An Evaluation of Greenspace Exposure as a Protective Factor in Dementia Risk among U.S. Adults 75 Years or Older

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Abstract

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Background: Green spaces such as parks and forests have been identified to potentially confer health benefits, such as protective neurocognitive effects, to those individuals regularly exposed to them. Possible mechanisms for greenspace exposure to act on cognition range from facilitation of cognitive restoration to supporting lower levels of air pollution. Some literature to date has demonstrated neurocognitive health benefits for greenspace exposure among children. There is limited information on the role of residential greenspace exposure among the elderly in risk of dementia.

Methods: The Gingko Evaluation of Memory Study (GEMS) is a well-characterized cohort of U.S. adults aged 75 years or older evaluated for dementia. After geocoding participant residences, three greenspace metrics were combined to create a composite residential greenspace exposure. Normalized difference vegetative index (NDVI) values were combined with polygon and buffer based assessments of percent park overlap and linear distance to nearest park. Dementia and its subtypes Alzheimer's disease (AD) and Vascular Dementia (VaD) were evaluated prospectively over 8 years using neuropsychiatric evaluations, MRI, and consensus adjudication by study neurologists. Risk of all-cause dementia, AD (without VaD) and VaD (with or without AD) was determined using Cox proportional hazards

regression, unadjusted and adjusted for potential confounders including demographics, health behaviors, and ApoE genotype.

Results: Of 3069 GEMS participants enrolled in 2000, 3048 (99%) were successfully geocoded. Analyses using Cox proportional hazards modeling showed that high residential greenspace (~25% of the sample) was associated with a reduced risk of dementia (HR=0.77, 95% CI: 0.59–0.99) in unadjusted models. With the model adjusted for demographic and behavioral characteristics, treatment arm, average neighborhood deprivation index, and Apolipoprotien E4 status, the association was attenuated (HR=0.82, 95% CI: 0.59–1.13), and did not remain statistically significant. When evaluating subtype, associations between greenspace and AD were not significant for the unadjusted model (HR=0.91, 95% CI: 0.65–1.27). Greespace was found to be significantly protective for risk of Mixed/VaD dementia in the unadjusted model when comparing high vs. low exposure. (HR=0.61, 95% CI: 0.41–0.93). Models for both subtypes were attenuated by adjustment. We did not find evidence of effect modification by sex, apolipoprotien E4 status, or neighborhood deprivation index.

Conclusions: We observed a modest relationship between residential greenspace exposure and all-cause dementia among the elderly although adjustment for confounders attenuated the relationship. Models evaluating subtype suggested a vascular pathway. Regular residential greenspace exposure may play a role in reducing the risk of dementia among the elderly in the United States.

Introduction & Background

Alzheimer's Disease and Related Disorders (ADRD) globally cost an estimated $818 billion dollars in 2013, with that figure expected to rise as the world's population continues to age (Alzheimer's Disease International, 2013). A recent study projected a 2-fold increase in ADRD burden from 1.6% of the U.S. population in 2014 to 3.3% by 2060 with 13.9 million Americans suffering from ADRD (Matthews et al., 2019). Alzheimer's disease is the 6th leading cause of death in the U.S., but some suggest with the combination of the other forms of dementia, ADRD may be as high as 3rd (National Institutes on Aging, 2019; James et al., 2014). The impact of ADRD is especially pronounced in high-income countries including the United States, where post World War II baby boomers are putting increasing strain on geriatric and healthcare services (Sarakr et al., 2016). It has been suggested that 35% of dementia cases worldwide could be prevented by addressing modifiable risk factors, with 15% of cases being modifiable during later life (>65 years) by addressing risk factors such as smoking, depression, physical activity, social isolation, and diabetes (Livingston, 2017). Several of these modifiable risk factors may be addressed by exposure to greenspace.

Possible Mechanisms of Action

A diffuse exposure such as greenspace has a multitude of theoretical mechanisms of action for impacting dementia risk, with these largely fall into two categories: physiological mechanisms and cognitive mechanisms.

Physiological Mechanisms

A straightforward mechanism for multiple health outcomes including dementia has been postulated that exposure to greenspace increases the amount of physical activity in those people exposed, but this relationship has had mixed results when tested with some research finding associations (Richardson et al., 2013) and others not (Barton, Hine, & Pretty, 2009). This mechanism could act upon dementia outcomes by reducing the risk of dementias associated with cardiovascular health, chiefly vascular dementias. Another mechanism for greenspace to influence health outcomes is through air pollution by providing cleaner air for those individuals who live near greenspaces with this relationship having a clearer positive association (Zupancic, Westmacott, & Bulthuis, 2015). Reducing air pollutants may reduce the risk of dementia outcomes by similar cardio pulmonary routes, which have been well established (Rückerl et al., 2011). Some studies have already documented a relationship between traffic-related air pollution and dementia incidence (Oudin et al., 2016). Other possible mechanisms greenspace that may influence health rely on connections between cognitive health and greenspace exposure.

Cognitive Mechanisms

Attention Restoration Theory or ART (Kaplan, 1989) is often cited as a potential mechanism for greenspace exposure to benefit cognitive health (Felsten, 2009) by reducing stress, anxiety, and other mental health concerns through exposure to greenspaces and thus improving concentration and other cognitive domains. This is perhaps the strongest single theory for greenspace to impact dementia outcomes.

By reducing negative mental health concerns such as stress and anxiety, greenspaces may help the brain to "reset" and restore some cognitive functions like attention and memory in particular for dementia. Another possible mechanism in a similar vein is Psychoevolutionary Theory (Plutchik, 1982) where emotions are influenced by greenspace exposure. For example, self-esteem was reported to increase in individuals who walked through United Kingdom National Trust sites (Barton, Hine, & Pretty, 2009). Similar to Attention Restoration Theory, the Psychoevolutionary Theory (PET) mechanism may be reducing negative mental health concerns, negative emotions in particular, and allowing the brain to reset and restore other domains like attention and memory. Another possible mechanism is through simple contact with nature. Some clinicians have begun using a therapeutic intervention for those with some psychiatric conditions called "wilderness therapy" or "adventure therapy" which involves exposing the participant to a natural greenspace and have reported better self-esteem, social adjustment, and reductions in PTSD symptoms (Russell, 2001). This more diffuse nature contact mechanism could impact dementia risk by combining elements of ART and PET to reduce negative emotional states and reduce negative mental health concerns, allowing the brain to reset and restore other domains. Yet another mechanism has been proposed related to improving social ties and having a socially integrated lifestyle in later life. Studies have suggested that having a strong social network in late life may protect against dementia (Fratiglioni, Paillard–Borg, & Winblad, 2004) by increasing cognitive reserve and more regular and varied use of different brain networks. Other studies have suggested that parks and other greenspaces may facilitate these

social networks among the elderly (Holton, Dieterlen, & Sullivan, 2014). Clearly greenspace has a variety of possible mechanisms to influence health outcomes depending on the population and location.

Evidence for the Role of Greenspace

Greenspace exposure is associated with a variety of health benefits for the elderly. Residing in neighborhoods with greater greenspace has been associated with longer life expectancy among the elderly (Takano, 2002), and improved social ties (Holtan, Dieterlen, & Sullivan, 2014). There is emerging research on the potential influences of greenspace on health outcomes, which may have direct implications for dementia risk. One study in Strasbourg, France evaluated the amount of air pollution removed by planting and managing trees throughout the city and found that the trees removed about 88 tons of pollutant in one year (Selmi et al., 2016). This removal of pollutants by vegetation would have clear impacts on multiple health outcomes, particularly those associated with cardiovascular function, including dementias like VaD. The Kaplan Attention Restoration Theory (Kaplan, 1989) has possibly influenced the strongest direct response for the potential benefits of greenspace on dementia with several organizations developing "Memory Gardens" for dementia patients with reported improvements in mood and functioning for individuals with mid to late stage dementia (White et al., 2018). The World Health Organization's review points to several studies where greenspace and perceived neighborhood greenness were strongly associated with mental health benefits, primarily stress reduction (Sugiyama et al., 2008; WHO Regional Office for Europe, 2016). Other

studies have documented greenspace being associated with less anxiety, depression, and healthier cortisol profiles when living in greener areas (Barton & Rogerson, 2017; Maas et al., 2009). Perhaps the strongest direct evidence for greenspace reducing the risk of dementia among the elderly comes from Australia, where individuals residing in nursing homes who engaged in regular gardening reported a 36% lower risk of developing dementia, compared to individuals in nursing homes not engaged in regular gardening (McCallum et al., 2007). In the absence of true randomized trials, observational studies offer some evidence for the impact of greenspace on dementia risk.

Defining Greenspace

Defining greenspace has been a major challenge to evaluating the evidence of greenspace influencing health or societal outcomes (Taylor & Hochuli, 2016). Greenspace can refer to a host of definable spaces like urban parks, greenways, national forests, and uninhabited land among many others. The compound word greenspace can be misleading as one could assume the area in question must be green or a significantly large space. However, some studies have looked into the role of blue spaces including oceans, rivers, and streams (White et al., 2010). Other studies have looked at the broad term "open spaces", which can include any largely uninhabited area (Giles–Corti et al., 2005).

