8-2022

Ecological differences in the associations between air pollution, greenness, and risk of stroke: The REGARDS study.

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A Dissertation Submitted to the Faculty of the
School of Public Health and Information Sciences of the University of Louisville
in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy
In Public Health Sciences

Department of Epidemiology and Population Health
University of Louisville
Louisville, Kentucky

August 2022

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A Dissertation Approved on

August 3, 2022

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ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my mentor and dissertation committee chair, Dr. Kathy Baumgartner. Having the opportunity to learn from her has made a lasting impact on my career that I am forever grateful for. I would like to thank my dissertation committee members: Dr. Richard Baumgartner, Dr. Stephanie Boone, and Dr. Suzanne Judd for their insights, comments, and support. I appreciate the time and invaluable expertise to help me throughout this process. A very special thanks to my committee member and mentor Dr. Aruni Bhatnagar for all of the encouragement and support throughout the years. I wouldn't be where I am today without your guidance and wisdom. A special thanks to the Envirome Institute, The Diabetes and Obesity Center, and the University of Louisville Superfund Center for the constant support and the many opportunities. Additionally, I would like to thank Dr. Shesh Rai, Dr. Sanjay Srivastava, Dr. Steve Jones, and Dr. Bradford Hill for the knowledge, mentoring, and guidance during my time at the University of Louisville. Finally, I would like to thank my wife, Dr. Krista Riggs, and children, Emma Riggs, and Mila Riggs for all the love, support, and patience throughout this process. Finally, I would like to acknowledge the investigators, participants, and funding source of the Reasons for Geographic and Racial Differences in Stroke Study for their valuable contributions (Grant: U01 NS041588).

ABSTRACT

ECOLOGICAL DIFFERENCES IN THE ASSOCIATIONS BETWEEN AIR POLLUTION, GREENNESS, AND RISK OF STROKE: THE REGARDS STUDY

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August 3, 2022

The adverse health effects of air pollution have long been recognized, with the majority of morbidity and mortality due to its effects on the cardiovascular system. Alternatively, living in areas with higher greenness has been found to be beneficial to a wide range of health outcomes. However, few studies have considered that these relationships may vary depending on the surrounding ecosystem. The purpose of this dissertation was to examine the effects of long-term exposure to air pollution and greenness on incidence of stroke, and how these relationships vary with the major ecological regions of the United States. We utilized the Reasons for Geographic and Racial Differences in Stroke study (REGARDS), a prospective cohort study of 30,239 participants recruited between 2003 and 2007. One-year and 3-year exposure to $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, and CO were assigned to participants' census block group. Residential greenspace was estimated by the Normalized Difference Vegetation Index (NDVI) and Enhance Vegetation Index (EVI). The risk of incident stroke associated with baseline pollutants and greenness was assessed using adjusted Cox proportional hazards models. Models were stratified by EPA created ecoregions to determine how associations varied by geographic areas with similar environmental features.

The hazard ratio (95% CI) for a 2.9 μg/m^3 (interquartile range) increase in 1-year PM_{10} was 1.07 (1.003, 1.15) for risk of stroke in the full study population. We did not find evidence of positive associations for $PM_{2.5}$, O_3, NO_2, SO_2, and CO in the full population. In our ecoregion specific analysis, we found positive associations for $PM_{2.5}$ in the Great Plains ecoregion, while associations for PM_{10} were strongest in the Eastern Temperate Forests region. There was suggestive evidence of a negative association between greenness and stroke incidence (hazard ratio: 0.989; 95% CI: 0.946, 1.033) for a 0.1 increase in NDVI within 250-m. In our analysis by ecoregions, we found negative associations between greenness and stroke incidence in the Eastern Temperate Forests region, but positive associations in the Great Plains and Mediterranean California regions. The associations between exposure to air pollution, greenness and stroke incidence varied by ecoregion, highlighting the importance of considering the complexities of the natural environment.

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1. INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality in the United States, with stroke accounting for roughly 17% of all CVD mortality.[1] Geographic differences in CVD rates are well-known and change in risk due to relocation is supported by migration studies.[2-5] Further, evidence indicates that geographic differences in stroke rates occur in the United States.[6] These effects may be explained by differences in the social environment and the natural environment, including greenness level and air pollution composition.

A growing number of studies have highlighted the health benefits of vegetation.[7] Living in areas of high greenness based on accepted vegetation indices is inversely associated with all-cause mortality[8] as well as mortality due to ischemic heart disease and cerebrovascular disease.[9] An ecological study using a natural experiment, studied the loss of 100 million trees due to the emerald ash borer, found that the tree loss was associated with an increase in cardiovascular-related mortality.[10] A number of biopsychosocial mechanisms may explain the association between greenness level and risk of stroke, including mitigation of exposures (air pollution, heat), stress recovery, and encouraging physical activity and social cohesion.[11] This can lead to lower body mass index, lower risk of depression, and improved cardiovascular risk factors.[11-13]

Exposure to fine particulate matter (PM) has been found to be strongly and robustly associated with an increase in CVD risk and mortality.[14] The Global Burden of disease study estimated that air pollution accounted for 21% of deaths due to stroke in 2015.[15] Previous work has found that long-term exposure to $PM_{2.5}$, PM_{10}, and gaseous pollutants is associated with increased stroke incidence and mortality.[16] However, the natural environment is rarely accounted for in these studies. Recent work suggests that living in areas of high vegetation reduces the harmful effects of $PM_{2.5}$ on CVD. [17-20] Previous studies have reported that living in areas of higher residential greenness is associated with lower volatile organic compound exposure, which are ubiquitous gaseous pollutants.[21] Harm from air pollution can also be affected by the climate, with an increased burden of CVD due to pollution when accompanied with extreme temperatures.[22,23] While intriguing, it is unclear how other features of the natural environment may modify the effects of $PM_{2.5}$ and other pollutants on CVD, and stroke specifically.

The current dissertation evaluates the association between air pollution and greenness levels with risk of stroke while also considering other major natural environmental features. Additionally, inter-dependence and combined interaction with pollution exposure was assessed. Although previous studies have assessed how individual characteristics of the natural environment may modify the effects of pollution or greenness on health, these characteristics together form a complex ecosystem, and this complexity has not been accounted for in previous studies. One approach is to categorize individuals into ecoregions, which are ecosystems of generally similar biotic and abiotic features.[24] This allows for an evaluation of

whether greenness and pollution levels influence stroke risk, and whether this varies by the type, quality, and quantity of the surrounding natural environment.

Our central hypothesis is that ambient air pollution ($PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, CO) is associated with increased risk of stroke, and surrounding greenness (Normalized Difference Vegetation Index, NDVI) is associated with decreased risk of stroke, defined as focal neurologic deficit lasting more than 24 hours or imaging consistent with ischemia or hemorrhage. This hypothesis will be tested in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort study with the following specific aims:

Aim 1 Characterize the REGARDS cohort, ambient air pollution, vegetation, and environmental characteristics by EPA ecoregions.

Aim 2 To determine the relationship between long-term ambient air pollution and risk of stroke in the REGARDS cohort.

Hypothesis: Adults with long-term exposure to high levels long-term of ambient air pollution will have increased risk of stroke, independent of relevant confounders.

Aim 3 To determine the extent to which the effects of long-term ambient air pollution exposure on risk of stroke are modified by the surrounding ecosystem.

Hypothesis: The association of long-term ambient air pollution with risk of stroke will be modified by the surrounding ecosystem.

Aim 4 To characterize the relationship between residential greenness and risk of stroke in the REGARDS cohort.

Hypothesis: Adults exposed to higher residential greenness will have lower risk of stroke, independent of relevant confounders.

Aim 5 To determine the extent to which the effects of surrounding greenness on risk of stroke are modified by the surrounding ecosystem.

Hypothesis: The association of surrounding greenness on risk of stroke will be modified by the surrounding ecosystem.

LITERATURE REVIEW

1. Stroke Classification and Etiology

The term ‘stroke’ refers to an umbrella of complex neurological conditions that are caused by an occlusion or hemorrhage of blood vessels that supply the brain.[25] The World Health Organization defines stroke as: “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer leading to death, with no apparent cause other than of vascular origin”.[26] Stroke can be classified pathologically as either ischemic or hemorrhagic disturbances of cerebral blood circulation. Ischemic stroke consists of an interruption of blood supply to the brain, resulting in a sudden loss of function, and accounts for roughly 80% of all strokes.[27] This can occur via several mechanisms, including thrombotic cerebral infarction, which results from an atherosclerotic obstruction in large cervical or cerebral arteries, and ischemia in the region of the occluded artery.[26] Embolic cerebral infarction occurs when a clot from other parts of the arterial system cause an embolism in the cerebral arteries. Lacunar cerebral infarctions, related to chronic hypertension, are when small deep infarcts occur in the small penetrating arteries. Hemorrhagic stroke consists of a rupture of the blood vessels that supply the brain or an abnormal vascular structure, and account for roughly 20% of all strokes.[27] The most common type of hemorrhagic stroke is intracerebral hemorrhage, accounting for 80%, which is a spontaneous rupture of the small vessels typically due to uncontrolled

hypertension.[27] The less common subarachnoid hemorrhage is predominantly due to the rupture of saccular aneurysms at the inferior surface of the brain, and may not cause direct damage to the brain. Transient ischemic attacks (TIA) are also commonly considered a primary outcome in stroke research and precede up to 23% of all strokes.[28] TIAs are defined by the American Stroke Association as brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.[29]

