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Psychosocial risk factors and Alzheimer's disease: the associative effect of depression, sleep disturbance, and anxiety

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Abstract

Objectives—Alzheimer's disease (AD) dementia is a neurodegenerative condition, which leads to impairments in memory. This study predicted that sleep disturbance, depression, and anxiety increase the hazard of AD, independently and as comorbid conditions.

Methods—Data from the National Alzheimer's Coordinating Center was used to analyze evaluations of 12,083 cognitively asymptomatic participants. Survival analysis was used to explore the longitudinal effect of depression, sleep disturbance, and anxiety as predictors of AD. The comorbid risk posed by depression in the last two years coupled with sleep disturbance, lifetime depression and sleep disturbance, clinician-verified depression and sleep disturbance, sleep disturbance and anxiety, depression in the last two years and anxiety, lifetime depression and anxiety, and clinician-verified depression and anxiety were also analyzed as predictors of AD through main effects and additive models.

Results—Main effects models demonstrated a strong hazard of AD development for those reporting depression, sleep disturbance, and anxiety as independent symptoms. The additive effect remained significant among comorbid presentations.

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Conclusion—Findings suggest that sleep disturbance, depression, and anxiety are associated with AD development among cognitively asymptomatic participants. Decreasing the threat posed by psychological symptoms may be one avenue for possibly delaying onset of AD.

Keywords

Alzheimer's disease; dementia; anxiety; depression; sleep disturbance

Introduction

Alzheimer's disease (AD) research has identified several risk factors that may be associated with to the development of AD including advancing age, the apolipoprotein (APOE) *ε*4 gene, female sex, family history of AD, mild cognitive impairment, smoking, obesity at midlife, diabetes, midlife hypertension, midlife high cholesterol, moderate and severe traumatic brain injury, fewer years of formal education, and lower levels of social and cognitive engagement (Albert et al., 2011; Alzheimer's Association, 2015a; Di Marco et al., 2014; Green et al., 2002; He, Zhang, & Zhang, 2000 Lautensclager et al., 1996; Loy, Schofield, Turner, & Kwok, 2014; Sando et al., 2008; Vincent & Velkof, 2010; Wang, Xu, & Pei, 2012; Wilson et al., 2013). Cardiovascular factors, such as high cholesterol, high blood pressure, and heart disease, are known to contribute to dementia risk (Diniz, Butters, Albert, Dew, & Reynolds, 2013). However, what is less established in the current literature are definitive conclusions on the relationships between the contribution of other factors such as depression, anxiety, and sleep disturbance, and eventual AD development. There is also limited information on whether these factors are symptoms of AD or if they contribute directly to the development of AD.

To date, depression has not been causally connected to AD, though many studies have yielded results that demonstrate a positive relationship between the two conditions (Andersen, Lolk, Kragh-Sorensen, Petersen, & Green, 2005; Burke et al., 2016a, 2016b; Chen, Ganguli, Mulsant, & DeKosky, 1999; Gracia-Garcia et al., 2015; Li, Meyer, & Thornby, 2001; Steffens et al., 2004). Contradictory evidence about the role of depression remains. Findings from Ownby, Crocco, Acevedo, John, and Loewenstein (2006) suggest depression may be a prodromal symptom to AD, as opposed to a suggested cause. Furthermore, findings from Gatz, Tyas, St. John, and Montgomery (2005) indicate that depression may act as a predictor of AD development among individuals over the age of 65. Psychosocial factors, including depression symptoms, have been linked to future cognitive decline and development of AD (Burke et al., 2016; Green et al., 2003; Kessing & Nilsson, 2003; Speck et al., 1995; Yaffe et al., 1999).

Some studies have suggested amyloid deposits and atrophy in frontal brain regions are related and contribute to AD development in a linear or even synchronous fashion (Becker et al., 2011; Ch etelat et al., 2010; Oh, Habeck, Madison, & Jagust, 2014). Very low levels of dysphoria, apathy, and anhedonia may be indicators to neurodegeneration in areas of the brain that are associated with AD, but this may be independent of amyloid burden (Donovan et al., 2015). Further, patients in a three-year prospective cohort study experiencing mild cognitive impairment and depression were at twice the risk of developing dementia

(Alzheimer's type) than those without depression. Of the depressed patients studied, 85% developed dementia as opposed to 32% of the non-depressed patients (Modrego & Ferr andez, 2004).