All of these interrelated terms can generate confusion among researchers when discussing greenspace. There are two main interpretations or contexts for

modern greenspace research: urban vegetation or an overarching concept of contact with nature. Greenspace in the context of urban vegetation deals largely with urbanization, urban farming, city planning, and accessibility. Ultimately this interpretation of greenspace requires human planning and intimate involvement with the creation of the greenspace (Kumar et al., 2010). The second more diffuse context of greenspace as an overarching nature exposure dealing more with land cover types, dichotomizing land between urban and natural areas, and is a more macroscopic scale for analyzing greenspace (McIntyre, Knowles–Yanez, & Hope, 2000). This study will primarily approach greenspace under this second interpretation as a more diffuse contact with natural areas that may be human created or naturally preserved lands. We have attempted to capture this diffuse exposure by combining multiple assessments of greenspace using a combination of conventionally bounded forms like managed parks and forests, and vegetation indices.

Motivation for this Study

While the molecular mechanisms involved in cognitive decline are still being uncovered, increasing emphasis is currently placed on understanding the various exposures during the lifespan that may be inducing or preventing the ADRD pathologies from occurring (Yu-Tzu et al., 2017; Keijzer et al., 2016; Lee & Maheswaran, 2010). Understanding which exposures may be either increasing or decreasing the risk of dementia is critical to moving our understanding of the mechanisms of dementia forward and developing therapies and prevention

strategies. The aforementioned potential mechanisms on how greenspace exposure may influence health make greenspace a promising candidate for a potential modifiable risk factor of dementia. Additionally, greenspace exposure is widespread and can be integrated into future city planning and revitalization projects while interacting with greenspaces requires very little on the part of the individual with free parks and public lands widely available. ART and the cognitive mechanistic routes may be the most plausible theories for greenspace impacting dementia risk among the elderly. The elderly may not be able to perform highly physical activities or have comorbid medical concerns that limit the potential influence of greenspace on dementia through physical activity or air pollution. Further evidence for the importance of the cognitive mechanism comes from studies that have emphasized the role of greenspace exposure and cognitive development in children (Nieuwenhuijsen et al., 2018; Dadvand et al., 2017; Engemeann et al., 2019). These studies provide evidence to suggest that individuals with regular greenspace access during childhood and adolescence often have better physical and mental health outcomes in later life. While emphasis has been placed on childhood greenspace exposure and subsequent health outcomes, there have been limited studies that have investigated the associations between greenspace and cognitive function in older adults. Particularly, the literature is sparse on residential greenspace exposure and dementia among the elderly.

Specific Aims

This study utilized data from the Gingko Evaluation of Memory Study (GEMS) and calculated greenspace metrics to examine whether availability of greenspace reduces the risk of incident dementia in a cohort of adults 75 years of age and older. The overall objective was to evaluate the role of greenspace associated with risk of incident all-cause dementia and its subtypes of AD and VaD.

Specific Aim 1: Using available parks and vegetative data sources to create composite greenspace variables and GEMS data to ascertain dementia status, this study examined associations between greenspace exposure and incident all-cause dementia, AD and VaD within the GEMS cohort with adjustments for demographic, behavioral, and biologic characteristics.

- Hypothesis: Greenspace will be associated with a reduced risk of dementia and the association will become attenuated after adjustment for covariates.

Specific Aim 2: Investigate potential effect modifiers (sex, neighborhood deprivation index, and Apolipoprotien E4 (APOE4) status) of the association between greenspace and dementia risk.

- Hypothesis: Greenspace will differentially impact risk of dementia based on sex, neighborhood deprivation index (NDI), and APOE4 status. Women, those with NDI values below the mean, and those with the APOE4 allele present are

expected to experience greater benefit and thus a lower hazard of dementia risk.

Three potential effect modifiers were chosen for analysis a priori: sex, Neighborhood Deprivation Index, and Apolipoprotien E4 status. These were selected due to their previously established associations with the outcome of dementia. Women have been documented to be at higher risk for dementia than men (Gao et al., 1998), which makes sex a worthwhile candidate for effect modification in this sample. Similarly, APOE4 has been well documented to be a risk factor for dementia, Alzheimer's disease specifically, and should be considered as a potential effect modifier (Liu et al., 2013). Lastly neighborhood deprivation, often used as a proxy for socioeconomic status or education, has been previously considered as a factor in the differential risks of dementia between the wealthy and poor (Cadar et al., 2018).

Methods

This section presents the study design, determination of the outcomes of interest, and definition of the composite exposure variable for greenspace. Additionally, this section presents the covariates included in analysis, the statistical approach used, and an overview of the study sample as exclusions and filters were applied in analysis.

The GEMS Cohort and Study Design

The Gingko Evaluation of Memory Study or GEMS was a randomized clinical trial developed to investigate the effect of *Gingko biloba* on dementia and its subtypes in older adults (DeKosky et al., 2008). Participants were randomized using a block design to either twice-daily doses of 120 mg *G. Biloba* extract or an identical appearing placebo (DeKosky et al., 2006, Fitzpatrick et al., 2006). The original trial ran from 2000 to 2008 with more than 3,000 participants from four major sites: Winston-Salem, North Carolina; Baltimore, Maryland; Pittsburgh, Pennsylvania; and Sacramento, California with a median follow-up of 6.1 years (DeKosky et al., 2008). Participants were adults 75 years of age or older at baseline, did not have dementia at enrollment, and had provided a home address, i.e. not institutionalized (DeKosky et al., 2006). As part of the study, participants were assessed every six months for up to 8 years. Primary outcomes include standardized assessments of dementia and its subtypes of AD and VaD. Information on the multiple covariates included in the GEMS trial (APOE4, BMI, health behaviors, etc.) was collected by physical examination, blood testing, and survey data. For more information on the GEMS trial refer to (DeKosky et al., 2006; DeKosky et al., 2008; https://nccih.nih.gov/).

Diagnosis of Dementia

The classification of dementia was based on DSM-IV criteria (American Psychiatric Association, 1994). Dementia due to AD was determined using criteria from the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)

(McKhann et al., 1984). Dementia assessment was extremely robust in the GEMS trial, using a combination of Global Clinical Dementia Rating (CDR), Alzheimer's Disease Assessment Scale (ADAS), and Modified Mini-Mental State Exam (3MSE) to screen participants and a series of neurophysiological tests to determine dementia and AD status during follow-up. At baseline participants were administered the full Neuropsychological Battery. Every six months thereafter, all participants were re-assessed with the cognitive screening instruments to determine if the full battery of dementia assessments should be readministered. For participants whose scores dropped a pre-specified number of points, dependent on individual participant baseline scores for 2 of the 3 tests (3MSE, CDR, or ADAS), if the participant proxy reported new cognitive issues, a private physician diagnosed dementia, or the participant was prescribed a medication for dementia, the full battery was repeated. A blinded panel of experts consisting of 2 neurologists, 2 neuropsychologists, and 1 psychometrician reviewed results from the full battery. Participants were then classified as having dementia and its subtypes of AD only, AD and VaD (mixed), VaD only, or other type of dementia according to criteria from the National Institute of Neurological and Communication Disorders and Stroke, Alzheimer's Disease and Related Disorders Association, National Institute of Neurological Disorders and Stroke-Association Internationale pour le Recherche et l'Enseignement en Neurosciences, and the Alzheimer's Disease Diagnostic and Treatment Centers.

For this study, the outcome of interest was incident all-cause dementia in GEMS participants. Individuals were classified as either having dementia or not by

study conclusion and coded in binary fashion. In total, 523 cases of dementia occurred during the GEMS trial. Secondary analyses to evaluate AD only and Mixed/VaD dementia using criteria described above were also conducted. Of the sample with geocoded data, 518 cases of dementia were available for analysis.

Greenspace Metrics

The data to assess greenspace rely heavily on satellite imagery and land management records. The three key data sources for this study's assessment of greenspace were NASA's eMODIS Normalized Difference Vegetative Index (NDVI), United States Geologic Survey Protected Areas Database (USGS–PAD), and The Trust for Public Land (ParkServe®). Each of these data sources brought their own strengths and weakness to assessing greenspace exposure, and were combined to create a composite and more complete picture of greenspace exposure.

Geocoding

GEMS participants provided residential addresses over the course of the study. Addresses provided at baseline were geocoded using Quantum Geographic Information System's version 3.4 (QGIS) MMQGIS plugin. Some of the provided addresses were Post Office Boxes and were then visually validated by using a Google Streetview overlay. If the geocoded P.O. box appeared to be at the end of a driveway or entrance of an apartment complex this location was kept. However, if the P.O. box appeared to be within a post office, vacant lot, or otherwise separate from housing units this address was dropped. In total 3048 of 3069 addresses were included in

analysis. Participant addresses were then merged in with other geographic attributes by location.

