331.82 (Lewy Body dementia).

Measurement of other covariates and potential confounders

Potential confounders or effect modifiers were identified based on review of the existing literature and included; demographic characteristics (i.e., age, gender, race/ethnicity and annual income), medical comorbidity (i.e., traumatic brain injury, hypertension, ischemic heart disease, cerebrovascular disease, atherosclerosis, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, and peptic ulcer disease/gastritis), and other psychiatric disorders (i.e., major depression, bipolar disorders, anxiety, insomnia and alcohol, tobacco and illicit substance abuse). In addition, because the frequency of primary or mental health clinic visits might influence likelihood of dementia detection and diagnosis, we included number of primary care and mental health clinic visits. Data on the participants' demographic characteristics, medical and psychiatric comorbidities and number of mental health and primary care clinic visits were abstracted from PTF Bed Section Files and OCF and diagnoses of the medical and psychiatric comorbidities were determined using ICD-9 codes (Table B.3, Appendix B).

Statistical analysis

Data were analyzed quantitatively using SAS software *version 9.3* and an alpha level of less than 0.05 was considered significant. Mann-Whitney U or chi-square tests determined whether participants with PTSD and the controls differed in terms of the continuous and categorical baseline covariates, respectively.

To determine the impact of psychotropic PTSD medication use on the association between PTSD and the risk of developing dementia, we used Cox proportional hazards models with age as time scale and performed the analysis in several steps. First, we adjusted for demographic characteristics including gender, race/ethnicity, and annual income. Second, we assessed for correlations among the medical and psychiatric comorbidities using Pearson correlation coefficients and excluded one covariate from each pair of strongly correlated comorbidities. Third, we adjusted for the remaining medical and psychiatric comorbidities, which included traumatic brain injury, hypertension, ischemic heart disease, cerebrovascular disease, atherosclerosis, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, and peptic ulcer disease/gastritis, major depression, bipolar disorder, anxiety, insomnia and alcohol abuse. Fourth, we adjusted for number of primary care and mental health clinic visits. Next, we included psychotropic PTSD medication use and tested for effect modification of the association between PTSD and the risk for dementia by psychotropic PTSD medication use using interaction terms between PTSD and each of the psychotropic PTSD medications classes. Finally, we developed a multivariate model that adjusted for demographics, medical and psychiatric comorbidities, number of mental and primary health clinic visits, psychotropic medication use, and the interactions between PTSD and psychotropic medication use, which were significant. The validity of the proportional hazards assumption was assessed for all covariates in all the models using log-log survival curves and weighted Schoenfeld residuals.

RESULTS

The average age of the participants at baseline was 67.7 (±8.1) years and mean follow-up duration for all participants was 9.03 (±1.13) years. The majority of participants (97.9%) were male and 82% were white.

Of the 417,172 veterans in the final sample, 22,674 (5.4%) veterans had a diagnosis of PTSD at baseline. Table 4.1 provides a summary of baseline characteristics of the veterans with and without PTSD. Overall, compared to those without PTSD, participants with PTSD were significantly younger (mean age 61 vs 68, $p<.0001$), and

were more likely to have diagnoses of certain medical and psychiatric conditions noted to be associated with dementia including traumatic brain injury (p<.0001), diabetes mellitus (p<.0001), chronic obstructive pulmonary disease (p<.0001), chronic liver disease (p<.0001), peptic ulcer disease (p<.0001), depression (p<.0001), bipolar disorder (p<.0001) and alcohol (p<.0001), tobacco (p<.0001), and illicit substance abuse (p<.0001). In addition, participants with PTSD were more likely to use the psychotropic PTSD medications of interest compared to those without PTSD.

A total of 25,639 veterans developed dementia during the 9 year follow up period. PTSD was associated with a significantly increased risk for dementia (HR=2.0; 95%CI=1.89-2.11) (Table 4.2). Adjustment for demographics including gender, race and annual income reduced the HR to 1.75 (95%CI=1.65-1.84). Adjustment for medical comorbidity had minimal impact on the HR for PTSD and dementia (HR=1.74; 95%CI=1.64-1.83); however, adjustment for psychiatric comorbidity substantially decreased the HR for PTSD and dementia (HR=1.29; 95%CI=1.22-1.36). After adjusting for demographics, medical and psychiatric comorbidities and number of primary and mental health clinic visits, PTSD was still associated with a significantly increased risk for dementia (HR=1.35; 95%CI=1.27-1.43).