Psychological distress, such as that experienced by individuals with anxiety, may also be associated with an increased risk of AD development (Russ, Hamer, Stamatakis, Starr, & Batty, 2011). Russ et al. (2011) indicated that higher levels of psychological distress may be correlated with AD-related deaths. The study results remained the same even when other risk factors were taken into account, such as age, diabetes, smoking, and cardiovascular disease. Recently, Pietrzak et al. (2015) found that elevated anxiety symptoms (measured by the Hospital Anxiety and Depression Scale) moderated the effect of amyloid-β on cognitive decline in a preclinical AD study sample (n = 333). That is, the presence of anxiety symptoms led to more rapid decline in verbal memory, language, and executive function. These domains suggest that impairment first occurred in the temporal and prefrontal cortical regions.

In addition, poor sleeping habits may also be a contributing factor to the risk of AD development (Burke et al., 2016; Xie et al., 2013). This risk may be further increased by homozygous or heterozygous APOE-ε4 carrier status, which is known to increase risk of AD in a dose-dependent fashion (Yoshizawa et al., 1994). Xie et al. (2013) found that cerebrospinal and interstitial fluid exchange increases substantially during sleep, which aids in β-amyloid protein removal. However, when sleep disturbance occurs (defined by less than five hours of sleep or frequent night fits), Aβ-amyloid deposition may increase, which may exacerbate the potential to develop AD (Spira et al., 2013). Lim et al. (2013) indicated that APOE-ε4 carriers with sleep disturbance may also have an increased chance of developing AD compared to ε4 carriers who sleep for the recommended duration of 7–8 hours a night. It has not been definitively concluded that the sleep disturbance instigates AD development, but the aforementioned results provide a platform for further investigation into this correlation. Given the continued debate in the scientific literature, further investigation of the role of psychosocial risk factors in predicting AD risk in a cognitively normal population is warranted.

It is important to not only view the concepts of depression, anxiety, and sleep disturbance as distinct and independent risk factors for AD, but to consider their interacting effect in AD development. For this purpose, the authors selected the syndemic perspective as the theoretical framework guiding the design and analysis of this study. While comorbidity is defined as the presence of multiple, but usually independent, diseases or disorders, a syndemic perspective involves an interaction between two or more diseases or disorders that result in additional negative health consequences (Singer, 2009). However, the syndemic perspective reaches beyond a person's biology, and takes account of stress, inequality, the community, and the environment, all over time, as potential cofactors in the exacerbation of illnesses (Singer, 2009). The syndemic perspective has often been used in the study of medical problems, such as HIV/AIDS and its co-infections like tuberculosis or malaria. A search of the Medline and PsycInfo databases provided no evidence that the syndemic has been used to explain AD development, suggesting that this may be a novel application of the syndemic perspective.

This study hypothesized that the presence of sleep disturbance, depression, and anxiety as individual factors increases the likelihood of meeting the criteria for AD diagnosis. It was also hypothesized that the synergistic effect (examined through additive effects) of two psychological factors, that induce stress, will increase the hazard of AD development beyond the hazard of possessing the presence of one psychosocial effect alone.

Methods

This study examined psychosocial risk factors for late-onset AD through a secondary data analysis of the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS). A prospective cohort design was utilized with individuals who were cognitively asymptomatic at the time of their initial visit (n = 12,053). The analysis sought to determine who among those initially unaffected demonstrated clinical signs of AD dementia by their last visit.

Participants

The participants volunteered from one of the 34 AD Centers (ADCs) in the United States. Data was collected between September 2005 and September 2015. Participants with dementia, mild cognitive impairment, and cognitively intact individuals were recruited by individual ADCs throughout the United States (n = 33,610). The UDS is not a nationally representative sample of the United States population with respect to AD or dementia, as these participants self-select and voluntarily present for an examination at one of the participating NIH/NIA sponsored ADCs. Written informed consent was obtained from all participants and/or self-designated informants by the individual ADC site (NACC, 2010). Participants eligible for this study were cognitively asymptomatic at visit one (n = 12,053). Of this initial sample, 9,184 participants were eligible for analysis as a result of their participation in the original examination and at least one follow-up visit. Therefore, all participants had at least two total visits to the ADC. Participants with more than one dementia-type diagnosis were excluded. This study received approval from the [blinded] University Institutional Review Board.