Percent Park Overlap & Distance to Nearest Park Centroid

The USGS–PAD is a unique database maintained by the USGS Gap Analysis Program. The Protected Areas Database is the official governmental inventory of all public parks and protected open spaces, covering over 3 billion acres (Gergely & McKerrow, 2016). The purpose of this database is not only to inventory protected spaces, but also to help build tools to meet national challenges in conservationism, public health, climate research, and infrastructure (Gergely & McKerrow, 2016). USGS–PAD data offers a depth and breadth not found elsewhere. All fee-protected areas from public parks to drainage easements are collected with land management agency (i.e. local city, utility company, national park service) documented and a land coding that includes a degree of access for public recreation (U.S. Geological Survey, Gap Analysis Program, 2016). The strength of USGS–PAD is the coverage and uniformity of the data collection. However, a chief limitation is lack of information on when a park or protected area was established. A variable is included to capture this element, but has high missingness within the database. Regardless, USGS–PAD provides a resource for capturing protected spaces with national coverage in a systematic and uniform manner.

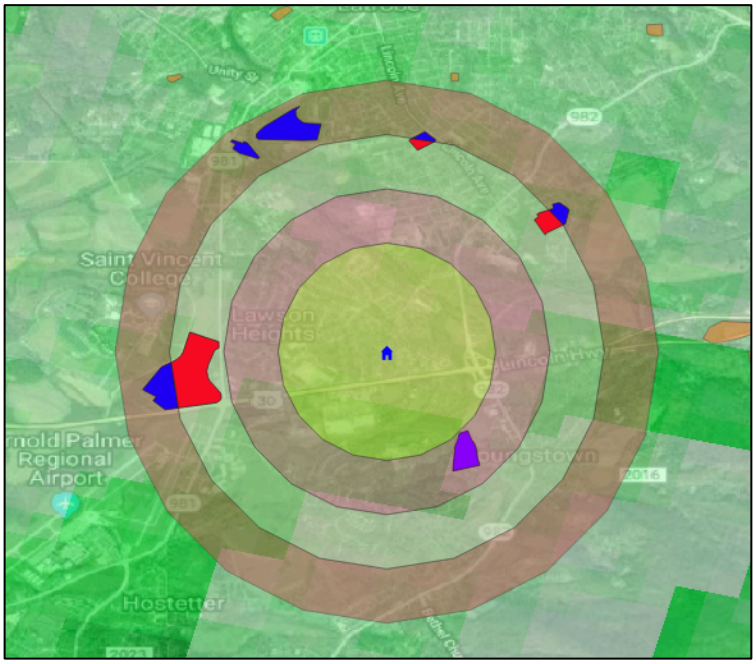
The Trust for Public Land is a national campaign with the goal of ensuring every American has access to a quality park with a 10-minute walk of their home.

The ParkServe® platform measures current access to parks in cities and towns nationwide (ParkServe®, 2018). ParkServe® is a standardized database of local parks in 13,913 cities, towns, and communities. Census designated urban areas are used to define where to collect and create local data. Geographic boundaries are obtained via the US Census 2010 Places geospatial dataset and associated population estimates are derived from ESRI's 2017 Demographic Forecasts (ParkServe®, 2018). Eligible areas for ParkServe® include: publicly owned local, state, and national parks, school parks, and privately owned parks that are managed for public use (ParkServe®, 2018). Areas excluded are privately owned spaces such as homeowner association parks, golf courses, and cemeteries (ParkServe®, 2018). ParkServe® provides a solid measure of local park access, especially for underserved populations, but does suffer from exclusion of those spaces that are not open to the public.

ParkServe® and USGS–PAD data were merged to create a single parks dataset that included more than 70,000 bounded areas ranging in purpose from public parks and forests to drainage easements and school yards. Participants had radial buffers around their geocoded residential addresses out to 2 kilometers in 500-meter increments. The amount of park/open space area that was overlapping each of the buffers was recorded and then cumulative totals calculated as a percent of the area of the buffer. For example, a participant has a park overlapping several of their buffers. Buffer areas are created as follows: the 500m buffer as a diameter of 500m and area of 196350m^2, the 1km buffer area is the area of 1km diameter circle

785398m^2-196350m^2=589048m^2. The area of the previous buffer is excluded from the subsequent buffer to ensure no doubling of park areas occurs. This pattern of subtracting the previous buffer areas from the subsequent buffer is repeated out to the 2km buffer. Next the area of overlap by the park is calculated in QGIS by locating intersecting areas between the parks layer and the buffer layers. For a park overlapping either completely within or partially within that buffer the area of overlap is calculated. If in this example, 1400m^2 are overlapping in the 1km buffer, and 80m^2 overlapping in the 500m buffer then the total percent overlap would be calculated as (1400/589048)*100, which equals 0.24% and (80/196350)*100, which equals 0.04%. The total percent for each buffer out to the 2km buffer are summed to get the total percent overlap. In our example this would be 0.24% plus 0.04% for a total percent overlap of 0.28%. Performing a distance matrix to the nearest park centroid assesses distance to nearest park, with a maximum allowable limit of 10km. This value is then recorded in meters. Map 1 provides a visual example of how greenspaces metrics were derived with buffers, park polygons, and NDVI pixels.

Map 1: Depiction of how greenspace metrics were calculated



Normalized Difference Vegetative Index

This study utilizes NDVI data collected from the National Aeronautics and Space Administration's (NASA) Earth Observing System (EOS) Moderate Resolution Imaging Spectroradiometer (MODIS), which is collectively referred to as eMODIS. The original MODIS system was released in 2000 and has been utilized in numerous vegetative studies, with the eMODIS program started shortly after to provide the data in more flexible file formats (Jenkerson et al., 2010). "The eMODIS suite of products includes either 7- or 10-day data composited data sets…Each data set delivers acquisition, quality and Normalized Difference Vegetation Index (NDVI) information at 250-meter (m) spatial resolution." (USGS, 2018). NDVI is calculated by recording the amount of surface area reflecting near infrared (NIR) wavelengths in a ratio of $(NIR - Red)/(NIR + Red)$. These values are then normalized to create

a -1 to 1 spectrum with values closer to 1 having more live vegetation or "greenness". Although limited by spatial resolution and confined to only more recent years (2000 and later), eMODIS provides a user-friendly way to extract NDVI values for most areas of the United States. NDVI values are extracted from the eMODIS raster for each buffer in similar fashion to the park overlap variable, but rather than areas being calculated it was mean pixel value and then averaged across the 4 buffers to create a single mean NDVI value for each participant. NDVI has been shown to be strongly correlated with environmental psychologists' ratings of greenness (Rhew et al., 2011).

Composite Greenspace

Combined, these three methods were used to create a composite metric of greenspace to assess the multiple dimensions of greenspace exposure, which classified individuals as having either low, medium, or high greenspace exposure. The three greenspace metrics (percent of park/open space overlap, distance to nearest park/open space, and NDVI) were each standardized with a mean of 0 and SD of 1 with distance to nearest park reverse coded so that longer distances correspond to low NDVI and low percent overlap. The three standardized metrics were then combined into a single score by taking the average across the three individual greenspace metrics z-scores. Participants were then grouped into high, medium, or low greenspace exposure based on percentile. 25th percentile and below were classified as low exposure. The 26th to the 75th percentiles were classified as medium exposure. 76th percentile and higher were classified as high exposure.

Covariates

Selected covariates were included in the analysis to address confounding and explore effect modification. Demographic covariates including age group at randomization (<80, 80-84, >85), sex (male or female), race/ethnicity (White, African-American, Asian, Other), treatment arm (*G.biloba* or placebo), and clinic site (Wake Forest University, University of Pittsburgh, Johns Hopkins University, University of California Davis) were extracted from the full GEMS data base located at the Collaborative Health Studies Coordinating Center in the UW Department of Biostatistics. Health behavior covariates including body mass index (BMI using standard cut points by $kg/m^{2)}$, smoking status (never, former, or current), drinking status (any alcohol in the past week: yes/no), and ADL mobility scores were also gathered from the GEMS data. Assessment of Activities of Daily Life (ADL) provides a standardized method of evaluating disability (Katz et al., 1963) by self report of difficulty with specific mobility and strength related tasks. This questionnaire evaluates ability to perform specific tasks, for example exiting a chair, dressing oneself, etc., classifying respondents on a 0-4 scale (0=independent and 4=total dependence). Lastly, the additional covariates of Apolipoprotien E4 status, as determined by genotype testing, and neighborhood deprivation index scores were also included. NDI was assessed with the same index used in the Multi-Ethnic Study of Atherosclerosis (Powell-Wiley et al., 2014). NDI based on residential address was derived using data from Census 2000 summary files and American Community Survey estimates at the census tract level. An overall deprivation index was