Analysis for effect modification due to psychotropic PTSD medication use showed statistically significant interactions between PTSD and use of SSRIs (p<.0001), NAs (p=.0016), and AAs (p<.0001) on the association between PTSD and the risk for dementia (Table 4.3). There were no significant interactions between PTSD and the use of either SNRIs (p=0.8306) or BZAs (p=0.1171) on the association between PTSD and the risk for dementia.

In the final multivariate analysis, following adjustment for demographic characteristics, medical and psychiatric comorbidity, number of primary care and mental health clinic visits, SSRI, SNRI, BZA, NA and AA drug use, and interactions between PTSD and use of SSRIs, NAs, and AAs, PTSD was associated with an increased risk for dementia among individuals who were not using any psychotropic PTSD medications at baseline

(HR=1.70, 95%CI=1.58-1.82) (Table 4.4). However, PTSD patients using SSRIs were significantly more likely to develop dementia compared to both those with and without PTSD and not using any psychotropic PTSD medications HR=1.24 (95%CI=1.08-1.42) and HR=2.10 (95%CI=1.82-2.41), respectively. In addition, PTSD patients using NAs were significantly more likely to develop dementia compared to both those with and without PTSD and not using any psychotropic PTSD medications HR=1.29 (95%CI=1.14-1.46) and HR=2.19 (95%CI=1.94-2.48), respectively. Furthermore, PTSD patients using AAs were significantly more likely to develop dementia compared to both those with and those without PTSD and not using any psychotropic PTSD medications HR=2.69 (95%CI=2.38-3.04) and HR=4.56 (95%CI=4.04-5.15), respectively. Participants using SSNRIs or BZAs were more likely to develop dementia regardless of PTSD diagnosis HR=1.35 (95%CI=1.26-1.46) and 1.40 (95%CI=1.35-1.45), respectively. Table 4.5 summarizes the other covariates that were associated with significant independent effects on the risk of developing dementia.

DISCUSSION AND LIMITATIONS

The purpose of this study was to determine the association between PTSD and the risk of developing dementia among U.S. veterans 56 years of age and older, and the impact of psychotropic medications commonly used in the management of PTSD on this association.

Association between PTSD and the risk of developing dementia

PTSD was associated with a significantly increased risk of developing dementia among veterans 56 years of age and older after adjusting for demographic characteristics, medical and psychiatric comorbidity, and health care utilization. These results are consistent with previous studies by Yaffe et al. (41), Qureshi et al. (42), and Meziab et al. (43) which reported significant associations between PTSD and the risk of developing dementia among U.S. veterans after similar adjustments for potential confounders.

There are several theoretical explanations for the observed association between PTSD and the risk of developing dementia; first, studies have identified several shared risk factors between PTSD and dementia including traumatic brain injury (82-86), and low education status (21, 23, 87). In addition, PTSD has been linked to increased risk of cardiovascular disease (38-40, 88), depression (35, 89) and diabetes mellitus (90, 91), all of which have been also associated with an increased risk for developing dementia (24, 25, 92, 93). Observations of shared risk factors between PTSD and dementia have been extended to genetic risk factors as well; for example in a recent study involving 172 Vietnam veterans, Lyons et al. (94) found a significant association between PTSD symptoms and apolipoprotein ε4 genotype, which is one of the most prominent genetic risk factors for dementia. Moreover, the association between combat exposure and PTSD varied significantly according to apolipoprotein ε4 genotype; however, to our knowledge these findings have not been replicated.

Secondly, PTSD has been linked to various cognitive decrements including impaired memory, executive functioning, learning, and attention (95-104). For example, in a study involving 26 Vietnam War veterans with PTSD and 21 veterans without mental disorders, veterans with PTSD performed significantly worse than the controls on measures of sustained attention, working memory, initial learning, and estimated premorbid intelligence (103). Similarly, in a study involving 20 Bosnian male combat veterans with PTSD and 20 age- and IQ-matched male combat veterans without PTSD, subjects with PTSD demonstrated significantly less proficiency in terms of attention, working memory, executive function, and memory (98). However, the evidence base is inconclusive because some studies (105, 106) found no evidence of an association between PTSD and cognitive impairments. Nevertheless, a meta-analysis of 28 studies on the association between memory impairment and PTSD, subjects with PTSD consistently demonstrated greater impairments relative to the controls (107) Johnsen et al. 2008). This is an important finding given that memory impairment is often the earliest and predominant cognitive deficit in majority of dementia cases.