Diagnosis, Treatment, and Prevention

Treatment options depend on the type of stroke and timely intervention, including the diagnose of a stroke in progress to determine recommended treatment. According to the CDC, treatments are most effective if the stroke is diagnosed within the first three hours of symptoms onset. Common symptoms include sudden numbness or weakness on one side of the body in the face, arms, or legs; sudden confusion or trouble speaking; sudden trouble seeing; sudden trouble walking, including dizziness or loss of balance; and sudden severe headache with no known cause. Previous work has found that the prevalence of stroke related symptoms is generally high in populations free of a prior diagnosis of stroke, suggesting that stroke may be underdiagnosed.[30] Diagnosis typically begins in the emergency room, with physicians asking about onset of symptoms and medical history. Other conditions with similar symptoms need to be ruled out to properly diagnose stroke, such as seizures, migraines, fainting, drug overdose, and other cardiovascular related problems. Physical and neurological exams are performed to determine whether the patient has trouble breathing, circulation

abnormalities, or cognitive impairment. All patients with stroke symptoms typically undergo neuroimaging by noncontrast computed tomography (CT) or MRI, to distinguish between ischemic and hemorrhagic stroke, and to rule out the presence of nonischemic central nervous system lesions.[31] If an acute ischemic stroke is identified, tissue plasminogen activator (tPA) is given to the patient, which is a thrombolytic, to help break up blood clots. Other diagnostic tests for patients with suspected acute ischemic stroke include, blood glucose levels, oxygen saturation, serum electrolytes, complete blood count, markers of cardiac ischemia, and ECG.[31]

Considerable advancement in ischemic stroke treatment has occurred over the past decades, however the benefits of treatment rely on timely intervention. Intravenous thrombolysis (tPA) is an FDA-approved acute therapy, and can be administered up to 4.5 hours after identification of an ischemic stroke.[32] Many stroke centers offer intra-arterial thrombolysis, either alone or in combination with intravenous tPA, though the efficacy is not definitive.[32] Another treatment option for ischemic stroke is mechanical thrombectomy, a surgery to remove blood clots from the arteries or veins. Despite the progress in treatment of ischemic stroke, advancements in hemorrhagic stroke treatment have occurred more slowly. Additionally, outcomes are dismal following hemorrhagic stroke, with mortality rates between 30%-50%.[33] Hypertension is a major risk factor for intracerebral hemorrhage (ICH), and elevated blood pressure is commonly found during the acute phase of ICH. Thus, antihypertensive therapy is one option for treatment. In

addition to blood pressure management, coagulopathy reversal and intracranial pressure control are common treatments of acute ICH.[34]

Preventative measures of stroke are tailored to the disease mechanism. Primary prevention strategies are focused on identifying known risk factors. This includes treatments for lowering blood pressure, statin use to lower cholesterol, controlling blood sugar levels, smoking cessation, and elimination of heavy drinking. Controlling these risk factors after a patient has had a stroke, is critical for preventing a recurrent stroke. Among individuals with carotid stenosis, a carotid endarterectomy to remove the inner lining of an artery has been shown to reduce the risk of ischemic stroke.[35] Angioplasty and stent placement are also feasible options for patients who are not good surgical candidates. Antiplatelet medications such as aspirin, ticlopidine, and clopidogrel have also shown to be effective in the secondary prevention of stroke.[35]

2. Epidemiology of Stroke

Stroke is the fifth leading cause of death in the United States.[1] In 2018, an estimated 7.6 million Americans over the age of 20 self-reported receiving a stroke diagnosis, with an estimated prevalence of 2.7%.[36] Approximately 795,000 people experience a stroke each year, with 610,000 being first attacks and 185,000 are recurrent attacks.[36] Stroke remains a major cause of disability, with an estimated 3.5 million survivors in the United States.[25] The high morbidity contributes to the burden of stroke, with up to 50% of stroke survivors being chronically disabled.[27] The estimated direct medical costs of stroke in 2015 was $36.7 billion, which is

expected to reach $94.3 billion by 2035, due to the rising age of the U.S. population.[36] Although there has been a remarkable 77% decrease in age-adjusted stroke mortality between 1968 and 2016, recent declines have plateaued.[37] A projected 3.4 million more adults expected to have a stroke by 2030, a prevalence of 3.9% of the population, representing a 20.5% increase from 2012.[36]

Risk Factors for Stroke

Stroke is a complex syndrome, and while many risk factors for both ischemic and hemorrhagic stroke are generally similar, there are some notable differences dependent on the specific pathogenesis of stroke. Risk factors can be categorized as either modifiable or nonmodifiable, with modifiable risk factors considered of utmost importance as targeted intervention strategies can result in reduced risk of stroke. The INTERSTROKE study, a case-control study including participants from 22 countries, found that 90% of the risk of stroke could be explained by 10 modifiable risk factors.[38] For ischemic stroke, these risk factors included: hypertension, current smoking, waist-to-hip ratio, diet risk score, regular physical activity, diabetes mellitus, binge alcohol use, psychosocial stress and depression, cardiac disease, and the ratio of apolipoprotein B to A1. For intracerebral hemorrhage, established risk factors included hypertension, smoking, waist-to-hip ratio, diet, and heavy alcohol use. Hypertension is considered the most important modifiable risk factor for stroke, with evidence from the INTERSTROKE study that estimated the population attributable risk at 54%.[38] Further, there is a positive relationship with blood pressure and risk of stroke even in normotensive

individuals.[39] Individuals with diabetes mellitus are estimated to have a 2-fold increased risk of stroke, and subsequently, stroke accounts for roughly 20% of deaths in diabetics. The duration of diabetes has been associated with increased risk of ischemic stroke, with an adjusted hazard ratio of 1.03 (95% Confidence interval: 1.02, 1.04) or 3% increased risk per duration year.[40] Other cardiovascular conditions considered risk factors for stroke include atrial fibrillation, potentially due to stasis of blood contributing to thrombus formation, and dyslipidemia.[39] Higher total cholesterol is associated with an increased risk of ischemic stroke, while elevated high-density lipoprotein is associated with decreased risk.[41,42] These associations may vary by subtype of ischemic stroke, with evidence pointing towards a stronger relationship with large artery ischemic stroke.[43] Similarly, total cholesterol is inversely associated with hemorrhagic stroke.[44] Physically inactive individuals have a higher risk of stroke and stroke mortality compared with those who are physically active, potentially through a decrease in blood pressure, reduced incidence of diabetes, or reduction in body weight.[39] The influence of diet on stroke is more complex, however studies have found a reduced risk for those on the Mediterranean diet,[45] an increased risk with salt intake,[46] and reduced risk with potassium intake.[47] The role of alcohol consumption is dependent on type of stroke, with evidence of a J-shaped curve between alcohol consumption and risk of ischemic stroke, suggesting low alcohol consumption may be protective.[48] For hemorrhagic stroke there is a linear relationship with alcohol consumption, where any amount of alcohol increases risk.[39] Similar to other cardiovascular diseases,

smoking is a major risk factor for stroke, and is estimated to contribute to 15% of stroke deaths.[49]

Nonmodifiable risk factors for stroke include age, sex, race, and genetics. The incidence of stroke increases with advancing age, and doubles for each decade after the age of 55.[36] The influence of sex on risk of stroke is dependent on age, with females having higher risk of stroke at young ages, likely related to pregnancy, but lower at older ages.[50] Racial disparities in stroke are well-known, with Black adults having a 2-fold higher risk of stroke than White adults.[51] Hispanic/Latino Americans and American Indians have also found to be at an increased risk of stroke compared with non-Hispanic white adults.[52] There are also known genetic risk factors for stroke, which vary by age, sex, and race. Genetics can contribute to stroke through several mechanisms: rare single gene disorders for which stroke is the primary manifestation; genetic polymorphisms have been associated with stroke; and genetic causes are linked to other stroke risk factors, such as hypertension and diabetes.[39]

There are also known rural-urban disparities in stroke mortality.[53] Between 1999 and 2010, the rural-urban disparity in stroke mortality increased from 15% to 25%, followed by a decrease to 8% by 2019.[53] This recent temporal pattern is driven by a plateauing of stroke mortality in urban areas coupled with a decline in rural areas, however, there is still a need to better understand what contributed to these temporal patterns, and rural-urban disparities in general. These disparities are likely due to higher incidence of stroke in rural areas, contributing to higher stroke mortality, with less evidence that the disparities are due to higher case

fatality.[53] In several studies, adjustment for traditional stroke risk factors did not completely explain rural-urban disparities, suggesting a higher prevalence of risk factors in rural areas only partially contributes to these disparities.[53]

3. Geographic Disparities in Stroke Risk

Geographic differences in CVD are well-known, and change in risk due to relocation is supported by evidence based on migration studies.[2-5] Specifically, there are substantial geographic disparities in stroke, with higher rates found in the Southeastern United States, termed the “stroke belt”.[6] This region is typically defined to include the 8 states of North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. The average stroke mortality has historically been up to 30% higher in the stroke belt compared with the rest of the United States, and up to 40% higher in the stroke buckle (North Carolina, South Carolina, Georgia).[54] Despite the recent national declines in stroke mortality, geographic disparities have persisted, and the Southeastern region has had a 4.2% increase in stroke deaths between 2006 and 2013.[37] These geographic disparities are thought to be due to higher risk factor burden, lower SES, and to a lesser extent, lifestyle choices, and environmental exposures.[37] However, more work is needed to understand the potential contributions of environmental exposures, such as greenness and air pollution, and the multilevel complexity of the environment, to geographic differences in stroke.