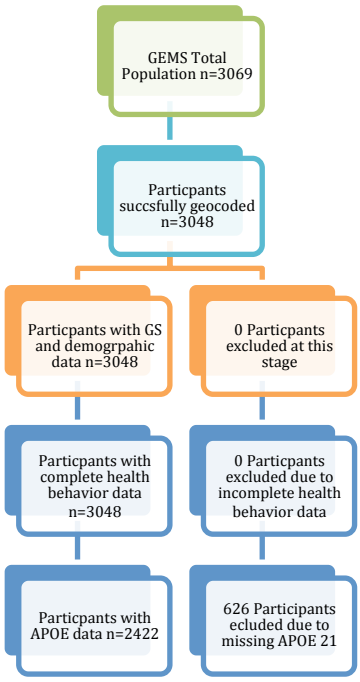
calculated using principal components factor analysis with orthogonal rotation of 21 variables that reflected aspects of race (percent Hispanic, percent non-Hispanic Asian, and percent non-Hispanic black), crowding (percent of households with crowing greater than 1 person per room), foreign born (percent or persons who are foreign born), education (percent of adults age 25 or older with at least a high school education and percent of adults age 25 or older with at least a Bachelor's degree), occupation (percent of persons age 16 and older with executive, managerial, or professional occupation), income and wealth (median value of housing units, percent of housing units without a telephone, percent of housing units without a vehicle, median household income, percent of households with income of at least $50,000, percent of household with interest, dividend, or net rental income, and percent of household receiving public assistance), poverty (percent below poverty level), employment (percent of those age 16 or older who are unemployed and percent of those age 16 and older who are not in the labor force), and housing (percent of occupied housing units, percent of housing units that are owner occupied, and percent of persons living in same house as previous census) (Christine et al., 2015). These covariates were used in multivariable models as described below.

Analysis

All analyses were conducted in Stata Version 15.1 (StataCorp, College Station, Texas). To estimate the association between greenspace and risk of dementia, Cox Proportional Hazards Regression was used to evaluate risk of all-cause dementia,

AD, and Mixed dementia/VaD with adjustment for potential confounders including demographic covariates: race, sex, age, clinic site, education, NDI; behavioral covariates: BMI, alcohol consumption, smoking status, and mobility score; and lastly APOE4 allele status. Covariates were added to regression models in a hierarchical fashion with demographics and NDI added first, followed by health behaviors, and APOE4 last due to high missingness of this variable. These models provide a flexible approach for assessing multiple predictors of right-censored time-to-event outcomes. Models were run using Breslow's method of approximation for ties in the time data. Default Huber standard errors; a standard significance level of 0.05, and a 95% confidence interval (CI) is also included. Testing for the proportional hazards assumption used Schoenfeld residuals with a global test p-value of 0.53 failing to reject the null hypothesis. Effect modification was assessed via interaction terms for the three potential modifiers (e.g., greenspace-x-sex). Clustered robust standard errors at the zip code level were used to account for the spatial clustering of the data. *Figure 1* depicts how the data was filtered down from the full GEMS dataset through the various hierarchical exclusions. Additionally, several sensitivity analyses were undertaken to look at the role of dementia subtype, mobility, and various methodologies for standardization of the greenspace measure on the regression model results.

Figure 1: Diagram of study sample size with hierarchical exclusions



During the GEMS trial a total of 379 deaths from any cause occurred and 195 individuals were either lost to follow-up or withdrew from the study. DeKosky et al. (2008) reported that these individuals did not differ significantly from the remaining participants in relation to age, sex, race, baseline health characteristics, or smoking status). The remaining 2874 participants were followed until study close out in 2008.

Results

This section presents descriptive statistics for the study sample as well as a summary of the Cox model results. Additionally, tables and figures of results are also presented here.

Study Population

Tables 1.1-1.3 present the findings of descriptive statistics of the study sample by sex, dementia status, and greenspace exposure classification. All participants were 75 years or older for the GEMS trail with 66% of the participants being less than 80 years at randomization. The population was fairly evenly split between the sexes with 54% of the sample male. The study sample was also predominantly white (95%) and largely well educated with an average of 14 years of education. Over two-thirds of participants reported having no disability (69%) based on an ADL score of zero, interpreted as independent. Additionally, approximately 40% of the sample never smoked. The study sample was also typical for a US older adult population with 74% reporting use of alcohol and having a mean BMI of 27 kg/m^2. The APOE4 allele was relatively uncommon in this sample with 24% having the allele present.

Tables 2.0-2.2 present the distribution of the variable of interest among the study sample and results from the sensitivity analysis of standardization method. This sensitivity analysis was done to determine which method of standardizing the greenspace metrics would be most interpretable and repeatable. Incident dementia was uncommon among this cohort with only 513 cases during the GEMS trials or 17%. Time to dementia was an average of 5.5 years with a standard deviation of 1.6 years. As shown in Table 2.2, the sample had a mean percent park overlap of 3.04% with and average distance of 1159 meters or 0.7 miles to the nearest park centroid. NDVI had a mean of 0.57 with a standard deviation of 0.18, giving this sample

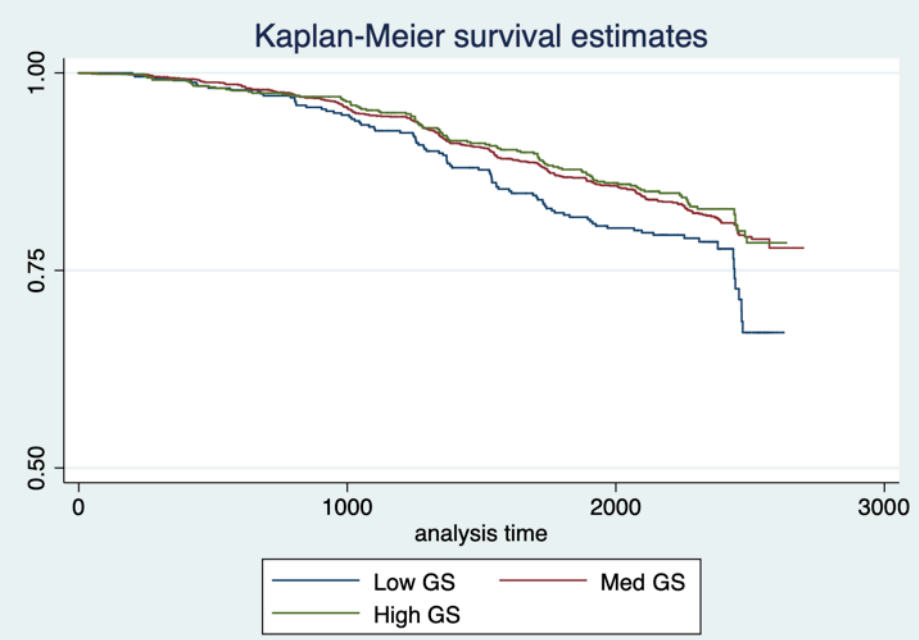
reasonably high NDVI values. Table 2.0 displays the correlations among the three greenspace metrics. These measures were not highly correlated with each other, suggesting they do measure different aspects of greenspace exposure.

Findings

Tables 3.0–3.5 display the results for the Cox Proportional Hazards models with different sets of covariates evaluating all-cause dementia and dementia subtypes. *Figure 2* depicts the Kaplan-Meier curves for the three greenspace exposure groups with a clear separation of low greenspace exposure having more incident dementia cases compared to medium and high greenspace exposure. Table 3.0 displays the results of the primary analysis where the unadjusted model (Model 1) showed marked decreases in the likelihood of incident dementia for individuals with medium and high greenspace exposure. For individuals with high greenspace exposure the likelihood of incident dementia was 23% lower (HR, 0.77; 95% CI, 0.59–0.99) compared to those with the lowest greenspace exposure. Adjustments for demographic characteristics (Model 2) attenuated the association and the difference in dementia risk between high and low greenspace exposure was no longer statically significant. The third model was adjusted for health behaviors: BMI, smoking status, alcohol consumption, and ADL mobility scores. This model produced the strongest findings with a 25% reduction in the likelihood of incident dementia among those individuals with a high greenspace exposure compared to those with low exposure (HR, 0.75; 95% CI, 0.58–0.97). The fourth model was adjusted for a known genetic risk factor for AD, APOE4. This model did not produce

significant results but did show possible attenuation of the association between greenspace and dementia risk. The primary model included adjustment of the standard errors for spatial clustering at the zip code level.

Figure 2:Kaplan-Meier plot for dementia according to low, medium, high greenspace



In order to ensure an appropriate classification method was developed for creating the composite greenspace variable (i.e. binary/hi-lo, standardized trinary, or a non-standardized distributional approach) sensitivity analyses were run to test differences between the various methods. Table 2.1 displays the results of these analyses. Ultimately the trinary method using the standardized z-scores for each greenspace metric was used. This method allows for the most interpretable results and is perhaps the best approach for replicating the composite greenspace metric in future studies.