Measures

Data are collected particiants or provided by a trusted informant by trained clinicians. These interviews acquire a wide range of demographic information; family history; medications used; health history; a physical; and imaging and labs. Participants respond to several neuropsychological rating scales, functional assessments, and from these measures a diagnosis regarding dementia status is determined through the Clinical Rating Scale (Morris, 1993). Probable AD was diagnosed within the UDS using criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984, 2011). Diagnoses arising from these interviews are assigned either by a consensus team or the examining physician (NACC, 2010). Individuals that began the study as cognitively normal, but were diagnosed with AD at a later visit are defined in this study as 'converters' to AD; their counterparts that did not develop AD during the course of the study were defined as 'non-converters' (Table 2).

The variables utilized for this study include self-reported depression in the last two years, other episodes of depression before the two-year timeframe, clinician-verified depression at the time of visit, self-reported sleep disturbance, and self-reported anxiety. Sporadic late-onset AD (probable AD) is the outcome of interest. Three depression measurements were used in the study. The first variable included active depression in the last two years self-reported by the participant. This includes depressive disorders for which a clinician was consulted, even if treatment or medication was not received. Depression includes major depressive disorder, situational depression, bipolar disorders, dysthymic disorders, and other mood disorders. The second measure of depression, depression: other episodes, includes self-reported depression episodes prior to the last two years and is considered to be the measure of lifetime depression. The third depression variable is the clinician's judgment of symptoms and measures the presence or absence of depression at the time of the visit. The *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) was utilized to inform the clinician's diagnosis of depression.

Sleep disturbance was measured by the self-reported presence or absence of nighttime behaviors. These behaviors include awakening during the night, rising too early in the morning, or taking excessive naps during the day. If any of the three symptoms were reported to occur in the past 30 days, participants were considered to have a sleep disturbance. Anxiety was also measured by self-report, specifically whether the person in question was 'very nervous, worried, or frightened for no apparent reason' and seemed 'very tense or fidgety' or is 'afraid to be apart from' the informant (Cummings, 2009, p. 12). The variables of anxiety and sleep disturbance were measured utilizing different questions of the Neuropsychiatric Inventory Questionnaire (NPI-Q), which measures the presence or absence of each individual psychiatric symptom (Cummings, 1977/2009). The NPI-Q has demonstrated adequate test–retest reliability and convergent validity for the individual symptomology with which the current study is concerned (Kaufer et al., 2000).

Survival analysis was used to estimate and interpret hazard functions (Kleinbaum & Klein, 2012). The primary goal was to assess the effect of psychosocial predictor variables on the eventual diagnosis of AD dementia. An event (outcome variable) was defined as a diagnosis of probable AD among individuals with normal cognition at baseline; a diagnosis of probable AD was the failure point and the participant's remaining observations were removed from the study once AD diagnosis was delivered. Right censoring (Kleinbaum & Klein, 2012) was utilized to account for the fact that a participant was not necessarily diagnosed with AD prior to their last observation. As a result, true survival time is unobserved unless a participant is diagnosed with AD on or prior to their last recorded observation. In order to exclude missing values from the analysis, but retain all other information from a participant's visit, missing information was recoded and excluded in a listwise fashion.

The statistical software, STATA (StataCorp, Release 14, 2015), was utilized for the analyses, and a p-value of <0.05 was considered statistically significant for the analysis. Participants' observations ranged from 1 to 10 visits. Observation intervals were measured in days to account for the staggered nature of the visits.

A descriptive analysis of the baseline sample was conducted and included distributions across predictor variables, percentages for categorical variables, and means and standard deviation for continuous variables. Baseline survival function was determined prior to the addition of predictors and covariates (age, race, education, $\varepsilon 4$ carrier status, the presence of hypertension and hypercholesterolemia) in the model. We also controlled for APOE as 30% of the sample were $\varepsilon 4$ carriers. Log-rank tests for equality were used to test for significant differences in survival curves between the various response categories within each predictor variable (i.e. those reporting 'yes' to anxiety versus those reporting 'no' to the same question). Chi-square and *t*-tests were conducted to assess whether there was a statistically significant difference between those who eventually developed AD and those who did not with respect to demographic and predictor variables.