4. Air Pollution and Stroke

Exposure to ambient air pollution increases the risk of mortality and morbidity and has been identified as a leading cause of global disease burden in the Global Burden of Diseases, Injuries and Risk Factors Study 2015.[55] Of special interest, a large body of epidemiologic evidence has identified robust relationships between environmental air pollution with cardiovascular disease and stroke.[56,57] The primary pollutants of concern include carbon monoxide (CO), nitrogen oxides (NOx), sulfur dioxide (SO_2), ozone, lead, secondhand smoke, and particulate matter. A wealth of evidence has focused on the harmful effects of particulate matter and CVD,[57] typically focusing on fine particulate matter ($PM_{2.5}$, aerodynamic diameter <2.5 μm), and to a lesser extent coarse particulate matter (PM_{10}; aerodynamic diameter <10 μm). Because of the ubiquitous nature of air pollution, exposure is often unavoidable for most people, contributing to a substantial burden of disease.

Air Pollutant Classes and Sources

Particulates come from a variety of sources, and are comprised of a mixture of substances in the air, which vary dependent on sources, geography, and climate.[58] Common sources of particulate exposure include dust, diesel exhaust, combustion emissions, transportation, construction, pesticide use, volcanic ash, and biomass burning.[59] The toxicity of particulates depends on the size, with smaller particles thought to be more dangerous due to easier penetration into the alveoli of the lungs, and entrance into the blood.[58] Toxicity is also determined by the chemical composition, which can include toxic metals such as lead and

mercury, as well as polyaromatic hydrocarbons, and persistent organic pollutants.[58]

Ozone plays a critical role in blocking harmful ultraviolet light in the stratosphere and protection from skin cancers, however, exposure at ground level is harmful to human health. Ambient ozone is formed by chemical reactions that involve volatile organic compounds (VOCs) and nitrogen oxides, dependent on the presence of heat and sunlight, which results in higher concentrations of ozone during the summer season.[59] The majority of ground level ozone is the result of man-made sources of VOCs (chemical solvents, combustion products, gasoline vapors, consumer products) and NOx (fossil fuel combustion).[59]

Sulfur dioxide is a gas formed by the combustion of coal, vehicle emissions, industrial processes, and emissions from refineries. Similarly, Nitrogen dioxides are produced by fossil fuel combustion. Major sources include power plants and motor vehicles, with local levels varying with traffic density.[59] Nitrogen dioxide can also be produce by reactions between oxygen containing molecules with nitrogen in the atmosphere.

Air Pollution Measurement

Air pollution is typically measured by air pollution monitoring systems, and in the United States, The Clean Air Act requires nationwide monitoring of the six criteria pollutants (carbon monoxide, lead, ground level ozone, particulate matter, nitrogen dioxide, and sulfur dioxide). The Environmental Protection Agency (EPA) has the responsibility of ensuring the standards of monitoring methods and

developing new monitoring methods. These monitoring systems are typically ground monitors that measure concentrations of air pollutants in populated areas and provide hourly or daily mean concentrations of pollutants. Individual exposures are typically estimated using mean concentrations of the combined monitoring systems in a geographical area, or extrapolating concentrations from the closest monitor to a residential address. Extrapolating exposures either from a geographical area or from the closest monitor to an individual, could result in several sources of exposure classification. First, this method does not consider that individuals spend time at places other than their residence and could either underestimate or overestimate exposure depending on exposure levels at other places. It could also result in differential exposure misclassification, as younger individuals are more likely to work, but less likely to have a stroke. Further, these methods cannot differentiate between time spent indoors and outdoors, which could vary by sociodemographic characteristics. Second, the amount of exposure misclassification could vary by pollutant. Some pollutants, such as particulate matter, are typically more homogenous than some gaseous pollutants, such as NOx, which could vary depending on proximity to roadway traffic, and distance to monitors. Another source of error in pollution studies involves confounding. Many studies adjust for environmental confounders, such as temperature, humidity, and season, which co-vary with many pollutants, but could also be related to health outcomes.[60] Finally, individuals are exposed to a mixture of co-varying pollutants, which are often highly correlated. Thus, single pollutant models should be

interpreted with caution, and multi-pollutant models could suffer from the presence of multicollinearity.

Air Pollution Exposure and Risk of Stroke

The Global Burden of Disease Study has estimated that air pollution accounted for 21% of deaths due to stroke in 2015.[15] Both short-term and long-term exposure to pollution have been linked to increased risk of stroke. A recent review concluded that the risk of ischemic stroke is increased after short-term or long-term exposure to air pollution, while short-term exposure increases the risk of hemorrhagic stroke, but the effects of long-term exposure hemorrhagic stroke are less clear.[60]

Long-term Exposure to Air Pollution and Risk of Stroke

Several recent studies have found associations between long-term exposure to air pollution and incident stroke. Long-term exposure can range from months to years and is used as a proxy for accumulated individual exposure. A study of 23,423 participants residing in Denmark found a hazard ratio for ischemic stroke of 1.12 (95% CI: 1.01-1.25) per 1 year mean of 3.9 $\mu g/m^3$ increase in $PM_{2.5}$.[61] However, no associations were found with PM_{10} or NO_2, nor with hemorrhagic stroke. A study conducted in England of 836,557 patients with over 5 years of follow-up found that stroke incidence increased by 4% per 2.2 $\mu g/m^3$ change in SO_2.[62] A cohort study by Jerrett et al. estimated the relative risk for stroke mortality was 1.07 per 5.3 $\mu g/m^3$ $PM_{2.5}$, 1.08 per 4.12 ppb NO_2, and 1.01 per 24.2 ppb O_3.[63] A study of 9,941 residents of China found that stroke mortality

increased by 49% per 10 μg/m^3 increase in PM_{10} and 144% per 10 μg/m^3 increase in NO_2. Finally, a cohort study in Japan found that the risk of hemorrhagic stroke (relative risk=1.28) was higher than ischemic stroke (relative risk=1.20) per 10 μg/m^3 increase in NO_2.[64]

Short-term Exposure to Air Pollution and Risk of Stroke

Short-term exposure consists of day-to-day variation in exposure in the days preceding stroke, and has typically been investigated using time-series studies or the case-crossover design.[65] In 2015, a meta-analysis of 94 articles combining 6.2 million events across 28 countries found strong associations with hospital admissions and stroke mortality for exposure to SO_2 (relative risk=1.019 per 10 ppb) and NO_2 (1.014 per 10 ppb).[66] They also found associations with increases in $PM_{2.5}$ (1.011 per 10 μg/m^3; 95% CI: 1.011, 1.012), PM_{10} (1.003 per 10 μg/m^3; 95% CI: 1.002, 1.004), and a weak association with ozone (1.001 per 10 ppb; 95% CI: 1.000, 1.002). More recently, a time-series analysis of 15,086 participants located in Ireland found significant associations between ischemic stroke and increases in PM_{10}, $PM_{2.5}$, and NO_2, 0-2 days prior to stroke, while no associations were found with hemorrhagic stroke.[67] Alternatively, a study using data from the Women's Health Initiative cohort in the United States found no associations between day-to-day variation in pollutants and ischemic stroke.[68] However, they did observe a positive association between risk of hemorrhagic stroke and NO_2. Another U.S. study found a small significant increase in ischemic stroke admissions of 1.03% (95% CI: 0.04, 2.04) per 22.96 10 μg/m^3 increase in PM_{10} concentrations 1-2 days prior to onset, with similar risk for NO_2 and SO_2.[69]

Prior studies have shown a link between exposure to several pollutants and risk of stroke, however there is heterogeneity in the results. This could be explained by differences in methods for stroke ascertainment, exposure measurement, statistical modeling approaches, pollution levels, pollution sources, or differences in the characteristics of the study populations. Stroke is an etiologically diverse disease, and even ischemic stroke contains multiple subtypes that can be due to several causes, commonly classified into five categories: larger artery atherosclerosis, small vessel disease, cardioembolic stroke, rare cause, and cryptogenic stroke.[60] These causes might be differently affected by air pollution but are typically not accounted for in epidemiological studies and their proportions could vary between studies. There is also evidence that associations between air pollution exposure and incident stroke is more pronounced in low- to middle-income countries, however it is unclear if this is solely due to higher levels of pollution, or if differences are modified by ethnicities or behaviors.[60] There is also evidence that characteristics that vary geographically could contribute to the heterogeneity of studies in the United States.[68]

Biological Mechanisms

There are three commonly proposed mechanisms by which air pollution can lead to cardiovascular disease, and specifically, trigger stroke events. First, inhalation of small particles ($PM_{2.5}$) and gaseous pollutants into the lungs enter the blood stream, while larger particles are taken up by macrophages, triggering inflammation of the lungs and the release of oxidative and inflammatory compounds.[60] Once in circulation, particulates and gaseous pollutants react with

nitric oxide, creating reactive oxygen species, and endothelial dysfunction. Additionally, exposure to $PM_{2.5}$ has been shown to increase markers of plaque vulnerability, systemic inflammation, and thrombogenicity, leading to acute cerebrovascular disease.[60] These mechanisms over time contribute to the development and progression of atherosclerosis, and could result in ischemic stroke.