Table 3.1 displays the results of Cox regression analysis of all cause dementia comparing the composite greenspace metric to the three individual measures of greenspace. This was done to assess if any one measure of greenspace was driving the results from the composite measure. NDVI is a possible better predictor compared to park overlap and proximity, but overall the results do not appear to be driven by any one measure in particular, with values similar to the composite models across the three greenspace metrics. Cut points were chosen based on dividing the sample into approximate thirds with approximation to allow for more interpretable cut points. For example, the short distance to park value was set at 500m instead of the precise 516.26m to make results more interpretable.

Table 3.2 depicts the results from the Cox models when looking at Mixed dementia/VaD as the outcome, by greenspace metric. These models showed some of the largest changes in the hazard ratio, suggesting that greenspace may be more beneficial for individuals with vascular dementias with or without AD. However, many of these results were not statistically significant after adjustment for confounders. Still, there was some insight into how greenspace may be impacting dementia risk with larger reductions in hazard ratios occurring among those with vascular pathologies regardless if AD was also involved.

Table 3.3 shows the results of Cox regression analyses in associations addressing participants classified with Alzheimer's dementia (without VaD) specifically. The results from these models are largely not statistically significant.

This could be due to reducing the sample to only 345 Alzheimer's cases. These results could also point to Alzheimer's pathology not being as affected by greenspace exposure as mixed or vascular dementia subtypes. These results suggest that the mechanism of action for greenspace may be more through cardiovascular routes.

Table 3.4 contains the regression results with participants who were immobile/totally dependent removed from the analysis. This was done under the premise that these individuals may not be able to interact with greenspaces and could be irrelevant to a protective effect involving physical activity. Although the point estimates and confidence intervals do vary slightly to those in the previous tables (chiefly table 3.0) the differences were minimal. Considering the total number of participants who were classified as totally depended is only 42, it seems unlikely that they would have large impact on the overall estimates.

Table 3.5 is a summary table comparing the hazard ratios across the different models by dementia subtype. Here a clear difference can be seen between the impact of greenspace on Mixed/VaD dementia compared to Alzheimer's specific pathologies as well as all cause dementia.

Table 4.0 displays the results stratified by the covariates tested as effect modifiers. Although the hazard ratios suggest some differential impact, the

interaction terms between greenspace and the effect modifiers did not reach statistical significance.

Discussion

The overarching aim of this study was to evaluate the relationship between residential greenspace exposure and incident dementia. To that end, this study demonstrated initial associations with unadjusted models that became attenuated with adjustment for confounders. The unadjusted Cox model showed evidence for a decrease in the likelihood of incident dementia for those individuals with medium to high greenspace exposure. However, unadjusted models do not account for variables that may influence the relationship. When adjusted for the demographic characteristics of age, sex, race, treatment arm, NDI, education, and clinic site the greenspace-dementia association became attenuated and was no longer statistically significant. The strongest evidence for a greenspace–dementia relationship comes from the model adjusted for health behaviors. Smoking status, alcohol consumption, BMI, and ADL mobility score were all included in this model. This model yielded the largest reduction in the likelihood of incident dementia among those with high greenspace exposure at 15% lower risk compared to those with low greenspace exposure. Adjustment for APOE4 also attenuated the association between greenspace and dementia. When investigating associations of greenspace and risk of AD only (excluding those with vascular dementia), results were primarily non-significant. However, analysis of dementia related to a vascular etiology, i.e. VaD with or without AD, suggested that greenspace may be more beneficial in preventing

this type of dementia. This is possibly due to cardiopulmonary and cardiovascular benefits of greenspace including exposure to reduced air pollution and influence on physical activity. Dropping immobile participants did not seem to alter the findings. This could be due to the small number of immobile participants in the GEMS trial (n=42). Additionally, because this study is assessing the role of residential greenspace and not activity within a greenspace, simply living near greenspaces may also confer reductions in dementia risk.

Understanding exposures that may reduce the likelihood of dementia will be critical in developing prevention strategies and possibly therapies for the future. The impact of the aging U.S. population is not yet fully felt by the healthcare infrastructure and having cost-effective interventions and prevention strategies will be crucial in handling the "silver tsunami". These interventions could include further "greening" of city planning to include more greenspaces, with studies providing evidence that greening vacant lots has improved mental health and societal outcomes (Branas et al., 2011; South et al., 2018). The elderly and their caregivers could also implement regular exposure to greenspaces with park days and picnics, something akin to the wilderness therapy for adolescents already in use. Additional use of "memory gardens" could also be a potential route for future therapy (White et al., 2018). Ultimately, the relationship between greenspace and dementia remains unclear, with only moderate evidence to suggest regular residential greenspace exposure may play a role in reducing the risk of dementia among the elderly in the United States.

Strengths

A major strength of this study was use the large GEMS cohort which prospectively collected data to evaluate risk of incident dementia. Another benefit of this study included the rigorous ascertainment of dementia and its subtypes within GEMS as well as the detailed covariate data collected at baseline and throughout the study. . Combining multiple measures of greenspace into a composite measure is another key strength. This allowed us to capture multiple dimensions of residential greenspace exposure and create a clearer picture of what this diffuse exposure entails.

Limitations

This study, like many greenspace studies, is limited somewhat in its ability to accurately include all greenspaces. Even with the combination of USGS–PAD, ParkServe®, and eMODIS NDVI some forms of greenspace exposure (mainly golf courses and other privately owned parks) may have been unaccounted for. A primary concern is the lack of being able to address formal and informal spaces that may be encountered when individuals travel outside of one's residential neighborhood for routine activities (grocery shopping, visiting friends and family, etc.). Similarly, trips for vacations and other locations outside of one's neighborhood are not accounted for in these types of studies. The geocoded residence is the assumed location of the individual for the majority of the day and this may not always be the case. This concern is somewhat ameliorated with the population

being 75+, as a daily work commute is unlikely although other daily travels may occur. Future research could track an individual throughout their day to more accurately map where they go and with what kinds of spaces they come in contact. Another caveat is that although we did investigate the impact of greenspace exposure on some subtypes of dementia, we may not have had sufficient sample size to explore each of these subtypes completely. Residual spatial clustering could still be a concern and accounting for standard error adjustments at a smaller scale (e.g., census tract or block group) may be preferred. While the mechanisms of various forms of dementia are still being discovered, it is worth noting that greenspace may not influence each etiology of dementia in the same way, as our results indicate. This concern is compounded by the multiple mechanisms upon which greenspace may influence health. The AD only and Mixed/VaD models provide some insight into mechanistic pathways that may be involved in a protective effect of greenspace, but this merits further investigation. Another limitation in this area is that with only 518 incident cases, this study does not have the large sample needed to investigate the diffuse exposure of greenspace at a subtype level. Nations with large national registries or national insurances may be better equipped to handle to questions around greenspace and dementia subtypes. Lastly, this study population is 75+ years of age and does not have much lifespan remaining to observe the impacts of diffuse exposures like greenspace readily in addition to these individuals possibly being uniquely robust in their survival and absence of dementia at 75.

Conclusion

This study partially corroborates previous studies investigating associations between greenspace and risk of dementia. Some of the models when adjusted for key variables such as APOE genotype did not show statistically significant results and may be interpreted as greenspace not having an association with dementia among the elderly similar to Clarke et al. 2012. However, other models when adjusted for key health variables including ADL mobility score, BMI, and smoking status found significant associations. This association between greenspace exposure and dementia risk accounting for health characteristics could be due to the heterogeneity of this dataset, which controls for morbidities of this aged population. Still, having a residence with high greenspace exposure could encourage certain behaviors such as increased physical exercise or mental/social behaviors like meditation and attendance to park functions (plays, games, etc.) which could impact dementia risk on several of the possible mechanisms simultaneously. While a vascular etiology was suggested, it is also likely that no single mechanism is responsible, but that several mechanisms are compounded for greenspace to confer a health benefit. For example, it may be a combination of attention restoration, lowering air pollution, and increasing social interaction through which greenspaces provide protection for cognitive decline rather than any one mechanism alone. Ultimately, this model suggests greenspace could play an important role in protection against various dementias similar to Wu et al. 2015. When looking at the sparse body of literature about greenspace and cognition Keijzer et al, 2016 found 13 studies, of various populations, and could derive the finding of greenspace being

"suggestive for cognitive benefit". This suggestion may be the strongest that evidence from observational studies can provide without truly experimental controlled trials around this very diffuse exposure.

The aim of future greenspace research should focus on understanding what types of greenspace and what activities are occurring in them that may be conferring health benefits. This will involve a level of participant tracking and modern data collection methodologies with GPS-tracking being utilized in some recent studies (Mennis, Mason, & Ambrus, 2018). This type of study may be more productive in identification of potential mechanisms by which greenspace may be improving health including cognition. Furthermore, studies similar to the one presented here can still be beneficial for providing more evidence about the greenspace–cognition relationship. It would also be useful for this broader approach to include multiple metrics of greenspace to better capture the possible effects of exposure. The hope for future studies specific to the GEMS cohort is that our findings will motivate additional longitudinal analyses to characterize specific subtypes of dementia and assess exposures at earlier times in the participant's life. In closing, this study does provide modest evidence that greenspace may be protective against dementia among the elderly, but that this relationship is still not definitively understood and merits further investigation.