The relationships of certain predictor variables were examined relative to the outcome variable using the Cox proportional hazards model (Cox, 1972). The time variable used for the cox analysis was number of days from the first visit until the first occasion of AD diagnosis. Regression modeling included simultaneous control of multiple predictors and covariates. Four models were developed to explore the main effects of the predictor variables. In the first model, unadjusted main effects of each individual predictor were examined. In the second model, the covariates, sex, age, education, and race were controlled. In the third model, probable AD was examined in relation to the aforementioned controlled variables with the addition of APOE genotypes. In the final model, all previous covariates were controlled, including the presence of hypertension and hypercholesterolemia. A similar structure was applied to the exploration of synergistic effects. The assumption of proportionality was examined through inspection of Schoenfeld residuals in order to determine whether the proportional hazards assumption had been met.

Results

The minimum amount of time participants were under observation was 208 days until the first occasion of AD diagnosis. The maximum observation interval was 3458 days (M = 1549.3; Mdn: 1456 days). The mean number of visits was 3.26 (SD: 2.12), with a range of 1 to 10 visits. There were 361 diagnoses of AD dementia by the end of the observation period among older adults who presented for at least an initial visit and at least one follow-up visit. The mean age of subjects with normal cognition at visit one was 71 years (SD: 10.86 years). At visit one, 80.5% of the sample population were White, 13.55% were African American, and 5.95% were from other ethnic groups. Almost 6% of the sample reported Hispanic origin. Approximately 35% of subjects reported that their mother had been diagnosed with dementia, while 16.45% reported that their father had been diagnosed with dementia. Almost 18% of subjects reported depression in the last two years or lifetime depression, 10.05% of subjects were diagnosed with clinician-verified depression, 10.55% reported a sleep disturbance, and 8.69% reported the presence of anxiety. Percentages, means, and standard deviations (where applicable) are displayed in Table 1.

Preliminary log-rank tests for equality of survivor functions revealed that those who reported depression in the last two years, clinician verified depression at the time of the visit, sleep disturbance, and anxiety expressed statistically significant ($p < 0.001$) different survival

curves than those who did not. The same was true for those reporting lifetime depression versus those who did not ($p < 0.05$). Chi-square and *t*-tests examined differences between participants who ultimately were diagnosed with AD and those who did not demonstrate a statistically significant difference on all psychosocial predictors and most demographic factors. There was not a significant difference between converters and non-converters with regard to race.

There was a significant association ($p < 0.001$) between individuals reporting depression in the last two years and the occurrence (diagnosis) of AD. Specifically, in model one, those who self-reported depression in the last two years experienced a significantly higher risk of AD dementia diagnosis (HR = 2.32 [95% CI, 1.87–2.88]) compared to those who had not. The hazard remained stable even when adjusted for covariates in model two, adjusting further for APOE-ε4 carrier status, and finally adjusting for high blood pressure and cholesterol in the fourth model.

The main effect of lifetime depression episodes, occurring more than two years earlier, presented a significant risk of AD diagnosis within the follow-up period compared to those who did not report such episodes (HR = 1.32 [1.04–1.68], $p < .05$). Similarly, depression verified by a clinician was significantly associated with the diagnosis of AD during the follow-up period as compared to those without verified depression symptoms in model one (HR = 2.72 [2.15–3.43], $p < .001$), and remained relatively similar when the effect of APOE-ε4 carrier status was controlled as well as demographic confounders (HR = 2.89 [2.24–3.72], $p < .001$).

The presence of sleep disturbance was also significantly associated with the eventual diagnosis of AD. The unadjusted hazard (HR = 2.86 [2.25–3.63], $p < .001$) was similar to that of clinician-verified depression (HR = 2.72 [2.15–3.43], $p < .001$).

Finally, anxiety symptoms were significantly associated with an increased hazard of eventual AD development (HR = 3.50 [2.77–4.44], $p < .001$), presenting the strongest association out of the aforementioned psychosocial predictors. Main effects for all primary predictors are displayed in Table 3.

Additive interactions

The hazard of eventual AD diagnosis for those experiencing both recent depression symptoms and sleep disturbance was statistically significant (HR = 4.95 [95% CI 3.53–6.94], $p < .001$), as compared to those experiencing neither symptom. The effect of lifetime depression and sleep disturbance in relation to AD indicated a strong positive relationship (HR = 3.26 [2.24–4.75] $p < 0.001$), compared to those who did not endorse these symptoms. Clinician-verified depression and sleep disturbance was also strongly correlated ($p < 0.001$) with eventual AD diagnosis; yielding a hazard three times greater than those without these symptoms (HR = 3.82 [2.47–5.90]). The findings for additive effects of those reporting anxiety symptoms are similar to participants with recent depression (HR = 5.09 [3.68–7.03], $p < .001$), lifetime depression (HR = 3.41 [2.30–5.05], $p < .001$), and clinician-verified depression (HR = 4.14 [2.86–6.01], $p < .001$) as compared to those who do not report anxiety nor depression symptoms. The additive effect of sleep disturbance and anxiety was

also statistically significant (HR = 4.67 [3.23–6.75], $p < .001$), compared to those without sleep disturbance nor anxiety. These figures are displayed in Table 4.