In addition, studies have also reported neuropathological similarities between PTSD and dementia, most notably, diminished hippocampal volume. Several studies (108-112) reported an association between PTSD and diminished hippocampal volume; for example, Villarreal et al. (111) compared hippocampal volumes in 12 subjects with PTSD and 10 controls using magnetic resonance imaging (MRI); absolute and normalized bilateral hippocampal volumes were significantly smaller in the subjects with PTSD even after adjusting for lifetime weeks of alcohol intoxication. In addition, in a meta-analysis of studies comparing hippocampal volume in PTSD subjects, Woon et al. (113) found hippocampal volumes were consistently smaller in the PTSD and trauma exposed subjects without PTSD compared to trauma-unexposed subjects. The hippocampus is important in both learning and memory, and diminished hippocampal volume and atrophy have been consistently associated with dementia (114-116). For example, Mueller et al. (116) examined the hippocampi of 18 patients with AD, 20 patients with mild cognitive impairment, and 53 controls using MRI; compared to controls, AD patients had significantly smaller sub- and total-hippocampal volumes.

Impact of psychotropic PTSD medication use on the association between PTSD and the risk for dementia

We found statistically significant interactions between PTSD and the use of SSRIs, NAs, and AAs on the risk of dementia, which suggests that the association between PTSD and the risk of dementia varies significantly depending on whether or not participants were using these medications. Indeed, among persons not using any psychotropic PTSD medications at baseline, PTSD was associated with a significantly increased risk of dementia; however, PTSD patients using SSRIs, NAs or AAs were significantly more likely to develop dementia compared to both those with and without PTSD but not using any psychotropic PTSD medications. We found no statistically significant interactions between PTSD and either SNRIs or BZAs; nevertheless, SNRIs and BZAs were associated with significant independent effects on the risk for dementia which suggests that use of SNRIs or BZAs is associated with increased risk of dementia regardless of PTSD status. A possible explanation for these findings is that use of the

various psychotropic PTSD medications indicates variations in either the symptomatology or severity of PTSD, which might influence the risk of dementia. To our knowledge, no previous study has examined the association between PTSD severity and the risk for dementia; however, PTSD symptom severity has been associated with increased likelihood of receiving a prescription for psychotropic PTSD medications (117).

Alternatively, the independent and effect modifying impacts of psychotropic PTSD medication use on the risk of dementia might represent effects of other underlying psychiatric disorders. Several psychiatric disorders associated with psychotropic medication use including depression (26-28, 118), bipolar disorder (29, 118), anxiety (119), insomnia (120), and schizophrenia (121, 122) have been associated with an increased risk for developing dementia. In addition, PTSD has been found to be associated with psychiatric comorbidity that increase the risk of dementia including depression (35), bipolar, anxiety and sleep disorders (35, 36, 123), and schizophrenia. Moreover, underlying psychiatric comorbidity strongly influences prescription of PTSD pharmacotherapy (117, 124, 125). Because of these observations, we adjusted for these various psychiatric comorbidity in our study.

Another possible explanation for the independent and effect modifying impacts of psychotropic PTSD medication use on the risk of dementia is that psychotropic PTSD medications independently affect the risk for the development of dementia. Our results showed that SNRIs and BZAs were associated with significantly increased risk of dementia regardless of PTSD status while SSRIs, NAs and AAs were associated with a higher risk of dementia among both those with and without PTSD compared to both those with and without PTSD and not using any psychotropic PTSD medications. Research examining the association between psychotropic medication use and the risk for dementia is limited; however, several studies have examined the association between long-term BZA use and the risk for developing dementia and reported similar results; for example, in a 15 year prospective cohort study involving 1063 participants without dementia and not using BZAs at baseline, incident use ever use of BZAs during follow-up was associated with significantly increased risk of dementia HR=1.60 (95%CI=

1.08-2.38) and HR=1.55 (95%CI=1.24-1.95), respectively (69). Similarly, in a nested case-control study of 3,777 elderly persons, ever use of benzodiazepines was associated with a significantly increased risk of dementia (OR=1.7; 95%CI=1.2-2.4) after adjustment for age, gender, education level, living alone, wine consumption, psychiatric history, and depressive symptoms (71). In addition, in a prospective cohort study involving 1134 men, regular use of BZAs increased the risk of dementia (OR=2.94; 95%CI=1.16-7.46) after adjustment for psychological distress and other covariates (70).