The second proposed mechanism is the instigation of autonomic nervous system imbalance.[56] Previous studies have found that particulate matter alters heart rate variability.[70] These studies suggest that inhaled pollutants lead to heightened sympathetic nervous system activity, likely resulting from a systemic stress response or a neural reflex response by various lung receptors. Inhalation of pollutants have been shown to trigger an autonomic reflex via pulmonary receptors, which leads to vascular resistance, arrythmias, and hypertension, which could potentially trigger cardioembolic ischemic stroke, or intracerebral hemmorhage.[60]

The third proposed mechanism involves the penetration of certain pollutants directly into cardiovascular tissues.[56] A few studies have suggested that ultrafine particulate matter, metals, and organic compounds may be capable of translocating into circulation and directly into cardiovascular tissues. Chronic exposure to PM and gaseous pollutants could also damage the brain by passing through the blood-brain barrier, causing neuro-inflammation and neuronal damage.[60] Ozone specifically has been associated with lobar intracerebral hemorrhage, but not with overall hemorrhagic stroke, with a hypothesized

mechanism that ozone may trigger the deposition of amyloid in cerebral amyloid angiopathy.[60] The three mechanisms discussed are not mutually exclusive, there is likely a large degree of overlap between mechanisms contributing to stroke. These pathways also could be activated at different times following exposure, and underlying comorbidities could play a role in which pathways dominate an individual's susceptibility to pollutant exposure.

5. Vegetation and Stroke

Exposure to green space has drawn increased attention from researchers in environmental health due to findings of positive associations with several health outcomes. An ecological study of 183 countries, investigating the relationship between NDVI and country-level disability adjusted life years (DALY) due to stroke found a consistent negative association of -4.387 (95% CI: -7.926, -0.085) in the DALY changes for a 0 to 1 increase in NDVI.[71] A recent umbrella review found beneficial associations with all-cause and stroke-specific mortality, CVD morbidity, cardiometabolic factors, mental health, low birth weight, physical activity, sleep quality, and urban crime.[72] A meta-analysis published in 2022, which included 53 studies and more than a million participants showed that a 0.1 increase in NDVI was associated with 3% lower odds of CVD mortality (95% CI: 0.96, 0.99), 2% lower odds or cerebrovascular mortality (95% CI: 0.97, 1.00), and 2% lower odds of stroke incidence/prevalence (95% CI: 0.96, 0.99).[73] Further, a study of stroke patients found that residential proximity to green space was associated with higher survival rates after ischemic stroke.[74] Further evidence of the beneficial effects of vegetation is seen from studies of individuals participating in "forest bathing".

These studies have found that acute exposure to forests is related to improvement in positive emotions, favorable changes in cardiovascular function, reductions in blood pressure, greater parasympathetic activity, and lower resting pulse rate.[75]

Not only is the amount of greenness important, but different types of vegetation may influence health to different extents. For example, broadleaf woodlands, which are found in the eastern United States, have been shown to have some of the greatest benefits to air quality,[76] and high associations with psychological restoration.[77] Although most studies have focused on trees, vegetation categorized as grassland (abundant in the Great Plains) has also been positively associated with good health.[78]

There is some evidence of effect modification on the greenspace and health association. A recent systematic review found evidence that younger individuals benefited more from green space exposure than the elderly in terms of cardiovascular health.[73] A possible explanation is that the elderly are likely to have stronger risk factors that could limit the cardioprotective benefits of greenspace. This same review found limited and inconsistent evidence of effect modification by sex on the greenspace-CVD relationship. A systematic review of urbanicity, greenspace, and health, found that the effects of greenspace on cardiovascular health tended to be stronger in more urban areas.[79] There are several reasons why greenspace could promote health better in more urban areas. First, greenspace may reduce harmful exposures such as pollution, noise, and heat, which are more abundant in urban area.[79] Second, urban areas are often designed to have greenspace that are accessible, and promote physical activity and social

cohesion. Finally, the restoring capacity of greenness could be greater in urban areas, where chronic stressors and attentional demands are often higher than non-urban areas.[79]

Vegetation Measurement

Greenspace exposure measures in epidemiologic studies have typically been classified into three categories: greenspace availability, accessibility, and visibility.[80] These categories are often linked to different, yet overlapping mechanistic pathways influencing health. Availability of greenspace has been associated with reductions in air and noise pollution, and heat mitigation.[81,82] Access to greenspace could encourage increased physical activity and social cohesion.[80] Visibility of greenspace is associated with stress recovery and attention restoration.[80] There are numerous methods to measure vegetation exposure, including self-report questionnaires, distance to parks, green ratio and vegetation index, soil-adjusted vegetation index, and enhanced vegetation index to name a few.[83] The most common method of estimating greenness is the normalized difference vegetation index (NDVI). NDVI is calculated from satellite data as the ratio of near-infrared radiation minus visible radiation and near-infrared radiation plus visible radiation. Near-infrared radiation is strongly reflected by vegetation, while visible radiation (red light) is absorbed by chlorophyll in plants.[84] NDVI ranges from -1 to 1, with higher values representing higher levels of vegetation density. Greenspace exposure is commonly assigned to participants at different radii around their geocoded residential address, however, individuals are exposed to vegetation at varying locations, and thus residential exposure cannot

fully capture duration, frequency, or intensity of total exposure. The optimal distance in which greenness exposure should be assigned to individuals is dependent on the health outcome and mechanism of action and is not well understood. A systematic review of residential greenness buffer sizes found that larger buffer sizes up to 2000 meters better predicted physical health than smaller ones.[85] However, this does not suggest that nearby greenspace is less predictive of health, but could be due to larger buffers requiring a substantially greater amount of vegetation to have the same relative NDVI as smaller buffers. Alternatively, it is known that the frequency of greenspace use declines with increasing distance, with a threshold of 300 meters, after which, use rapidly declines.[86] Many studies have investigated several radii, with some of the more common including: 250 meters, a measure of greenness directly accessible outside of the home, and 1250 meters, a measure of greenness within a 10-15 minute walk.[8] Another consideration when estimating greenspace is the effects of seasonality on vegetation. Previous studies have calculated contemporaneous NDVI, the greenness value for the current season as an estimate of short-term exposure, average NDVI, a measure of long-term exposure over the year,[8] or the average of summer NDVI, an average of peak greenness.[87] There are several limitations of using NDVI as a measure of greenspace exposure. Using average NDVI within a given radii does not distinguish whether the greenness is homogenous throughout the region or is concentrated in one specific area. Thus, NDVI cannot differentiate the type of greenness, quality, or accessibility to greenspace.

Mechanisms Underlying Greenspace and Health

The mechanisms underlying the relationship between exposure to greenspace and human health have not been fully elucidated. An expert workshop held in 2016 reviewing greenspace and health hypothesized that the potential benefits of greenspace on health can be organized into three domains.[83] The first domain involves reducing harm, or mitigation of exposures. Several studies have shown that vegetation can improve air quality by directly lowering air pollution levels, including PM, ozone, and volatile organic compounds.[88-90] Vegetation also absorbs direct solar radiation, which can lower temperatures, reducing the effects of urban heat islands.[83] Further, greenspace can buffer the effects of traffic noise, through either a direct reduction in noise levels, or by reducing the stress response of noise.[83]

The second domain by which greenspace can improve health is through psychological restoration, predominantly guided by two theories from environmental psychology.[83] The stress reduction theory proposes that viewing natural environmental features, including vegetation, can evoke positive emotions that block negative thoughts, resulting in a muted stress response. Alternatively, attention restoration theory proposes vegetation and environmental features can attract attention without effort, freeing up effort for other neurocognitive mechanisms.[83] Subsequently, greenspace could enhance the ability to deploy executive functions and perform on standardized tests.

The third domain involves building capacities, or instoration.[83] Greenspace provides an attractive setting to perform physical activity, and some evidence suggests that physical activity produces greater benefits when performed in greenspace.[83] This can lead to lower BMI, lower risk of depression, and improved cardiovascular risk factors.[11-13] However, the presence of greenspace by itself is not sufficient for physical activity use. Previous studies have found that more attractive green spaces and larger green spaces with well-maintained paths are more likely to be used for physical activity.[91] Greenspace also provides a setting to facilitate social cohesion. Social cohesion is related to positive health and wellbeing,[92] especially mental health, and is hypothesized to be one of the primary mediators between greenspace and health.[93,94]

6. The Natural Environment and CVD

Despite advances in cardiovascular treatments, interventions, public health campaigns and research, cardiovascular disease (CVD) remains the leading cause of death worldwide, killing 850,000 people per year in the United States alone.[1] The recent declines in CVD since the 1960's have halted, and clearly new approaches are needed to understand the nature of CVD, including the determinants of the disease and its risk factors, and how it can be prevented more effectively. Current treatment and prevention approaches assume that because CVD is affected by lifestyle choices and genetic factors, that the disease is representative of individual dysfunction, however this overlooks the role of the environment. It does not consider the possibility that much CVD could arise from

living in unconducive natural environments, therefore, considering CVD as an environmental disease may provide new ways of preventing the disease.