Discussion

This study examined correlations between depression, sleep disturbance, and anxiety with eventual AD dementia development, both as individual factors as well as comorbid conditions. Previous empirical literature on the association between mental health symptoms and AD and/or dementia focuses on the synchronous relationship between the two. Specifically, studies have examined the correlation between the level of psychiatric symptoms and dementia stage (Lopez et al., 2003; Verkaik, Nuyen, Schellevis, & Francke, 2007), the incidence of psychiatric comorbidity (Steinburg et al., 2008), and psychiatric symptoms impacting dementia caregiver burden and the risk of subsequent nursing home placement (Buhr, Kuchibhatla, & Clipp, 2006).

Few studies have focused on psychological symptoms, such as depression (Richard et al., 2013), anxiety, and sleep disturbance as independent and combined predictors of AD dementia. Similar studies often sample or examine an already impaired population, tracking the progression from MCI to dementia to understand the association between psychiatric symptoms and progression rate (Gabryelewicz et al., 2007). In these studies, the assumptions and hypotheses indicate that psychosocial or psychological symptoms are behavioral manifestations or challenging behaviors associated with dementia as opposed to independent mental health symptoms. Symptoms which precede dementia diagnosis are often assumed to be prodromal symptoms and perhaps a signal of advancing AD pathology (Jorm, 2001).

An estimated 50–70 million Americans suffer chronically from a sleep disorder, impacting their health across daily functioning and lifetime longevity. The Centers for Disease Control and Prevention (2015) reports that 10% of the US population reports chronic insomnia, which is just one facet of the sleep disturbance described in the current study. There are approximately 90 unique sleep disorders, many of which share the following symptoms ‘excessive daytime sleepiness, difficulty initiating or maintaining sleep, and abnormal events occurring during sleep’ (Naismith et al., 2011). In the fifth edition of the *Diagnostic and Statistical Manual* (DSM-V), the characteristics of various sleep disorders were taken into consideration and organized into 11 sleep–wake disorder diagnostic groups (American Psychiatric Association, 2013). Likewise, diagnostic indicators of depression as outlined in the DSM-V include the following: depressed mood daily or nearly daily, decreased interest in activities most of the day, significant weight and appetite change, change in sleep, change in activity, fatigue, guilt/worthlessness, diminished capacity for concentration, and thoughts of death or suicide (American Psychiatric Association, 2013). Sleep disturbance among the aging may be a prognostic indicator for decline in cognitive functioning. Among older adults, sleep disturbance may predict depression. Sleep disturbance in depressed patients can represent the presence of a residual mood disorder. Its presence can linger and may be a precursor for a later depressive episode (Lee et al., 2013).

A recent study of Manhattan residents ($n = 2160$) over the age of 65 (Richard et al., 2013) found depression to be associated with an increased risk of dementia diagnosis, but that

depression did not precede dementia development. Alternatively, a study focusing on diabetes and depression, both as independent and combined factors, found depression to be independently associated with risk of dementia development; the hazard of which was further increased for people diagnosed with diabetes. The study included a wide age range (30–75) and a large sample (n = 19,239). These investigations suggest that ongoing research is examining the relationships between depression and AD but not yet conclusive on how depression may act as an independent risk factor of AD. Similarly, anxiety was found to be a risk factor dementia in men (n = 1481) 17 years after baseline anxiety assessments (Gallacher et al., 2009).

Furthermore, a recent study found that daytime sleepiness was associated with increased incidence of dementia (Tsapanou, Gu, Scarmeas, & Stern, 2015). In a study of Swedish men followed from age 50 to 88 between 1970 and 2010 for the Uppsala Longitudinal Study of Adult Men, researchers found self-reported sleep disturbance (as evidenced by difficulty falling asleep, inability to fall back asleep if waking too early, or the use of sleeping pills three or more times per week) increased the risk of dementia development (+33%) and AD development (+51%; Benedict et al., 2015). Using data from the survey of Health, Aging and Retirement in Europe, researchers found that self-reported sleep disturbance measured as ‘sleeping problems in the past 6 months’, ‘recent trouble sleeping or change in pattern’, and ‘restless sleep’ were also significantly related to the development of dementia (Theou, Rusak, & Rockwood, 2004). Finally, Jorm’s (2001) comprehensive meta-analysis indicate that affective symptomology, such as depression, anxiety, and sleep disturbance are worthy risk factors for exploration in relation to AD risk and development.