Additionally, Kessing et al. (58) examined the associations between the use of various antidepressants including SSRI, non-SSRIs and older antidepressants with the risk for dementia and found purchase of SSRIs, non-SSRIs and older antidepressants at least once to be associated with and increased risk for dementia, (relative risk [RR] = 4.74; 95%CI=4.43-5.07) and RR=1.77 (95%CI=1.67-1.86), respectively. Despite the limited data examining the relationship between SSRI and SNRI use and the risk for dementia, there is theoretical evidence that both serotonergic and noradrenergic neurons play a significant role in cognition particularly, in memory and learning, and attention, respectively. Moreover, dementia neuropathology has been associated with both serotonergic and noradrenergic neuronal degeneration (126, 127), decreased serotonin and norepinephrine levels (128) and serotonergic receptor depletion (129, 130) Cross et al. 1984; Lai et al. 2005). Thus, because SSRIs and SNRIs sustain higher extracellular activity of serotonin, and serotonin and noradrenaline, respectively, these medications could possibly affect cognitive function and the risk of dementia among PTSD patients.

Finally, to our knowledge, the association between AA drug use and the risk for dementia has not been previously determined. Thus, although our results showed significant independent and effect modifying impacts, the association between psychotropic PTSD medication and the risk of dementia, remains an area for further inquiry especially by studies that account for dosage, duration, and indications for use

Other risk factors for dementia

Results showed significant independent associations between non-Caucasian race/ethnicity, traumatic brain injury, hypertension, ischemic heart disease, cerebrovascular disease, diabetes mellitus, alcohol abuse, depression, and bipolar disorder with the risk for dementia. These findings are consistent with results from previous studies, which have shown significant associations between African-American or Hispanic race/ethnicity (131-134), traumatic brain injury (16-19), hypertension (135, 136), cardiovascular disease (24, 25), diabetes mellitus (137, 138), alcohol abuse (139, 140), depression (26-28) and bipolar disorder (29) with an increased risk for dementia among older adults.

Strengths and Limitations

Our study has several limitations; first, we did not adjust for genetic risk factors for dementia such as apolipoprotein ε4 allele status, which is one of the major risk factors for dementia. In addition, our assessment of the impact of psychotropic PTSD medication use on the association between PTSD and dementia did not include adjustments for dosage and duration of medication use. Furthermore, although we adjusted for psychiatric comorbidity associated with both psychotropic PTSD medication use and the risk of dementia, there are other indications for psychotropic medications use such as schizophrenia and personality disorders that we did not account for in our analyses. Thus, these limitations could result in residual confounding in our analyses. Nevertheless, we adjusted for many potential confounders or effect modifiers including demographic characteristics (age, gender, and race/ethnicity), medical and psychiatric comorbidities, and number of primary care and mental health clinic visits.

In addition, our findings are limited to veterans with continual access to the VA system. Because the associations between PTSD, and psychotropic PTSD medication use with the risk of dementia might differ between veterans who use the VHA system and those who do not, the results of this study might not be generalizable to all U.S. veterans, non-U.S. veterans, or non-military persons.

Strengths of this study include the retrospective cohort study design, large sample size, adjustment for various potential confounders and the use of the VHA database, which includes electronic medical records for all patient encounters at VAMCs throughout the country; thus, our data was largely complete, accurate, and representative of veterans throughout the country.

Conclusions and recommendations

After adjusting for potential confounders, PTSD is associated with a significantly increased risk for dementia among individuals not using psychotropic medications; however, PTSD patients using SSRIs, NAs and AAs were significantly more likely to develop dementia compared to both those with and without PTSD and not using any psychotropic PTSD medications. Patients using BZAs or SNRIs are significantly more likely to develop dementia regardless of PTSD diagnosis. Further research is required to determine whether the independent and the effect modifying impacts of psychotropic PTSD medication use on the risk for dementia are due to differences in PTSD severity and symptomatology, other psychiatric comorbidity, or whether they represent independent and direct effects on dementia neuropathogenesis.

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Table 4.1 Comparisons of the baseline characteristics of the participants with and without PTSD