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Tables

Table 1.1 Descriptive Statistics by Sex

		Sex			
		Male (N = 1,637)	**Female (N = 1,411)**	**Total (N = 3048)**	**P–value*** **
Participant Demographics	***Race****				<0.01
	White	96.33%	94.40%	95.44%	
	African-American	2.02%	4.04%	2.95%	
	Other	1.65%	1.56%	1.61%	
	Age (group)*				0.17
	<80	65.85%	66.76%	66.27%	
	80–84	28.65%	26.44%	27.62%	
	>80	5.50%	6.80%	6.10%	
	Clinic Site*				0.05
	Wake Forest University	25.36%	23.06%	24.12%	
	University of Califonia Davis	27.38%	31.50%	29.61%	
	Johns Hopkins University	14.31%	15.04%	14.70%	
	University of Pittsburgh	32.95%	30.30%	31.57%	
	Education (years)*	14.79 (3.30)	13.96 (2.89)	14.40 (3.15)	<0.01
	Education (group)*				<0.01
	No High School Diploma	10.63%	11.41%	10.99%	
	High School Diploma	21.56%	28.84%	24.93%	
	Some College	21.75%	29.34%	25.26%	
	College Graduate	46.06%	30.40%	38.81%	
	BMI (kg/m2) *	27.32 (3.75)	26.89 (4.84)	27.14 (4.30)	<0.01
	BMI (group)*				<0.01
	Underweight	0.37%	1.35%	0.82%	
	Normal	26.71%	36.92%	31.44%	
	Overweight	52.08%	39.12%	46.08%	
	Obese	20.84%	22.61%	21.66%	
Participant Behavior	***Alcohol Consumption****				0.05
	Yes	75.98%	72.46%	74.35%	
	No	23.96%	27.54%	25.62%	
	Smoker Status*				<0.01
	Never	27.91%	55.68%	40.74%	
	Former	67.00%	40.55%	54.78%	
	Current	5.10%	3.77%	4.48%	
	ADL Mobilty Score*				<0.01
	0–Independent	74.16%	62.27%	68.66%	
	1–Supervision	15.46%	20.64%	17.85%	
	2–Limited Assistance	5.86%	9.86%	7.71%	
	3–Extensive Assistance	3.60%	5.32%	4.40%	
	4–Total Dependance	0.92%	1.91%	1.38%	
Neighborhood Deprivation Index	***NDI average over 8 study years****	-0.33 (0.98)	0.57 (0.95)	0.01 (0.96)	0.01
	NDI at Baseline*	-0.28 (1.02)	0.79 (0.99)	0.03 (1.01)	<0.01
Apolipoprotien E4 Status	***APOE4****	Male (N = 1,321)	Female (N = 1,101)	Total (N = 2,422)	0.02
	Allelle Present	21.80%	25.70%	23.58%	
	Allelle Absent	78.20%	74.30%	76.42%	

*** Categorical Variable – (%)**

**** Continuous Variable – Mean (standard deviation)**

***** Utilizes Pearson chi square and t-testing to compare means**

Table 1.2 Descriptive Statistics by Dementia Status

		Dementia Status			
		Dementia (N = 513)	**No Dementia (N = 2,519)**	**Total (N = 3032)**	**P–value*** **
Participant Demographics	***Race****				0.30
	White	93.96%	95.79%	95.48%	
	African-American	4.09%	2.66%	2.90%	
	Other	1.95%	1.54%	1.61%	
	Sex				0.17
	Male	51.07%	54.43%	53.86%	
	Female	48.93%	45.57%	46.14%	
	Age (group)*				<0.01
	<80	51.27%	69.43%	66.36%	
	80–84	37.43%	25.65%	27.64%	
	>80	11.31%	4.92%	6.00%	
	Clinic Site*				<0.01
	Wake Forest University	24.25%	24.06%	24.09%	
	University of Califonia Davis	31.61%	29.24%	29.64%	
	Johns Hopkins University	18.89%	13.86%	14.70%	
	University of Pittsburgh	25.25%	32.85%	31.57%	
	Education (years)*	14.30 (3.49)	14.43 (3.07)	14.41 (3.15)	0.40
	Education (group)*				0.02
	No High School Diploma	14.81%	10.24%	11.02%	
	High School Diploma	22.81%	25.25%	24.84%	
	Some College	23.59%	25.61%	25.26%	
	College Graduate	38.79%	38.90%	38.89%	
	BMI (kg/m2) *	26.57 (4.14)	27.24 (4.31)	27.12 (4.30)	<0.01
	BMI (group)*				0.04
	Underweight	1.17%	0.75%	0.82%	
	Normal	35.35%	30.69%	31.47%	
	Overweight	45.90%	46.17%	46.12%	
	Obese	17.58%	22.39%	21.58%	
Participant Behavior	***Alcohol Consumption****				<0.01
	Yes	65.30%	76.35%	74.48%	
	No	34.70%	23.61%	25.49%	
	Smoker Status*				0.40
	Never	43.11%	40.23%	40.72%	
	Former	53.15%	55.15%	54.81%	
	Current	3.74%	4.62%	4.47%	
	ADL Mobilty Score*				0.04
	0–Independent	65.50%	69.62%	68.92%	
	1–Supervision	18.71%	17.63%	17.82%	
	2–Limited Assistance	7.41%	7.70%	7.65%	
	3–Extensive Assistance	6.43%	3.89%	4.32%	
	4–Total Dependance	1.95%	1.15%	1.29%	
Neighborhood Deprivation Index	***NDI average over 8 study years****	0.09 (1.03)	-0.01 (0.95)	0.01 (0.97)	0.04
	NDI at Baseline*	0.09 (1.06)	0.00 (1.01)	0.02 (1.01)	0.08
Apolipoprotien E4 Status	***APOE4****	Demented (N = 388)	Non-Demented (N = 2,034)	Total (N = 2,422)	<0.01
	Allelle Present	36.86%	21.04%	23.58%	
	Allelle Absent	63.14%	78.96%	76.42%	

*** Categorical Variable – (%)**

**** Continuous Variable – Mean (standard deviation)**

***** Utilizes Pearson chi square and t-testing to compare means**

Table 1.3 Descriptive Statistics by Greenspace Exposure Group

		Greenspace Exposure Group				
		Low Exposure (N = 762)	**Medium Exposure (N = 1,524)**	**High Exposure (N = 762)**	**Total (N=3048)**	**P–value*** **
Participant Demographics	***Race****					<0.01
	White	92.13%	96.39%	96.85%	95.44%	
	African-American	4.33%	2.82%	1.84%	2.95%	
	Other	3.54%	0.79%	1.31%	1.61%	
	Sex					0.15
	Male	50.97%	54.27%	55.51%	53.71%	
	Female	49.21%	45.73%	44.49%	46.29%	
	Age (group)*					0.27
	<80	64.04%	65.88%	69.29%	66.27%	
	80–84	29.13%	28.15%	25.07%	27.62%	
	>80	6.82%	5.97%	5.64%	5.64%	
	Clinic Site*					<0.01
	Wake Forest University	23.94%	23.55%	25.43%	24.12%	
	University of Califonia Davis	60.37%	22.69%	12.65%	29.61%	
	Johns Hopkins University	4.92%	15.97%	21.97%	14.70%	
	University of Pittsburgh	10.77%	37.79%	39.95%	31.57%	
	Education (years) **	14.39 (3.30)	14.50 (3.03)	14.22 (3.22)	14.41 (3.15)	<0.01
	Education (group)*					0.01
	No High School Diploma	10.63%	9.58%	14.17%	10.99%	
	High School Diploma	24.28%	25.20%	25.07%	24.93%	
	Some College	28.22%	25.07%	22.70%	25.26%	
	College Graduate	36.88%	40.16%	38.06%	38.81%	
	BMI (kg/m2) **	27.20 (4.35)	27.07 (4.26)	27.17 (4.30)	27.13 (4.29)	0.78
	BMI (group)*					0.44
	Underweight	0.66%	1.12%	0.39%	0.82%	
	Normal	30.88%	31.50%	31.89%	31.44%	
	Overweight	45.47%	46.85%	45.14%	46.08%	
	Obese	23.00%	20.54%	22.57%	21.66%	
Participant Behavior	***Alcohol Consumption****					0.50
	Yes	76.48%	73.60%	73.72%	74.35%	
	No	23.52%	26.33%	26.28%	25.62%	
	Smoker Status*					0.40
	Never	39.46%	40.27%	42.95%	40.74%	
	Former	55.17%	55.67%	52.62%	54.78%	
	Current	5.37%	4.07%	4.43%	4.48%	
	ADL Mobilty Score*					0.16
	0–Independent	66.62%	69.69%	68.64%	68.66%	
	1–Supervision	16.82%	17.85%	18.90%	17.85%	
	2–Limited Assistance	10.38%	6.69%	7.09%	7.71%	
	3–Extensive Assistance	4.86%	4.40%	3.94%	4.40%	
	4–Total Dependance	1.31%	1.38%	1.44%	1.38%	
Neighborhood Deprivation Index	***NDI average over 8 study years*** **	0.20 (1.04)	-0.08 (0.94)	-0.01 (0.91)	0.01 (0.97)	<0.01
	NDI at Baseline **	0.24 (1.09)	-0.08 (0.99)	0.00 (0.95)	0.02 (1.01)	<0.01
Apolipoprotien E4 Status	***APOE4****	Low Exposure (N = 582)	Medium Exposure (N = 1,218)	High Exposure (N = 622)	Total (N=2,422)	0.16
	Allelle Present	22.85%	25.12%	21.22%	23.58%	
	Allelle Absent	77.15%	74.88%	78.78%	76.42%	