The findings from the current investigation support the hypothesis that the presences of psychosocial factors of sleep disturbance, depression, and anxiety as individual factors (which may induce stress), increasing the likelihood of meeting the criteria for AD diagnosis. When these factors were combined to create hypothetical scenarios in which a participant experienced two of these symptoms simultaneously, the synergistic effect remained significant, growing beyond the simple sum of the main effects when covariates were taken into account. These finding provide partial support for the study’s second hypothesis; that the co-occurrence of two psychosocial factors will increase the hazard of AD development beyond the hazard of possessing the presence of one psychosocial effect alone. The mechanism behind such increasing risk, however, is unknown. This, in turn, provides evidence of a syndemic framework or perspective in which the interaction between some of the factors of interest in this study exacerbates AD development.

The strength of this novel study is the inclusion of psychosocial symptoms and cognitive status related to the onset and progression of AD. All participants in this study were determined by a physician or a consensus team to possess normal cognition at visit one. The symptoms explored in this study were reported at baseline.

This study has several limitations. It cannot be confirmed without neuroimaging results that the subjects did not possess underlying AD pathology. It is unlikely that they would be diagnosed with ‘normal cognition’ and not some form of cognitive impairment if this was the case, however, previous studies have shown that up to a third of subjects categorized as

not-demented (Storandt, Grant, Miller, & Morris, 2006) or with pre-MCI (Storandt et al., 2006) during their lifetimes demonstrate AD pathology at autopsy (Storandt et al., 2006; Jack et al., 2002). In addition, we now know that AD pathology likely begins developing 10–20 years prior to any observable manifestations (Sperling et al., 2011). Future studies of this nature would benefit from confirmation of normal cognition through neuroimaging at baseline. Also, the sample was not randomly selected, but it was comprised of individuals volunteering themselves to at least two visits: the initial visit plus one follow-up. Therefore, the results of this study cannot be generalized to the aging population at large, though it provides preliminary evidence that could inform future research with a nationally representative sample. This study also did not compare cognitively normal participants with at least two visits to those with less than two visits (also known as those not eligible for survival analysis).

Additionally, the measures used in the UDS measure depression in three ways – past two years, depression in the lifetime outside of the past two years, and clinician verified depression at the time of visit. Lifetime depression is difficult to interpret without additional treatment data, and it does not distinguish between a chronic mood disorder and an acute episode of depression. The measures also do not define depression by more explicit DSM diagnoses; for example bipolar depressive episodes are not distinguished from clinical depression or dysthymia. Finally, while this study gives insight into the relationships between self-reported depression, lifetime depression, clinician verified depression at the time of visit, anxiety, sleep disturbance, and AD development, more research is needed to refine the causal pathways. Specifically, utilizing the syndemic perspective requires further investigation with societal, political, and economic inequality factors that may be relevant to survival modeling.

The total estimated worldwide costs of Alzheimer's and dementia in 2015 was $818 billion in US dollars (Prince et al., 2015). The World Alzheimer's Institute estimates that total dementia costs will reach $1 trillion worldwide per year by 2018 and $2 trillion per year worldwide by 2030 (Prince et al., 2015). In the United States, total health care, long-term care, and hospice care costs for AD in 2016 are estimated to be $236 billion, with Medicare and Medicaid paying for approximated 68% of these costs (Alzheimer's Association, 2016). Without any changes, Alzheimer's costs are expected to surpass $1 trillion in the United States alone by 2050, presenting a nearly 500% increase in Medicare and Medicaid spending (Alzheimer's Association, 2016).

The Alzheimer's Association (2015b) estimates that if treatment providing a delay in AD diagnosis becomes available by 2025, costs of the disease have the potential to drastically decrease over the subsequent five years. Within the first year alone, savings could amount to about $3 billion in Medicare costs and by 2035 this amount could increase to $67 billion (Alzheimer's Association, 2015b). Even further, they predict that Medicaid savings could amount to $1 billion and $38 billion by 2035 (Alzheimer's Association, 2015b). Cumulatively, these government-funded programs could have a total savings of $535 billion over a 10-year period and $935 billion for payer sources that are not government funded (Alzheimer's Association, 2015b). Additionally, the out-of-pocket expenditures for patients

and their families have the potential to decrease by $2 billion by 2026 (Alzheimer's Association, 2015b).