Variable	No PTSD n=394,498 (94.56%) n (%)	PTSD n=22,674(5.44%) n (%)	P-value
Demographic characteristics			
Age (mean/SD)	68.09(7.96)	60.93(7.50)	<0.0001
Gender			
Male	386,141(97.88)	22,395(98.77)	<0.0001
Race			<0.0001
White	327,221(82.95)	15,192(67.00)	
Black	40,167(10.18)	4,808(21.20)	
Other	27,110(6.87)	2,674(3)	
Annual income (percentile)			<0.0001
25th	102,119(25.89)	2,190(9.66)	
50th	95,820(24.29)	8,458(37.30)	
75th	95,067(24.10)	9,227(40.49)	
>75th	101,492(25.73)	2,799(12.34)	
Medical comorbidity			
Traumatic brain injury	941(0.24)	165(0.73)	<0.0001
Hypertension	279,202(70.77)	14,494(63.92)	<0.0001
Ischemic heart disease	120,675(30.59)	5,251(23.16)	<0.0001
Cerebrovascular disease	28,944(7.34)	1,436(6.33)	0.0001
Atherosclerosis	5,883(1.49)	365(1.61)	0.1531
Hyperlipidemia	198,141(50.23)	10,103(44.56)	<0.0001
Diabetes	110,962(28.13)	6,749(29.77)	<0.0001
Chronic obstructive pulmonary disease	9,274(2.35)	699(3.08)	<0.0001
Kidney disease	8,652(2.19)	409(1.80)	0.0001
Liver disease	129(0.03)	19(0.08)	<0.0001
Gastric/peptic ulcer disease	12,025(3.05)	982(4.33)	<0.0001
Psychiatric comorbidity			
Depression	35,146(8.91)	10,327(45.55)	<0.0001
Bipolar disorder	3,371(0.85)	1,120(4.94)	<0.0001
Anxiety	13,352(3.38)	2,787(12.29)	<0.0001
Insomnia	6,591(1.67)	901(3.97)	<0.0001
Substance abuse			
Tobacco abuse	39,000(9.89)	4,711(20.78)	<0.0001
Alcohol abuse	46,321(11.74)	7,177(31.65)	<0.0001
Drug abuse	3,023(0.77)	1,920(8.47)	<0.0001

Table 4.1 Continued

PTSD medication use			
SSRI	37,680(9.55)	3,316(14.62)	<0.0001
SNRI	5,276(1.34)	1,591(7.02)	<0.0001
Benzodiazepines	37,142(9.42)	4,119(18.17)	<0.0001
New antidepressants	33,647(8.53)	4,170(18.39)	<0.0001
Antipsychotics	11,146(2.83)	2,783(12.27)	<0.0001
Clinic visits			
Primary care (mean/SD)	23.40(14.75)	30.31(19.57)	<0.0001
Mental health (mean/SD)	5.58(40.94)	64.31(115.902)	<0.0001

SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor

Table 4.2 Sequential multivariate Cox proportional hazards models for PTSD VS No-PTSD and the risk for dementia

Covariates included in the model	**HR(95% CI)**	**P-value**
Unadjusted	2.00 (1.89-2.11)	<0.0001
Demographic characteristics	1.75 (1.65-1.84)	<0.0001
Demographic + medical comorbidity	1.74 (1.64-1.83)	<0.0001
Demographic + medical and psychiatric comorbidity	1.29 (1.22-1.36)	<0.0001
Demographic + medical and psychiatric comorbidity + number of primary care and mental health clinic visits	1.35 (1.27-1.43)	<0.0001

Table 4.3 Interactions between PTSD and psychotropic PTSD medication classes

Variable	**P-value**
Selective serotonin reuptake inhibitors*PTSD	<0.0001
Serotonin-norepinephrine reuptake inhibitors*PTSD	0.8306
Benzodiazepines*PTSD	0.1171
Novel antidepressants*PTSD	0.0016
Antipsychotics*PTSD	<0.0001

Table 4.4 Hazard ratios for dementia according to PTSD status and psychotropic PTSD medication use

Group	Hazard ratio (95%CI)
PTSD+/No medication VS PTSD-/ No medication	1.70 (1.58-1.82)
PTSD+/SSRI+ VS PTSD-/SSRI-	2.10 (1.82-2.41)
PTSD+/SSRI+ VS PTSD+/SSRI-	1.24 (1.08-1.42)
PTSD+/NA+ VS PTSD-/NA-	2.19 (1.94-2.48)
PTSD+/NA+ VS PTSD+/NA-	1.29 (1.14-1.46)
PTSD+/AA+ VS PTSD-/AA-	4.56 (4.04-5.15)
PTSD+/AA+ VS PTSD+/AA-	2.69 (2.38-3.04)
SNRI	1.35 (1.26-1.46)
BZA	1.40 (1.35-1.45)

AA, atypical antipsychotic; BZA, benzodiazepine; CI, confidence interval; NA, novel antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

Table 4.5 Hazard ratios for associations between potential confounders included in the final multivariate analysis and risk of dementia