*** Categorical Variable – (%)**

**** Continuous Variable – Mean (standard deviation)**

***** Utilizes Pearson chi square, t-testing to compare means, or ANOVA in cases of multiple means**

Table 2.0 Correlation Values of Greenspace Metrics

	% Park Overlap	Distance to Nearest Park Centroid	Cumulative Average NDVI
% Park Overlap	1		
Distance to Nearest Park Centroid	-0.09	1	
Average NDVI	0.03	0.17	1

Table 2.1 Sensitivity Analysis of Composite Greenspace Variable with Unadjusted Cox Models*

	Hazrad Ratio	Default SE	95% Confiden Interval	P-value
Non-Standardized	0.69	0.10	(0.52–0.92)	0.01
Z-Score Average (Trinary Method)	0.77	0.10	(0.60–0.98)	0.03
Z-Score Average (Binary Method)	0.82	0.07	(0.69–0.98)	0.03

*Results for highest greenspace exposure group reported

Table 2.2 Descriptive Statistics for the greenspace metrics & dementia measures

All-Cause Dementia	Yes: 16.9% (n=513)	No: 83% (n=2519)
Dementia Subtypes		
AD Only	67.25% (n=345)	
Vascular Only	4.68% (n=24)	
Mixed	23.78% (n=122)	
Neither	4.29% (n=22)	
Time to Dementia	Mean=2007 days	Std. dev.= 589 days
Park Overlap	Mean % overlap=3.04	Std. dev.= 7.06%
Distance to Nearest Park Centroid	Mean=1158.8 meters	Std. dev.=1705.5 meters
NDVI	Mean= 0.57	Std. dev.=0.18

Table 3.0 Hazard Ratios for All Cause Dementia Risk by Greenspace Exposure Group and Covariates with SE Adjustment for Spatial Clustering*

	Low Greenspace Exposure		Medium Greenspace Exposure			High Greenspace Exposure		
			Hazard Ratio	95% CI	P–value	Hazard Ratio	95% CI	P–value
Unadjusted Model	REF	REF	0.88	(0.72–1.07)	0.20	0.77	(0.59–0.99)	**0.04**
Treatment Group	REF	REF	0.88	(0.72–1.08)	0.20	0.77	(0.60–0.99)	**0.05**
Age	REF	REF	0.90	(0.74–1.10)	0.30	0.81	(0.63–1.05)	0.11
Sex	REF	REF	0.88	(0.72–1.08)	0.22	0.77	(0.60–0.99)	**0.05**
Race	REF	REF	0.89	(0.73–1.08)	0.23	0.78	(0.60–1.00)	0.05
Clinic Site	REF	REF	0.92	(0.75–1.13)	0.43	0.81	(0.62–1.07)	0.14
Education	REF	REF	0.88	(0.72–1.08)	0.21	0.77	(0.59–0.98)	**0.04**
NDI Average	REF	REF	0.91	(0.72–1.15)	0.44	0.78	(0.59–1.02)	0.07
Model Adjusted by Demographic Characteristics	REF	REF	0.99	(0.78–1.26)	0.94	0.87	(0.65–1.17)	0.36
BMI	REF	REF	0.87	(0.71–1.06)	0.16	0.77	(0.59–0.98)	**0.04**
ADL Mobility	REF	REF	0.89	(0.73–1.08)	0.25	0.77	(0.60–0.99)	**0.05**
Smoking Status	REF	REF	0.86	(0.71–1.04)	0.13	0.75	(0.58–0.97)	**0.03**
Drinking Status	REF	REF	0.87	(0.71–1.06)	0.17	0.76	(0.59–0.98)	**0.04**
Model Adjusted by Health Behaviors	REF	REF	0.85	(0.71–1.03)	0.10	0.75	(0.58–0.97)	**0.03**
APOE_4 Status	REF	REF	0.87	(0.70–1.08)	0.22	0.80	(0.59–1.07)	0.13
Model Adjusted by All Covariates	REF	REF	0.90	(0.70–1.16)	0.42	0.82	(0.59–1.13)	0.22

*Uses Clusterd Robust SE's clustered by zipcode

Table 3.1 Hazard Ratios for All Cause Dementia Risk by Greenspace Metric

	Unadjusted Model			Model Adjusted by Demographic Characteristics			Model Adjusted by Health Behaviors			Model Adjusted for APOE4 Status		
	Hazard Ratio	**95% CI**	**P–value**	**Hazard Ratio**	**95% CI**	**P–value**	**Hazard Ratio**	**95% CI**	**P–value**	**Hazard Ratio**	**95% CI**	**P–value**
Standardized Composite Greenspace Variable												
Low Exposure	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Medium Exposure	0.88	(0.72–1.07)	0.20	0.99	(0.78–1.26)	0.94	0.85	(0.71–1.03)	0.10	0.87	(0.70–1.08)	0.22
High Exposure	0.77	(0.60–0.99)	**0.04**	0.87	(0.65–1.17)	0.36	0.75	(0.58–0.97)	**0.03**	0.80	(0.59–1.07)	0.13
% Park Overlap[a]												
Low Overlap	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Moderate Overlap	0.86	(0.73–1.03)	0.09	0.92	(0.77–1.10)	0.38	0.88	(0.74–1.04)	0.12	0.96	(0.78–1.17)	0.66
High Overlap	0.84	(0.57–1.22)	0.35	0.89	(0.61–1.33)	0.59	0.86	(0.59–1.26)	0.45	0.93	(0.63–1.38)	0.73
Distance to Nearest Park[b]												
Short Distance	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Moderate Distance	1.00	(0.82–1.23)	0.97	1.03	(0.83–1.29)	0.78	1.06	(0.86–1.30)	0.60	0.96	(0.75–1.22)	0.74
Long Distance	0.93	(0.75–1.14)	0.47	0.94	(0.75–1.18)	0.60	0.97	(0.79–1.19)	0.81	0.92	(0.72–1.17)	0.50
NDVI[c]												
Low NDVI	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Moderate NDVI	0.88	(0.73–1.06)	0.17	0.96	(0.77–1.21)	0.75	0.85	(0.70–1.02)	0.08	0.85	(0.67–1.09)	0.20
High NDVI	0.75	(0.60–0.95)	**0.02**	0.88	(0.65–1.16)	0.33	0.72	(0.57–0.91)	**<0.01**	0.83	(0.63–1.08)	0.17

a: low=less than 2% overlap, moderate=2%–10% overlap, high=more than 10% overlap

b:short=less than 500m, moderate=500m–1200m, long=more than 1200m

c: low=less than 0.45, moderate=0.45–0.65, high=more than 0.65

Table 3.2 Hazard Ratios for Mixed/VaD Dementia Risk by Greenspace Metric*

	Unadjusted Model			Model Adjusted by Demographic Characteristics			Model Adjusted by Health Behaviors			Model Adjusted for APOE4 Status		
	Hazard Ratio	**95% CI**	**P–value**	**Hazard Ratio**	**95% CI**	**P–value**	**Hazard Ratio**	**95% CI**	**P–value**	**Hazard Ratio**	**95% CI**	**P–value**
Standardized Composite Greenspace Variable												
Low Exposure	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Medium Exposure	0.61	(0.44–0.88)	**<0.01**	0.76	(0.52–1.12)	0.17	0.61	(0.43–0.85)	**<0.01**	0.67	(0.42–1.06)	0.08
High Exposure	0.61	(0.41–0.93)	**0.02**	0.71	(0.44–1.16)	0.17	0.61	(0.40–0.92)	**0.02**	0.67	(0.39–1.15)	0.14
% Park Overlap[a]												
Low Overlap	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Moderate Overlap	1.17	(0.88–1.55)	0.28	1.26	(0.93–1.70)	0.13	1.17	(0.88–1.58)	0.28	1.43	(1.02–1.99)	**0.04**
High Overlap	0.49	(0.20–1.22)	0.12	0.58	(0.23–1.49)	0.26	0.52	(0.21–1.26)	0.15	0.55	(0.20–1.52)	0.25
Distance to Nearest Park[b]												
Long Distance	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Moderate Distance	0.87	(0.60–1.25)	0.46	0.97	(0.66–1.42)	0.86	0.92	(0.63–1.35)	0.68	0.73	(0.49–1.09)	0.13
Short Distance	0.91	(0.59–1.38)	0.64	0.90	(0.57–1.41)	0.64	0.93	(0.61–1.42)	0.74	0.90	(0.56–1.43)	0.65
NDVI[c]												
Low NDVI	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Moderate NDVI	0.69	(0.48–0.99)	**0.04**	0.88	(0.60–1.29)	0.52	0.66	(0.46–0.95)	**0.02**	0.68	(0.42–1.10)	0.11
High NDVI	0.61	(0.40–0.93)	**0.02**	0.72	(0.43–1.18)	0.19	0.60	(0.39–0.90)	**0.01**	0.68	(0.41–1.13)	0.14