Given the current state of knowledge regarding possible risks of AD development, it is essential to identify and develop ways to reduce occurrence before the pathophysiological disease progression begins. This may be beneficial to those at risk but also to the national economy and overall healthcare costs. The Centers for Disease Control and Prevention's Syndemics Prevention Network suggest the use of system dynamics models to identify the course and development of health ailments, then to use those models to create a more balanced system of health protection (Milstein, 2008). In this scenario, screening and treatment for depression, sleep disturbance and anxiety are relatively low-cost and potentially preventive measures to be considered in a more holistic approach to AD prevention. This point of view for treating AD broadens the focus from the individual's biology at the moment of AD diagnosis to the individual within his or her environment over time before AD development. Seeing these factors as modifiable ailment ties in a syndemic system, versus comorbidities or prodromal symptoms of AD, may provide an avenue of treatment that delays the onset of AD development.

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Table 1

Demographic overview of sample and predictor variables.

		Depression – last two years		Depression – lifetime		Depression – clinician verified		Sleep disturbance		Anxiety	
	At visit one – baseline	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Normal cognition	12,083	2163 (17.97%)	9871 (82.03%)	2160 (18.09%)	9782 (81.91%)	1214 (10.05%)	10,869 (89.95%)	1180 (10.55%)	10,000 (89.45%)	971 (8.69%)	10,209 (91.31%)
Female	7,865 (65.09%)	1586 (20.17%)	6245 (79.40%)	1590 (20.22%)	6183 (78.61%)	908 (11.54%)	6957 (88.46%)	734 (9.33%)	6542 (83.18%)	644 (8.19%)	6632(84.32%)
Age	X = 71.05 (SD = 10.86)	X = 68.65 (SD = 10.78)	X = 68.14 (SD = 10.59)		X = 68.59 (SD = 10.79)		X = 72.13 (SD = 11.18)		X = 72.24 (SD = 11.43)		
Race											
White	9653 (80.5%)	1865 (19.32%)	7751 (80.30%)	1846 (19.12%)	7699 (79.76%)	1001 (10.37%)	8652 (89.63%)	994 (10.30%)	7944 (82.30%)	821 (8.51%)	8117 (84.09%)
African American	1625 (13.55%)	171 (10.52%)	1488 (91.57%)	185 (10.02%)	1418 (87.26%)	111 (6.83%)	1514 (93.17%)	103 (6.34%)	1397 (85.97%)	80 (4.92%)	1420 (87.38%)
Hispanic	714 (5.93%)	166 (23.24%)	545 (76.33%)	135 (19.12%)	571 (80.88%)	128 (17.93%)	586 (82.07%)	112 (17.5%)	528 (82.5%)	66 (18.86%)	284 (81.14%)
Other	713 (5.95%)	104 (14.58%)	604 (84.71%)	102 (14.31%)	602 (84.43%)	77 (10.80%)	636 (89.20%)	75 (10.52%)	591 (82.89%)	59 (8.27%)	607 (85.13%)

Note: Row percentages are displayed.

Table 2

Demographic overview of converters and non-converters.

	Converters to AD (n = 712)	Non-Converters (n = 1039)	*t* or χ^2 Statistic[a]
Age (years)	84.64 (SD:8.49)[b]	81.93 (SD: 9.44)	−6.18, df = 1763, $p = 0.00$
Female	476 (62.58%)[c]	642 (57.42%)	4.27, df = 1, $p = 0.039$
Education (years)	16.36 (SD: 4.66)	15.62 (SD: 9.84)	−2.12, df = 1763, $p = 0.03$
Race			1.77, df = 2, $p = 0.412$
White	614 (86.24%)	872 (83.93%)	
African-American	75 (10.53%)	129 (12.42%)	
Other	23 (3.23%)	38 (3.66%)	
Hispanic	41 (5.75%)	28 (2.69%)	10.42, df = 1, $p = 0.001$
ε4 Carrier	277 (38.90%)	289 (27.82%)	25.69, df = 1, $p = 0.00$
Depressed 2 Years	277 (38.90%)	275 (26.47%)	31.09, df = 1, $p = 0.00$
Depression – Lifetime	206 (28.93%)	238 (22.91%)	8.68, df = 1, $p = 0.003$
Clinician-Verified Depression	205 (28.79%)	210 (20.21%)	16.86, df = 1, $p = 0.00$
Anxiety	196 (27.53%)	163 (15.69%)	38.64, df = 1, $p = 0.00$
Sleep Disturbance	185 (25.98%)	163 (15.69%)	30.00, df = 1, $p = 0.00$

[a] χ^2 test statistics are displayed for categorical variables, *t* test statistics for continuous variables.