The view that CVD is an environmental disease is supported by extensive evidence in migration studies. Moving from Japan to the United States, or from India to Great Britain, results in increased coronary heart disease and its risk factors.[2,3] Similarly, a study of Finnish twins found a decrease in coronary heart disease for siblings that moved to Sweden, compared with their twin.[4] There are also geographic differences in ischemic heart disease found within Great Britain,[5] and it is well known that geographic differences in stroke (stroke belt) occur in the United States.[6] Although these affects could partially be explained by differences in social environments, it would be a failure to not take into consideration the role that the natural environment may play.

The natural environment provides mankind with the resources necessary to sustain human health. Although humans have evolved by adapting to their natural environment, we have been increasingly separated from nature, towards a more complex social and built environment. This desynchrony with the natural environment could partially explain the high rates of cardiovascular disease in the modern world. The natural environment encompasses all non-man-made things, both living and nonliving. It includes the geosphere, comprised of location, climate, geography, and natural pollutants. And the biosphere, consisting of microbes, plants, and animals. Not only do we have to consider the objects in the natural environment, but also the relationships between them.

The geosphere is characterized by location, which can be measured as latitude, longitude, and altitude. There is evidence that individuals living at higher altitudes have lower levels of mortality due to cardiovascular disease and stroke.[95] A longitudinal study of 4.2 million individuals residing in Sweden found a lower risk of ischemic heart disease for those living at >1500m compared with those living at <600m.[96] Additionally, a cross sectional study in China found that at very high altitudes (>3000m) the risk of obesity and dyslipidemia decreased, however, the risk of hypertension increased.[97] People born at high altitudes also have lower CVD after moving to areas of low altitudes,[98] suggesting that exposure to high altitudes at critical periods has long lasting effects later in life. Latitude has also been associated with CVD risk, with populations living closer to the equator having lower blood pressure than those living further away.[99] This could be due to differences in climate. The climate is characterized by sunlight, temperature, rainfall, humidity, air pressure, winds, and seasons. Numerous studies have linked inadequate sunlight exposure and low vitamin D levels to increased CVD risk.[100] Many studies have also shown an inverse association between temperature and blood pressure, where an average of 1°C decrease is associated with 0.26 mmHg increase in systolic blood pressure.[101] Both low and high temperatures have been shown to increase the risk of stroke mortality.[102] Further, diurnal temperature, the difference between the maximum and minimum temperature, has been associated with higher systolic blood pressure and pulse pressure, a measure of arterial stiffness.[103] Precipitation is also inversely associated with odds of stroke mortality.[104] It is well known that higher incidence of CV events occur during the

winter months than summer, further underscoring the effect that climate has on CVD.[105,106] The natural environment is also a source of particulate matter, from volcanoes, sands, and forest fires, however there is evidence that these sources may be less harmful to CVD than that from combustion sources.[107 108,109] Harm from pollution can also be affected by the climate, with an increased burden of CVD due to pollution when accompanied with extreme temperatures.[22,23] Although wind may not be independently associated with CV risk, the RIOPA study found that wind speed was a determinant of gasoline related volatile organic compound exposure, suggesting that individuals living in windy areas may be exposed to greater amounts of pollution.[110] Similar to climate, the physical features of the natural environment (land features, geology, terrain) can impact CVD risk. Blue space (water) has profound influence on human health and wellbeing.[111] Blue space has also been shown to modify the effects of heat related mortality, where individuals living within 4 km from water showing mitigated effects of heat.[112] Geography can also be characterized by soil type. Soil can also have a deep impact on human health, both positive by providing essential nutrients, and negative, as a source of toxic exposure.[113] In the REGARDS study, individuals living in areas with higher levels of selenium in the soil showed an increased risk of stroke.[114]

Like the geosphere, the biosphere also has influence on cardiovascular health. The biosphere consists of microbes, plants, and animals, and has played a critical role in human evolution, both as a source of food, shelter, and parasites. Biodiversity is one measure of the biosphere, which can be characterized by the

variability among living things. This could be measured by variability in species, such as birds, mammals, and amphibians, but also by vegetation levels.[115] The loss of biodiversity, due to population expansion, can have drastic consequences on human health, potentially due to microbial deprivation, known as the "biodiversity hypothesis".[116] We also know there is a strong connection between the gut microbiome and CVD.[117]

Recent work suggests that living in areas of high vegetation reduces the harmful effects of $PM_{2.5}$ on CVD. [17-20] Previous studies have reported that living in areas of higher residential greenness is associated with lower volatile organic compound exposure, which are ubiquitous gaseous pollutants.[21] Harm from air pollution can also be affected by the climate, with an increased burden of CVD due to pollution when accompanied with extreme temperatures.[22,23] While intriguing, it is unclear how other features of the natural environment may modify the effects of $PM_{2.5}$ and other pollutants on CVD, and stroke specifically.

2. LONG-TERM EXPOSURE TO AIR POLLUTION AND RISK OF STROKE BY ECOREGIONS: THE REGARDS STUDY

Background: Several cohort studies have found associations between long-term air pollution and stroke risk. However, it is unclear whether the surrounding ecology may modify these associations. This study evaluates associations of air pollution and risk of stroke by ecoregions, which are areas of similar type, quality, and quantity of environmental resources.

Methods: We estimated the relationship between long-term exposure to $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, and CO and risk for stroke in 26,792 participants, recruited between 2003 and 2007 in the Reasons for Geographic and Racial Differences in Stroke study (REGARDS). The risk of incident stroke associated with baseline 1-year and 3-year exposures was estimated using Cox proportional hazards models, adjusting for environmental variables, demographics, and other risk factors. Models were stratified by EPA designated ecoregions to determine how associations varied by geographic areas with similar environmental characteristics.

Results: The hazard ratio (95% CI) for a 5.4 $\mu g/m^3$ (interquartile range) increase in 1-year PM_{10} was 1.07 (1.003, 1.15) for risk of stroke in the full study population. We did not find evidence of positive associations for $PM_{2.5}$, O_3, NO_2, SO_2, and CO

in the fully adjusted models. In our ecoregion-specific analysis, we found evidence of effect modification for several pollutants. Associations for $PM_{2.5}$ were significantly stronger in the Great Plains ecoregion (HR=1.44), while associations for PM_{10} were stronger in the Eastern Temperate Forests region (HR=1.15).

Conclusion: The associations between long-term exposure to air pollution and risk of stroke varied by ecoregion. This suggests that the type, quality, and quantity of the surrounding ecology can modify the effects of air pollution on risk of stroke.

INTRODUCTION

Stroke is the fifth leading cause of death in the United States.[1] In 2018, an estimated 7.6 million Americans over the age of 20 years self-reported having a stroke, an estimated prevalence of 2.7%.[36] There are substantial geographic disparities in stroke, with higher rates found in the Southeastern United States, termed the “stroke belt”.[6] The average stroke mortality has historically been up to 30% higher in the stroke belt compared with the rest of the United States, and up to 40% higher in the stroke buckle (North Carolina, South Carolina, Georgia).[54] Despite the recent national declines in stroke mortality, geographic disparities have persisted, and the Southeastern region has had a 4.2% increase in stroke deaths between 2006 and 2013.[37] These geographic disparities are thought to be due to higher risk factor burden, lower SES, lifestyle choices, and environmental exposures.[37] However, more work is needed to understand the potential contributions of environmental exposures, such as air pollution, and the role of the environment, to geographic differences in stroke.

Exposure to fine particulate matter has been found to be strongly and robustly associated with an increase in CVD risk and mortality.[14] The Global Burden of disease study estimated that air pollution accounted for 21% of deaths due to stroke in 2015.[15] Previous work has found that long-term exposure to $PM_{2.5}$, PM_{10}, and gaseous pollutants is associated with increased stroke incidence and mortality.[16] However, there is evidence that the health effects of air pollution are modified by the natural environment. Recent work suggests that living in areas of high vegetation reduces the harmful effects of $PM_{2.5}$ on CVD.[17-20] Previous studies have reported that living in areas of higher residential greenness is associated with lower volatile organic compound exposure, which are ubiquitous gaseous pollutants.[21] Harm from air pollution can also be affected by the climate, with an increased burden of CVD due to pollution when accompanied by higher temperatures or humidity.[22,23,118,119] Taken together, these characteristics are only part of a complex ecosystem, which if unaccounted for, may leave an incomplete picture of the full effects of air pollution on human health.

Ecologically, The United States is a mosaic, with many of its ecosystems possessing unique individual features, ranging from tropical climates to deserts, mountain ranges, and dense natural forests. The natural environment and human activities are highly interrelated, highlighting the importance of an “ecological perspective” on human health, viewing humans as part of, rather than separate from their ecosystem.[120]

The aim of our study was to evaluate the effects of long-term exposure to air pollution on the risk of stroke while also considering the surrounding ecology.