a: low=less than 2% overlap, moderate=2%–10% overlap, high=more than 10% overlap

b:short=less than 500m, moderate=500m–1200m, long=more than 1200m

c: low=less than 0.45, moderate=0.45–0.65, high=more than 0.65

***146 Mixed Dementia Cases (VaD & Mixed)**

Table 3.3 Hazard Ratios for Alzheimer's Risk by Greenspace Metric*

	Unadjusted Model			Model Adjusted by Demographic Characteristics			Model Adjusted by Health Behaviors			Model Adjusted for APOE4 Status		
	Hazard Ratio	**95% CI**	**P–value**	**Hazard Ratio**	**95% CI**	**P–value**	**Hazard Ratio**	**95% CI**	**P–value**	**Hazard Ratio**	**95% CI**	**P–value**
Standardized Composite Greenspace Variable												
Low Exposure	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Medium Exposure	1.04	(0.79–1.37)	0.77	1.12	(0.83–1.52)	0.45	1.01	(0.77–1.32)	0.94	0.98	(0.74–1.32)	0.93
High Exposure	0.91	(0.65–1.27)	0.59	1.00	(0.70–1.43)	0.98	0.88	(0.63–1.24)	0.48	0.93	(0.64–1.34)	0.70
% Park Overlap[a]												
Low Overlap	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Moderate Overlap	0.75	(0.60–0.93)	**<0.01**	0.80	(0.64–1.00)	0.06	0.76	(0.62–0.94)	**0.01**	0.8	(0.63–1.02)	0.08
High Overlap	0.90	(0.58–1.40)	0.63	0.93	(0.58–1.49)	0.76	0.92	(0.60–1.42)	0.71	1.03	(0.66–1.63)	0.89
Distance to Nearest Park[b]												
Long Distance	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Moderate Distance	0.80	(0.63–1.02)	0.08	1.06	(0.82–1.36)	0.68	1.08	(0.85–1.36)	0.54	1.02	(0.77–1.34)	0.91
Short Distance	1.03	(0.66–1.62)	0.89	0.95	(0.74–1.22)	0.69	0.98	(0.77–1.25)	0.88	0.93	(0.70–1.23)	0.59
NDVI[c]												
Low NDVI	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
Moderate NDVI	0.97	(0.75–1.24)	0.79	1.00	(0.76–1.33)	0.96	0.94	(0.74–1.20)	0.62	0.92	(0.69–1.23)	0.59
High NDVI	0.88	(0.65–1.18)	0.39	1.00	(0.71–1.40)	0.99	0.84	(0.62–1.12)	0.23	0.96	(0.69–1.33)	0.80

a: low=less than 2% overlap, moderate=2%–10% overlap, high=more than 10% overlap

b:short=less than 500m, moderate=500m–1200m, long=more than 1200m

c: low=less than 0.45, moderate=0.45–0.65, high=more than 0.65

*** 345 Alzhiemer's Specfic Cases**

Table 3.4 Hazard Ratios for Dementia Risk by Greenspace Exposure Group and Covariates with Immobile Particpants Removed*

	Low Greenspace Exposure		Medium Greenspace Exposure			High Greenspace Exposure		
			Hazard Ratio	95% CI	P–value	Hazard Ratio	95% CI	P–value
Unadjusted Model	REF	REF	0.88	(0.72–1.06)	0.18	0.77	(0.60–0.99)	**0.05**
Treatment Group	REF	REF	0.88	(0.72–1.07)	0.20	0.78	(0.60–1.00)	0.05
Age	REF	REF	0.90	(0.75–1.09)	0.30	0.82	(0.63–1.05)	0.12
Sex	REF	REF	0.88	(0.72–1.07)	0.19	0.77	(0.60–1.00)	0.05
Race	REF	REF	0.88	(0.73–1.07)	0.20	0.78	(0.60–1.01)	0.06
Clinic Site	REF	REF	0.92	(0.75–1.12)	0.40	0.82	(0.62–1.07)	0.15
Education	REF	REF	0.88	(0.72–1.07)	0.19	0.77	(0.60–0.99)	**0.05**
NDI Average	REF	REF	0.91	(0.72–1.14)	0.40	0.78	(0.60–1.03)	0.07
Model Adjusted by Demographic Characteristics	REF	REF	0.99	(0.78–1.25)	0.93	0.88	(0.65–1.17)	0.38
BMI	REF	REF	0.86	(0.71–1.04)	0.14	0.77	(0.60–0.99)	**0.05**
ADL Mobility	REF	REF	0.88	(0.73–1.07)	0.22	0.77	(0.60–1.00)	0.05
Smoking Status	REF	REF	0.86	(0.71–1.04)	0.12	0.75	(0.58–0.97)	**0.03**
Drinking Status	REF	REF	0.87	(0.72–1.05)	0.15	0.76	(0.60–0.99)	**0.04**
Model Adjusted by Health Behaviors	REF	REF	0.85	(0.71–1.03)	0.09	0.75	(0.58–0.98)	**0.03**
APOE_4 Status	REF	REF	0.86	(0.69–1.07)	0.17	0.80	(0.59–1.07)	0.13
Model Adjusted by All Covariates	REF	REF	0.89	(0.69–1.15)	0.37	0.81	(0.59–1.12)	0.22

* N=42 Totally Dependant Mobility Participants

Table 3.5 Risk of Dementia, AD and Mixed/VaD Dementia by Greenspace Exposure with SE Adjustment for Spatial Clustering

		Unadjusted			Adjusted for Demographics			Adjusted for Health Behaviors			Adjusted for APOE4 Status		
		HR	95% CI	P-Value	HR	95% CI	P-Value	HR	95% CI	P-Value	HR	95% CI	P-Value
All Cause Dementia (N=513)	Low GS	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
	Med GS	0.88	(0.72–1.07)	0.20	0.99	(0.78–1.26)	0.94	0.85	(0.71–1.03)	0.10	0.87	(0.70–1.08)	0.22
	High GS	0.77	(0.60–0.99)	**0.04**	0.87	(0.65–1.17)	0.36	0.75	(0.58–0.97)	**0.03**	0.80	(0.59–1.07)	0.13
Alzhiemer's Dementia Only (N=345)													
	Low GS	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
	Med GS	1.04	(0.79–1.37)	0.77	1.12	(0.83–1.52)	0.45	1.01	(0.77–1.32)	0.94	0.98	(0.74–1.32)	0.93
	High GS	0.91	(0.65–1.27)	0.59	1.00	(0.70–1.43)	0.98	0.88	(0.63–1.24)	0.48	0.93	(0.64–1.34)	0.70
Mixed Dementia (N=146)													
	Low GS	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF	REF
	Med GS	0.61	(0.44–0.88)	**<0.01**	0.76	(0.52–1.12)	0.17	0.61	(0.43–0.85)	**<0.01**	0.67	(0.42–1.06)	0.08
	High GS	0.61	(0.41–0.93)	**0.02**	0.71	(0.44–1.16)	0.17	0.61	(0.40–0.92)	**0.02**	0.67	(0.39–1.15)	0.14

Table 4.0 Effect Modification Results

	Low Greenspace Exposure			Medium Greenspace Exposure			High Greenspace Exposure		
	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value
Sex									**0.26***
Male	REF	REF	REF	0.82	(0.62–1.10)	0.19	0.79	(0.62–1.10)	0.17
Female	REF	REF	REF	0.94	(0.71–1.26)	0.69	0.75	(0.53–1.07)	0.11
APOE4									**0.10***
Absent	REF	REF	REF	0.82	(0.61–1.10)	0.19	0.77	(0.55–1.09)	0.14
Present	REF	REF	REF	0.98	(0.66–1.46)	0.90	0.85	(0.52–1.38)	0.50
NDI									**0.30***
Above Mean	REF	REF	REF	0.89	(0.68–1.16)	0.20	0.82	(0.68–1.16)	0.39
Below Mean	REF	REF	REF	0.89	(0.65–1.23)	0.49	0.70	(0.48–1.05)	0.09

*=Internaction p-values