[b] Continuous variables are described with mean and standard deviation.

[c] Categorical variables are described with sample size and percentage.

Table 3

Main effects (Probable Alzheimer's Disease Dementia as Outcome Variable).

Predictor	Model 1 Hazard Ratio (95% CI)	Model 2 Hazard Ratio (95% CI)	Model 3Hazard Ratio (95% CI)	Model 4Hazard Ratio (95% CI)
Depression – last 2 years	2.32 (1.87–2.88) **	2.51 (2.02–3.12) **	2.53 (2.00–3.21) **	2.53 (1.99–3.21) **
Depression – lifetime	1.32 (1.04–1.68) *	1.50 (1.18–1.90) **	1.53 (1.19–1.98) **	1.53 (1.19–1.98) **
Depression – clinician verified	2.72 (2.15–3.43) **	2.67 (2.10–3.37) **	2.89 (2.24–3.72) **	2.88 (2.23–3.71) **
Sleep disturbance	2.86 (2.25–3.63) **	2.57 (2.01–3.27) **	2.57 (1.98–3.34) **	2.56 (1.97–3.33) **
Anxiety	3.50 (2.77–4.44) **	3.25 (2.56–4.12) **	3.17 (2.45–4.10) **	3.16 (2.44–4.09) **

Model 1: Main effect unadjusted.

Model 2: Main effects adjusted for sex, education, age, and race.

Model 3: Main effects adjusted for adjusted for sex, age, education, race, $\varepsilon 4$ carrier status.

Model 4: Main effects adjusted for adjusted for sex, age, education, race, $\varepsilon 4$ carrier status, the presence of hypertension and hypercholesterolemia.

* indicates statistical significance at $p < 0.05$,

** indicates $p < 0.001$.

Table 4

Additive effects among psychosocial predictor variables (Probable Alzheimer's disease as outcome variable).

Predictor	Model 1Hazard ratio (95% CI)	Model 2 Hazard ratio (95% CI)	Model 3Hazard ratio (95% CI)	Model 4Hazard ratio (95% CI)
Depressed 2 years + sleep disturbance	4.95 (3.53–6.94) **	4.81 (3.42–6.75) **	4.66 (3.22–6.75) **	4.65 (3.21–6.74) **
Depression lifetime + sleep disturbance	3.26 (2.24–4.75) **	3.24 (2.22–4.74) **	3.32 (2.20–5.00) **	3.31 (2.19–5.00) **
Clinician-verified depression + sleep disturbance	3.82 (2.47–5.90) **	3.76 (2.43–5.81) **	4.13 (2.58–6.59) **	4.10 (2.56–6.55) **
Sleep Disturbance + anxiety	4.67 (3.23–6.75) **	4.27 (2.94–6.21) **	4.21 (2.79–6.35) **	4.19 (2.77–6.32) **
Depressed 2 years + anxiety	5.09 (3.68–7.03) **	5.09 (3.67–7.05) **	4.75 (3.31–6.80) **	4.75 (3.31–6.82) **
Depression lifetime + anxiety	3.41 (2.30–5.05) **	3.47 (2.34–5.15) **	3.26 (2.10–5.07) **	3.26 (2.10–5.08) **
Clinician-verified depression + anxiety	4.14 (2.86–6.01) **	4.03 (2.78–5.85) **	4.28 (2.88–6.38) **	4.26 (2.86–6.35) **

Model 1: Main effect unadjusted

Model 2: Main effects adjusted for sex, education, age, and race.

Model 3: Main effects adjusted for adjusted for sex, education, age, race, and $\varepsilon 4$ carrier status.

Model 4: Main effects adjusted for adjusted for sex, education, age, race, $\varepsilon 4$ carrier status, the presence of hypertension and hypercholesterolemia.

* indicates statistical significance at $p < 0.05$,

** indicates $p < 0.001$.