We utilized the Reasons for Geographic and Racial Differences in Stroke study (REGARDS), a prospective cohort study, with participants recruited across the contiguous United States. Although previous studies have assessed how individual characteristics of the natural environment may modify the effects of pollution on health, these characteristics together form a complex ecosystem, and this complexity has traditionally been unaccounted for in previous studies. To address this, we categorized individuals into ecoregions, which are ecosystems of generally similar biotic and abiotic features.[24] This allows for an evaluation of whether pollution levels influence stroke risk, and whether this varies by the type, quality, and quantity of the surrounding natural environment.

METHODS

Participants

The REGARDS study is a national, population-based, prospective cohort study of 30,239 Black and White adults aged ≥ 45 years designed to assess racial and geographic differences in stroke incidence, risk factors, and mortality. Full details of the REGARDS study have been previously published.[121] In brief, participants were randomly sampled from a commercially available nationwide list, with oversampling of Black individuals, and individuals living in the stroke belt (North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas). The final sample consists of 21% of participants from the “stroke buckle” (coastal region of North Carolina, South Carolina, and Georgia),

35% from the rest of the stroke belt, and 44% from outside the stroke belt throughout the contiguous United States.

Participants were recruited by mail, then telephone, between January 2003 and October 2007 for a baseline exam and survey. Participants were contacted by telephone at 6-month intervals to document suspected strokes. Written informed consent was obtained prior to data collection, and the institutional review boards for the participating institutions approved the study.

Participants were excluded from the current analysis who reported a previous stroke (n=1,930), missing data on stroke (n=102), had data anomalies (n=56), missing geocoded data (n=11), lack of follow-up information (n=529), or were missing relevant covariates (n=819). The final sample size consisted of 26,792 participants.

Incident Stroke

The outcome of interest was incident stroke, defined as any focal neurologic symptoms lasting more than 24 hours or those with neuroimaging data consistent with stroke.[122] Self-reported stroke, transient ischemic attacks, death, hospitalization or emergency room visit for brain aneurysm, brain hemorrhage, stroke symptoms, or unknown reason were followed by a medical records review. Medical records of suspected strokes were adjudicated by physicians. Death certificates and proxy interviews were used to confirm deaths in the absence of medical records. Strokes were classified as ischemic or hemorrhagic when

possible. Ascertainment of stroke events through September 30, 2020, were included in the analysis.

Covariates

Demographic characteristics were obtained from the baseline computer assisted telephone interview. Diabetes status was defined as fasting glucose ≥ 126 mg/dL or non-fasting glucose ≥ 200 mg/dL or self-reported use of diabetes medications. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg or self-reported current use of medication to control blood pressure. Atrial fibrillation was defined as self-reported or evidence from electrocardiogram (ECG). History of heart disease was defined as self-reported myocardial infarction, CABG, bypass, angioplasty, or stenting, or evidence of myocardial infarction from ECG.

Air Pollution Exposure

Yearly averages of $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, and CO levels for the 1-year, and 3-year period prior to baseline were assigned to each participant by their geocoded address at the block group level. These data are publicly available from the Center for Air, Climate & Energy Solutions (https://www.caces.us/). Full details of the exposure modeling and performance have been provided elsewhere.[123] This method used monitored pollutant data from the EPA Air Quality System data repository for all available years (1979-2015) to compute annual averages (except O_3) for all pollutants. For O_3, season averages from May thru September were computed, because O_3 is predominant in the summer due to photochemical

reactions catalyzed by heat and sunlight. Annual averages were based on hourly measurements for gaseous pollutants (NO_2, SO_2, and O_3), and daily measurements for PM. NO_2, SO_2, and O_3 are available for the entire period (1979-2015), while PM_{10} and $PM_{2.5}$ are available starting at 1988 and 1999, respectively. An integrated empirical geographic regression modeling approach was used to generate block group level average yearly pollutant concentrations.[123] This approach uses universal kriging and partial least squares from ~350 geographic characteristics, including measures of traffic, population, land use, land cover, elevation, and satellite-based air pollution estimates, to construct exposure estimates. Model performance was evaluated using 10-fold cross-validation.

Ecoregions

REGARDS participants were classified into unique ecological regions by classifying their geocoded residence at baseline into EPA level I ecoregions, and the nested area EPA level II ecoregions (https://www.epa.gov/eco-research/ecoregions-north-america) (Figure 1.1, Supplemental Figure 1.1). Level I ecoregions consisted of the Eastern Temperate Forests (n=22,222, Great Plains (n=1,675), and Mediterranean California (n=2,014). We classified all remaining participants into one region, labeled “Other” (n=881), which was comprised of Northern Forests, Northwestern Forested Mountains, and North American Deserts. Because a large percentage of our participants were located within the Eastern Temperate Forests, we focused on this region for the more detailed level II ecoregion analysis. Within the Eastern Temperate Forests, level II ecoregions consisted of Mixed Wood Plains (n=2,004), Central USA Plains (n=2,239),

Southeastern USA Plains (n=11,745), Ozark/Ouachita-Appalachian Forests (n=1,812), and Mississippi Alluvial and Southeast USA Coastal Plains (n=4,459).

Environmental factors

We used the Normalized Difference Vegetation Index (NDVI) to estimate the amount of vegetation around each participant's address. NDVI varies from -1 to 1, where negative values correspond to water, urban areas, values near zero correspond to areas of little greenness, and values close to 1 represent areas of dense vegetation. Satellite data were obtained from the Moderate Resolution Imaging Spectroradiometer (MODIS) from the Terra satellite (MODIS MOD13Q1 product) via the Google Earth Engine (https://earthengine.google.com/), which provides fully processed averages of NDVI.[124] The data is on a 250 m X 250 m grid, with a temporal resolution of 16 calendar days. We calculated the average NDVI for the summer months (June to August). Because there is little yearly variation in NDVI estimates, a single average NDVI estimate was calculated for the baseline years of 2003 to 2007. Pixels values were averaged across radii of interest (1,250m) surrounding the participants' geolocated residences.

Participants were assigned to neighborhood level covariates by their geocoded address. Urbanicity was assigned at the census tract level using data from the 2010 census. Urbanicity was categorized into three levels as rural (≤ 25% urban), mixed urbanicity (25-75% urban), and (≥ 75% urban). Environmental covariates were aggregated to the block group level to represent a small area, homogenous characterization of participants' neighborhoods. High spatial

resolution (4-km) temperature and specific humidity, derived from PRISM and the National Land Data Assimilation System (NLDAS)[125] were obtained via Google Earth Engine. One-year and 3-year averages prior to baseline enrollment were assigned to each participant.

Statistical Analysis

Baseline characteristics of the REGARDS cohort, environmental characteristics, and exposures were stratified by level I and level II ecoregions and reported as mean ± SD for continuous variables and frequency (percentage) for categorical variables.

Cox Proportional Hazard models were used to estimate the associations between air pollution ($PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, CO), and the incidence of stroke. Survival time was calculated in days as the difference between the in-home visit date and incidence of stroke. Censored survival time was calculated as the difference between survey date and end of follow-up (September 30, 2020) or loss to follow-up or death. Proportionality was verified by checking the slope of the Schoenfeld residuals, and by including interaction terms of each exposure and calendar time to determine statistically significant violations. Two-pollutant models were used to assess whether single pollutant effects are confounded by covarying pollutants. Pearson correlations were used to test for correlations between pollutants, and multicollinearity between pollutants was assessed by examining variance inflation factors. The primary set of models were reanalyzed using quartiles of exposures. Models were adjusted for age, sex, race, age*race,

education, BMI, alcohol use, smoking status, exercise, year of baseline, urbanicity, and ecoregion.

Cox proportional hazard models were stratified to assess effect modification by the surrounding ecosystem. A priori stratified models include level I ecoregions and level II ecoregions, to obtain ecoregion specific effect estimates. We examined effect modification by factors that may be associated with stroke disparities and/or that may be associated with differential effects of air pollution. We included interaction terms for air pollutants and race, sex, and environmental characteristics (temperature, specific humidity, greenness, urbanicity) in the full model. All analyses were performed using SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina), and R software (version 4.1.1).

RESULTS

The average age of participants was 64.6 years, 44.5% of participants were male, and 40.3% Black (Table 1.1). The majority of participants lived in urban neighborhoods (78.0%) and reported hypertension at baseline (57.6%). Participants predominantly lived in the Eastern Temperate Forests level I ecoregion (82.9%), located in the eastern half of the United States (Figure 1.1, Table 1.1). The remaining participants resided in the Mediterranean California (7.5%), and Great Plains (6.3%) ecoregions, with 3.3% residing in other regions. Participants residing in the Eastern Temperate Forests were more likely to have diabetes or hypertension, and less likely to be college graduates than participants in other regions. Participants located within the Mediterranean California ecoregion

were predominantly in urban neighborhoods (96.2%), more likely to be college graduates and have higher income, and less likely to be male (40.2%) or White (51.7%) than participants in other ecoregions. Participants characteristics stratified by stroke and by all level I ecoregions in the contiguous United States are provided in supplemental tables 1.1 and 1.2.