Variable	Hazard ratio (95%CI)	P-value
Demographics		
Gender		
Female	(reference)	--
Male	0.89(0.81-0.96)	0.0047
Race		
White	(reference)	--
Black	1.90(1.83-1.97)	<0.0001
Other	1.48(1.41-1.55)	<0.0001
Annual income (percentile)		
25th	0.69(0.67-0.72)	<0.0001
50th	(reference)	--
75th	0.98(0.95-1.02)	<0.3208
>75th	0.75(0.73-0.78)	<0.0001
Medical comorbidities (Yes vs No)		
Traumatic brain injury	2.27(1.91-2.69)	<0.0001
Hypertension	1.29(1.25-1.33)	<0.0001
Ischemic heart disease	1.11(1.08-1.14)	<0.0001
Atherosclerosis	1.29(1.18-1.40)	<0.0001
Cerebrovascular disease	1.71(1.65-1.77)	<0.0001
Diabetes	1.45(1.41-1.49)	<0.0001
Chronic obstructive pulmonary disease	1.33(1.23-1.43)	<0.0001
Gastric/Peptic ulcer disease	1.14(1.07-1.22)	<0.0001
Chronic liver disease	1.50(0.71-3.14)	0.2871
Chronic kidney disease	1.09(1.01-1.17)	0.0250
Psychiatric comorbidities (Yes vs No)		
Depression	1.75(1.68-1.81)	<0.0001
Bipolar	1.61(1.45-1.78)	<0.0001
Anxiety	1.14(1.08-1.21	<0.0001
Insomnia	1.11(1.02-1.20)	0.0124
Alcohol abuse	1.31(1.26-1.37)	<0.0001
Number of clinic Visits		
Primary care	0.95(0.95-0.96)	<0.0001
Mental health clinic	1.00(1.00-1.00)	0.7060

APPENDIX B

SUPPLEMENTARY TABLES FOR PTSD, PSYCHOTROPIC PTSD MEDICATION USE, AND THE AND THE RISK OF DEMENTIA AMONG U.S. VETERANS: A RETROSPECTIVE COHORT STUDY

Table B. 1 Exclusion criteria ICD-9 diagnosis codes

Exclusion criteria	**ICD-9 diagnosis codes**
Other neurodegenerative disorders	332 Parkinson's disease 331.11 Pick's disease 340 Multiple sclerosis 335.20 Amyotrophic lateral sclerosis 333.4 Huntington's chorea 331.3-331.5 Hydrocephalus
Chronic inflammatory disease	579 Celiac disease 555 Crohn's, disease 556 Ulcerative colitis 710 Diffuse diseases of the connective tissues 714 Rheumatoid arthritis and other inflammatory polyarthropathies 720 Ankylosing spondylitis and other inflammatory spondylopathies 696 Psoriasis and related disorders
Cancer	140-239 Neoplasms
Vitamin b12 deficiency	266.2 Other vitamin b complex deficiency 266.9 Vitamin b12 deficiency not otherwise specified 281.0 Pernicious anemia 281.1 Other vitamin b12 deficiency anemia
Hypo and hyper-thyroidism	242.9 Hyperthyroidism 243-244 Hypothyroidism
HIV infection	042 HIV infection
Central nervous system infections	046.1 Creutzfeldt-Jakob disease 094 Neurosyphilis 320 Bacterial meningitis 062 Mosquito-borne viral encephalitis 064 Viral encephalitis transmitted by other and unspecified Arthropods 323 Encephalitis, myelitis, and encephalomyelitis in viral diseases classified elsewhere 321 Cryptococcal meningitis

Table B. 2 List of drugs considered in each psychotropic PTSD medication class

Medication class	**Drug**
Selective serotonin reuptake inhibitors (SSRI)	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline
Serotonin-norepinephrine reuptake inhibitors (SNRI)	Desvenlafaxine Duloxetine Venlafaxine
Benzodiazepines (BZA)	Alprazolam Chlordiazepoxide Clonazepam Clorazepate Diazepam Estazolam Flurazepam Halazepam Lorazepam Oxazepam Prazepam Quazepam Temazepam Triazolam
Novel antidepressants (NA)	Bupropion Mirtazapine Nefazodone Trazodone
Atypical antipsychotics (AA)	Aripiprazole Clozapine Olanzapine Quetiapine Risperidone

Table B. 3 ICD-9 codes for diagnosis of the potential confounders and effect modifiers