Figure 1.2 displays the distribution of 1-year pollutant levels for each EPA level I ecoregion. One-year $PM_{2.5}$ levels were highest for participants in the Mediterranean California region, followed by the Eastern Temperate Forests which were both above the U.S. Environmental Protection Agency annual standard of 12 $\mu g/m^3$. We observed multimodal distributions for many of the pollutants within the Mediterranean California region, likely due to multiple cities within the region, and the high percentage of participants from urban areas. Participants in the Mediterranean California region also experienced the highest levels of PM_{10}, O_3, NO_2, and CO, while participants in the Eastern Temperate Forests experienced the highest levels of SO_2 (Table 1.2). Three-year pollutant levels were generally higher than 1-year levels but showed the same patterns across ecoregions. Supplemental Figure 2 shows the detailed distribution and correlations of 1-year pollutant levels for full study. The Pearson correlations for 1-year levels were highest for NO_2 with CO (0.75), and NO_2 with PM_{10} (0.63). $PM_{2.5}$ was moderately correlated with PM_{10} (0.58) and NO_2 (0.56).

Table 1.3 shows hazard ratios for the relationship between pollutants and incident stroke for the full unstratified models (including multi-pollutant), expressed as an IQR increase in pollutants. No significant associations were observed for 1-

year annual average of $PM_{2.5}$, O_3, NO_2, SO_2, or CO. For a 5.4 $\mu g/m^3$ increase in 1-year PM_{10} we observed a 7.0% higher risk of stroke (95% CI: 1.003, 1.15). The association between 1-year PM_{10} and stroke remained significant when controlling for other pollutants, as well as NDVI, 1-year temperature, and 1-year specific humidity, with estimates ranging from 7%-12% higher risk per IQR of PM_{10}. We did not observe a significant association between 3-year PM_{10} exposure and risk of stroke in single pollutant models, however, when additionally controlling for 3-year $PM_{2.5}$ or 3-year CO, we found a 10% higher (95% CI: 1.01, 1.19), and 9% higher (95% CI: 1.01, 1.17) risk of stroke for a 5.0 $\mu g/m^3$ increase in PM_{10}, respectively (supplemental table 1.6). We also found an inverse association between exposure to 3-year O_3 and risk of stroke, which largely persisted when controlling for other pollutants.

We found evidence of effect modification by level I ecoregions for exposure to $PM_{2.5}$, PM_{10}, and NO_2 (p-value for interaction < 0.05; Table 1.4). We found 61% higher risk of stroke (95% CI: 1.05, 1.25) for a 2.88 $\mu g/m^3$ increase in 3-year $PM_{2.5}$ for participants within the Great Plains region (supplemental table 1.7). No significant associations were found for $PM_{2.5}$ in other ecoregions. For PM_{10}, we found positive associations in the Eastern Temperate Forests region, but not in other regions. For NO_2, there was a suggestion of a negative association within the Mediterranean California ecoregion, and positive association within the “Other” region. Associations for pollutants were generally positive for participants in the ecoregion labeled “Other”, and negative in the Mediterranean California ecoregion.

For participants residing within the Eastern Temperate forests, we further stratified our Cox models by level II ecoregions (Table 1.5). Within the Mississippi Alluvial and Southeast USA Coastal Plains we found positive associations for $PM_{2.5}$ and PM_{10}. There was suggestive evidence of inverse associations for pollutants and risk of stroke within the Ozark/Ouachita-Appalachia Forests ecoregion. No associations were found in the Mixed Wood Plains, Central USA Plains, or Southeastern USA Plains level II ecoregions.

Effect modification by neighborhood level variables was most pronounced for urbanicity and specific humidity (Table 1.6). Stratifying our Cox models by urbanicity categories, we found positive associations for 1-year $PM_{2.5}$, PM_{10}, O_3, and NO_2 for participants in mixed census tracts, but not for those considered urban or rural census tracts. Stratifying by tertiles of specific humidity, we found positive associations for 1-year PM_{10}, NO_2, and SO_2 for those in the highest tertile of specific humidity. For SO_2, we found some evidence of effect modification by temperature (interaction p-value= 0.112). For participants in the highest tertile of temperature, we observed a 22% higher risk of stroke (1.00, 1.48) for a 1.44 ppb increase in SO_2. Tests for interaction showed little evidence of effect modification by greenness.

DISCUSSION

This study evaluated the relationship between long-term exposure to $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, and CO with incident stroke, and whether these relationships vary by ecoregions. In the full study population, we found positive associations of

long-term exposure to PM_{10} with stroke. This association was robust when controlling for other pollutants, as well as NDVI, temperature, and specific humidity. Conversely, we found evidence of a protective effect for long-term exposure to O_3 on stroke. Among level I ecoregions, a higher risk of stroke was associated with PM_{10} in the Eastern Temperate Forests, and with $PM_{2.5}$ in the Great Plains. Further stratifying our analysis by more detailed level II ecoregions within the Eastern Temperate Forests, we found stronger effects for $PM_{2.5}$ and PM_{10} within the Mississippi Alluvial and Southeast USA Coastal Plains ecoregion. We also found evidence that the magnitude of risk for gaseous pollutants (NO_2, SO_2, CO) was larger in areas with high specific humidity.

There is substantial evidence linking long-term exposure to air pollution with increases in the risk of stroke, a majority focusing on $PM_{2.5}$. A recent study in the USA of hospital admissions,[126] a study of two UK cohorts,[127] and a pooled analysis of six European cohorts,[128] found increased hazard ratios for stroke. Several recent reviews and meta-analysis also provide evidence for increased stroke risk for long-term exposure to PM_{10} as well as other individual gaseous pollutants such as O_3, NO_2, SO_2, and CO.[60,129,130] We found that exposure to PM_{10} was significantly associated with a 7% higher risk of stroke for a 5.4 $\mu g/m^3$ increase in 1-year PM_{10}. The PM_{10} and stroke association was robust to all model choices that adjusted for climate and other pollutants. Our effect estimate is in line with previous studies assessing the relationship between PM_{10} and stroke risk.[130] A study of 49,603 participants in the United States found a 4% higher risk of total stroke per 10 $\mu g/m^3$ increase in 1-year PM_{10} levels.[131]

Although it is well known that environmental characteristics such as temperature, humidity, season, barometric pressure, and greenness can confound the effects of long-term exposure to air pollution on cardiovascular disease,[132] few studies have considered how the totality of the surrounding ecology may influence the effects of pollution on human health. These confounding factors are related to pollutant dispersion, transportation and socioeconomic status, and could explain varying effects sizes of previous associations between air pollution and stroke.[132] To address this, we utilized ecoregions which define areas in an ecologically meaningful way by categorizing spaces of similar type, quality, and quantity of environmental resources. This includes phenomena such as geology, landforms, soils, vegetation, climate, land use, wildlife, and hydrology. We found significant variation in the associations between several pollutants and stroke risk when stratifying by level I ecoregions. Level I ecoregions highlight the major ecological areas in the United States allowing for comparisons at the global or intercontinental scale. Although we did not find significant associations between $PM_{2.5}$ and stroke risk in the full study population, when stratifying our models to the Great Plains region we found a 61% higher risk of stroke for a 2.9 $\mu g/m^3$ increase in $PM_{2.5}$. The Great Plains is located in the central part of the United States, and is distinguished by little topographic relief, vegetation consisting predominantly of grasslands with little forests, and a subhumid to semiarid climate while agriculture is the dominant land use in the region. Our finding is consistent with a previous study that utilized the National Health Interview Survey (NHIS), which found substantially stronger associations between $PM_{2.5}$ and all-cause mortality in the Great Plains region.[133]

Although we found stronger effects of $PM_{2.5}$ in the Great Plains region, for PM_{10}, we found stronger effects in the Eastern Temperate Forests Region. The Eastern Temperate Forests region dominates the eastern part of the United States and is characterized by a high density of human inhabitants. The vegetation consists of dense forest canopy, predominantly tall broadleaf, deciduous trees, and needle-leaf conifers.

Within the Eastern Temperate Forests, further stratifying our analysis by the more detailed level II ecoregions, we found significant positive associations for both $PM_{2.5}$ and PM_{10} in the Mississippi Alluvial and Southeast USA Coastal Plains region. This region has a humid subtropical climate, lying at lower elevation due to proximity to the ocean. Land cover ranges from wetlands and with vegetation mostly consisting of pines and hardwood forests.[120] This ecoregion also contains the stroke buckle (coastal plain of North Carolina, South Carolina, and Georgia), an area known to have the highest stroke mortality in the United States. This population contains a large proportion of black persons, a higher prevalence of traditional stroke risk factors, and lower socioeconomic status, suggesting that this population could be at heightened susceptibility to the effects of air pollution.[37] Conversely, we found evidence on inverse associations between air pollution and stroke in the Ozark/Ouachita Appalachian Forests ecoregion. This region is at high elevation, containing the Appalachian Mountain range, with extensive forest cover, predominantly hardwood forests at lower altitudes, and coniferous forests at higher altitudes.