Covariate	ICD-9 Diagnosis codes
Medical comorbidity	
Hypertension	401 - 405 Hypertensive disease
Ischemic heart disease	410 - 414 Ischemic heart disease
Cerebrovascular disease	430 - 438 Cerebrovascular disease
Atherosclerosis	440 Atherosclerosis
Hyperlipidemia	272.4 Other and unspecified hyperlipidemia
Diabetes mellitus	250 Diabetes mellitus
Traumatic brain injury	800 - 804 Fracture of the skull 850 Concussion 851 Cerebral laceration and contusion 854.0 Intracranial injury of other and unspecified site 959.01 Head injury, unspecified
Chronic kidney disease	585 Chronic kidney disease V420 Kidney transplant V451.1x Renal dialysis V56. X Encounter for dialysis
Chronic obstructive pulmonary disease	490 Bronchitis 491 Chronic bronchitis 492 Emphysema 494 Bronchiectasis 496 Chronic obstructive airway, not specified
Chronic liver disease	571.0x Chronic liver disease and cirrhosis
Gastritis/peptic ulcer disease	535 Gastritis and duodenitis 531 Gastric Ulcer 532 Duodenal Ulcer 533 Peptic ulcer, site unspecified

Table B.3 continued

Psychiatric comorbidity	
Depression	296.2 major depressive disorder, single episode 296.3 Major depressive disorder, recurrent episode 311 Depressive disorder, not elsewhere classified
Bipolar disorder	296.0x Bipolar disorder, single manic episode 296.1x Manic disorder recurrent episode 296.4x Bipolar disorder, current episode, manic 296.5x Bipolar disorder, current episode, depressed 296.6x Bipolar disorder, current episode, mixed 296.7x Bipolar disorder, current episode, unspecified 296.8x Other and unspecified bipolar disorder
Anxiety	300.02 Generalized anxiety 300.00 Anxiety not otherwise specified 300.09 Other anxiety
Insomnia	780.51 Insomnia, with sleep apnea 780.52 Insomnia, unspecified 327.0x Insomnia
Alcohol abuse	305 Nondependent alcohol abuse 303 Alcohol dependence syndrome
Tobacco use	305.1 Tobacco use disorder
Illicit drug abuse	304.xx Drug dependence 305.xx Nondependent drug abuse 292.0 drug withdrawal 292.1x Drug induced psychotic disorder 292.8x Other drug induced mental disorders, specified 292.9 Other drug induced mental disorder, unspecified

CHAPTER 5

CONCLUSIONS

Dementia is a major public health problem worldwide that is expected to increase almost threefold by the year 2050 without appropriate intervention (1). Emerging research indicates that clinical central nervous system (CNS) (2-9) and systemic bacterial infections (10-12), and posttraumatic stress disorder (PTSD) (13-15) could possibly influence the risk for the development of dementia among humans. However, existing research on infections and risk of dementia has primarily examined effects of CNS infections. Epidemiological studies on the association between systemic bacterial infections and dementia are limited while previous studies on the association between PTSD and dementia did not account for psychotropic medications commonly used in the management of PTSD and could affect cognitive function and possibly influence the risk for developing dementia. The purpose of this study was to review the existing evidence for CNS infections as possible causes of Alzheimer's disease (AD), which is the leading cause of dementia worldwide (16), and using data from the Veterans Health Administration (VHA) national repository of databases, conduct original retrospective cohort data analyses to determine the associations between several different severity levels of clinical systemic bacterial infections, PTSD, and psychotropic PTSD medication use, with the risk for developing dementia.

Review of the literature pertaining to the infectious AD etiology hypothesis found the evidence linking AD to an infectious cause to be largely inconclusive; however, the amount of evidence suggestive of an association is too substantial to ignore. Thus, further epidemiologic, clinical, and basic science studies that could elucidate the associations between AD and infections and possibly uncover ways to control this highly prevalent and debilitating disease are suggested. This review adds to the literature 1) examination of the evidence for the various mechanisms through which different clinical and subclinical infections could cause or promote the progression of AD, and 2) the concordance between putative infectious agents and the epidemiology of AD.

We examined the associations between several different severity levels of clinical systemic bacterial infections including septicemia, bacteremia, pneumonia, osteomyelitis, septic arthritis, cellulitis, and urinary tract infections (UTI), with risk of developing dementia in a large, nationally representative sample of U.S. veterans aged 56 years and older. Results showed that exposure to any systemic bacterial infection was associated with a significantly increased risk for developing dementia (hazard ratio [HR] = 1.20; 95% confidence interval [CI] = 1.16-1.24) after adjustment for demographic characteristics, and medical and psychiatric comorbidity. In addition, septicemia (HR=1.39; 95%CI=1.16-1.66), bacteremia (HR=1.22; 95%CI=1.0-1.49), osteomyelitis (HR=1.20; 95%CI=1.06-1.37), pneumonia (HR=1.10; 95%CI=1.02-1.19), UTI (HR=1.13; 95%CI=1.08-1.18), and cellulitis (HR=1.14; 95%CI=1.09-1.20) were independently associated with a significantly increased risk of developing dementia. Moreover, the hazard ratio for severe infections (e.g., septicemia) was higher than that for less severe infections (e.g., UTI and cellulitis) which suggests a dose-response type of association. To our knowledge, this study is the first to show that both severe (e.g., sepsis), and less severe (e.g., cellulitis) systemic bacterial infections are associated with an increased risk of dementia among older U.S. veterans after adjustment for demographic characteristics, medical comorbidity as well as psychiatric comorbidity not accounted for in prior analyses. These results indicate that prevention of systemic bacterial infections could positively impact the risk for dementia in older adults. However, further basic and epidemiologic research in veterans and other populations is required to elucidate the mechanisms and determine the associations between systemic bacterial infections and the risk for dementia.

Consistent with prior research, analysis of the association between PTSD and psychotropic PTSD medication use with the risk for developing dementia showed a significant association between PTSD and the risk for dementia (HR=1.35; 95%CI=1.27-1.43) after adjustment for demographic characteristics, medical and psychiatric comorbidity, and number of primary and mental health clinic visits. Our results also showed significant interactions between PTSD and use of selective serotonin reuptake

inhibitors (SSRIs) (p<.0001), novel antidepressants (NAs) (p=.0016), and atypical antipsychotics (AAs) (p<.0001) on the association between PTSD and the risk for dementia which indicates that the association between PTSD and the risk for dementia is influenced by SSRI, NA and AA use. In the final multivariate analysis, results showed significant association between PTSD and an increased risk for dementia among individuals not using any psychotropic PTSD medications at baseline (HR=1.70; 95%CI=1.58-1.82). However, PTSD patients who were using SSRIs (HR=2.10; 95%CI=1.82-2.41), NAs (HR=2.19; 95%CI=1.94-2.48) or AAs (HR=4.56; 95%CI=4.04-5.15) at baseline, were significantly more likely to develop dementia compared to those without PTSD and not using any psychotropic PTSD medications. Also, PTSD patients using SSRIs (HR=1.24; 95%CI=1.08-1.42), NAs (HR=1.29; 95%CI=1.14-1.46) or AAs (HR=2.69; 95%CI=2.38-3.04) were significantly more likely to develop dementia compared to those with PTSD and not using any psychotropic PTSD medications. Participants using serotonin-norepinephrine reuptake inhibitors or benzodiazepines at baseline were more likely to develop dementia regardless of PTSD diagnosis HR=1.35 (95%CI=1.26-1.46) and 1.40 (95%CI=1.35-1.45), respectively. However, further research is required to determine if the independent and effect modifying impacts of psychotropic PTSD medication use on the risk for dementia are related to differences in PTSD severity, other psychiatric comorbidity, or whether psychotropic PTSD medication use is an independent risk factor for dementia.

However, because our original data analyses were conducted using administrative data, these studies have several limitations. First, we did not adjust for certain potential confounders such as genetic risk factors for dementia that were not available in the administrative databases. Second, we utilized ICD-9 codes with limited sensitivity for the diagnosis of the outcome and key independent variables as well as the medical and psychiatric comorbidity, which could lead to bias in our assessment of the association between the dementia and the key independent variables. Finally, our studies were limited to veterans with continual access to the VA system. Because the associations between PTSD, and psychotropic PTSD medication use with the risk of

dementia might differ between veterans who use the VHA system and those who do not, the results of this study might not be generalizable to all U.S. veterans, non-U.S. veterans, or non-military persons. Despite these limitations, our studies found significant associations between systemic bacterial infections, PTSD and psychotropic PTSD medication use and the risk for dementia.

Strengths of these studies include the retrospective cohort study design, large sample size, adjustment for various potential confounders and the use of the VHA database, which includes electronic medical records for all patient encounters at Veterans Affairs Medical Centers throughout the country; thus, our data was largely complete, accurate, and representative of veterans throughout the country.

In summary, CNS and systemic infections, PTSD and psychotropic medication use could be associated with dementia neuropathogenesis and possibly influence the risk for developing dementia among older adults. Our next step is to determine 1) the cumulative impact of infections on the risk for dementia, 2) the independent impacts of psychotropic PTSD medication use on the risk for dementia, and 3) the associations between clinical infections, PTSD and psychotropic medication use with the risk for dementia in veterans and other populations.

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