In the full study population, we found a negative association between 3-year ozone exposure and stroke risk. Previous evidence for a causal relationship between long-term exposure to ozone and stroke risk is inconclusive. Recent reviews have reported no associations between ozone and cardiovascular mortality,[134,135] while other studies have reported positive findings.[126,136,137] Similar to our results, several studies have found an inverse relationship between ozone and stroke related outcomes.[119,128,138] A previously published study reported an inverse association between ozone and ischemic stroke morbidity in Beijing.[138] This study found that among type 2 diabetes patients, low ozone levels had a beneficial effect in the elderly population, while younger adults were more susceptible to extremely high ozone levels. This could explain our findings in that the average age of our participants was 64.6 years at the beginning of the study. The discrepancies in study populations could also be explained by differences in geography. A study of Medicare beneficiaries in the contiguous United States found a negative association between ozone and cerebrovascular hospitalization in the full cohort, however, they found a positive association when restricting the study to participants in the northern regions of the US that were exposed to levels below 40 ppb.[119] Although we found negative associations in the full cohort, we did find a positive association for participants residing in mixed urbanicity census tracts. Thus, it appears that the discrepancies in findings could be a combination of differences in population characteristics, geography, and pollution concentrations.

Previous studies on the relationship between air pollution and incident stroke have suggested modification by greenness of the exposure and health relationship.[87,139,140] In contrast, we did not find evidence of effect modification by greenness; however, we did find effect modification by specific humidity. We found substantially more harmful effects for gaseous pollutants (NO_2, SO_2, CO) and to a lesser extent PM_{10}, in areas with a high specific humidity. Studies have reported that decreases in humidity are associated with stronger effects for short-term air-pollution.[141,142] The effects of long-term exposure to high humidity levels are not well understood. A recent study found that decreases in summer and winter specific humidity was associated with stronger $PM_{2.5}$ and NO_2 associations.[119] We used yearly averages of specific humidity, which could wash out known seasonal and short term effects of humidity influence on pollution. Humidity is known to have an impact on air pollution concentrations, chemical mixtures, and dispersion.[143] In more humid conditions, the size of the particles could increase by moisture absorption.[144] This could explain why we found significant associations for $PM_{2.5}$ in the Great Plains region, a subhumid, semiarid climate. Thus, characterizing the effects of humidity independent of other features of the environment could be confounding our results.

For many of these pollutants, we found substantially more harmful effects in mixed urbanicity neighborhoods, areas where 25-75% of a census tract is considered urban. Few studies have compared air pollution-related health outcomes between rural and urban areas because most studies are conducted in urban areas. This result is likely due to a combination of differences in air pollution

composition and population characteristics. It is known that higher stroke mortality and stroke incidence occur in rural regions of the United States.[53,145]

This study has several strengths. A major strength is the geographically heterogeneous REGARDS study with over 1,500 incident stroke events, offering the opportunity to longitudinally estimate ecoregion specific effects of pollution exposure. This analysis of ecoregions across the United States allows us to reduce the likelihood of confounding due to features of the natural environment. Ecoregions transcend state and political boundaries. Although we cannot rule out sociopolitical influence in our results, the findings likely represent ecosystem related variations in the associations between air pollution and stroke risk. We included multiple pollutants in our models to estimate associations for each exposure while accounting for other exposures. Our exposures were assigned at the census block group level, which are relatively small geographic areas, which minimizes exposure misclassification.

Our study also has some limitations. Air pollution and environmental covariates were assigned to participants' baseline residence. This does not account for changes in residence during the study period and could result in misclassification bias. Exposure was assigned at the census block group level which may result in some measurement error depending on the amount of time the individual spends in the block group. We also had limited sample size in several of the geographically smaller level I ecoregions. Although we combined these participants in our analysis, this approach did not allow for a homogenous ecoregion consistent with the criteria of ecoregions created by the EPA, making

interpretation of this combined region difficult. Further, we were only able to analyze level II ecoregions located within the Eastern Temperate Forests.

Conclusions

Long-term exposure to PM_{10} was associated with an increased risk of stroke in a prospective study in the United States. We found that the relationship between air pollution and stroke varied by ecoregion, suggesting an important influence of the natural environment on the effects of pollution. Further studies are needed to assess reasons why environmental resources may influence air pollution exposure effects on stroke.

III. TRANSITION CHAPTER

Epidemiologic studies have consistently demonstrated that long-term exposure to air pollution is associated with increased risk of cardiovascular morbidity and mortality, including stroke. In the previous chapter we have provided evidence that these associations vary by ecological regions in the United States. These ecoregions represent distinct ecosystems in which the type, quality, and quantity of environmental resources are generally similar. Several studies have investigated how the relationship between exposure to air pollution is modified by individual climate features,[22,23,119] or surrounding vegetation, [17-20] however these aspects of the natural environment are intertwined. It is likely that their influence on the effects of pollution, and their direct effects on human health are not independent.

Likewise, an increasing body of evidence has found that living in areas of high greenness has beneficial effects on humans. However, these studies predominantly estimate how the generic abundance of greenspace associated with health, they do not account for the differences in vegetation types, or that vegetation is affected by characteristics of the natural environment, such as precipitation, sun light, humidity, and soil types. Therefore, in the following chapter we explored the relationship between residential greenness and incidence of

stroke and assessed how these relationships vary by ecological regions within the contiguous United States.

IV. ASSOCIATION BETWEEN RESIDENTIAL GREENNESS AND RISK OF STROKE BY ECOREGIONS: THE REGARDS STUDY

Background: Living in areas with higher greenness has been associated with beneficial health outcomes. However, few studies have examined associations of greenness with incidence of stroke, and it is unclear how these associations may vary with the type of vegetation and surrounding ecology. This study evaluated associations between greenness and incidence of stroke by the major ecological regions in the United States.

Methods: We assessed the incidence of stroke in the Reasons for Geographic and Racial Differences in Stroke study (REGARDS), a prospective cohort of 27,369 participants recruited across the contiguous United States. Greenness was estimated by the Normalized Difference Vegetation Index (NDVI) and Enhanced Vegetation Index (EVI) within 250-, 500-, and 1,250-m buffers around home addresses. We estimated the association between residential greenness and incidence of stroke using Cox proportional hazards models, after controlling for individual characteristics and contextual characteristics. Models were stratified by EPA created ecoregions to assess how associations varied by areas with unique environmental resources.

Results: We observed 1,581 incident cases of stroke during the study period. In the full study population, there was suggestive evidence of a negative association between greenness and stroke incidence (hazard ratio: 0.989; 95% CI: 0.946, 1.033) for a 0.1 increase in NDVI within 250-m. Similar results were obtained using EVI, and with larger radii. In our analysis by ecoregions, we found negative associations between greenness and stroke incidence in the Eastern Temperate Forests region, but positive associations in the Great Plains and Mediterranean California regions. We also found substantially stronger effects in areas of higher humidity and higher precipitation.

Conclusions: The associations between exposure to greenness and stroke incidence varied by ecoregion. Our results stress the importance of considering the complexities of the natural environment in studying the relationship between greenness and health.

INTRODUCTION

A growing number of studies have highlighted the health benefits of vegetation.[7] Living in areas of high greenness is inversely associated with all-cause mortality[8] as well as mortality due to ischemic heart disease and cerebrovascular disease.[9] An ecological study using a natural experiment, studied the loss of 100 million trees due to the emerald ash borer, found that the tree loss was associated with an increase in cardiovascular related mortality.[10] Fewer studies have assessed the associations between greenness and incident stroke. A population-based cohort of 1,263,721 residents in Rome found an inverse

association with leaf area and stroke incidence.[146] A case-control study reported 19% lower odds of stroke for participants living in the highest quartile of greenspace.[147] However, a study conducted in Southern Israel reported null findings for the association between greenness and stroke.[148] While a study of patients hospitalized with acute ischemic stroke found that higher residential surrounding greenness was associated with lower risk of severe stroke.[149] A number of biopsychosocial mechanisms may explain the benefits of exposure to greenness level on risk of stroke, including mitigation of exposures (air pollution, heat), stress recovery, and encouraging physical activity and social cohesion.[11] This can lead to lower BMI, lower risk of depression, and improved cardiovascular risk factors.[11-13]

The oversimplification of natural environments in much of the previous research could explain inconsistencies in findings. Greenspace is commonly measured by normalized difference vegetation index (NDVI), derived from satellite imagery, and used as a generic measure of the abundance of greenness in an area. This measure of greenspace fails to consider that different types and qualities of vegetation may have differential impacts on human health, and through different mechanisms. For example, broadleaf woodlands, which are found in the eastern United States, have been shown to have some of the greatest benefits to air quality,[76] and strong associations with psychological restoration.[77] Although most studies have focused on trees, vegetation categorized as grassland (abundant in the Great Plains) has also been positively associated with good health.[78] Not only is the type of vegetation important, but the effects of vegetation

could vary with the surrounding ecology, which can also directly impact human health. Plants, shrubs, and trees grow only when compatible with their surrounding environment, which varies with soil, temperature, rainfall, and sunlight.

In this study, we aimed to investigate the association between residential greenness and incidence of stroke, while also considering the surrounding ecosystem. We utilized the Reasons for Geographic and Racial Differences in Stroke study (REGARDS), a national cohort study with participants recruited across the contiguous United States. We classified participants into ecoregions, which are areas of similar environmental resources to examine the influence of unique ecosystems on our results. We hypothesized that higher levels of surrounding greenness would be associated with lower incidence of stroke, and that these associations would vary by ecoregion.

METHODS

Participants

REGARDS is a population-based longitudinal cohort study of 30,239 black and white participants aged ≥45 years. Participants were recruited across the contiguous 48 US states by mail and telephone between 2003 and 2007. Full details of the study are available elsewhere.[121] Participants were oversampled in the Southeastern region of the United States, termed the Stroke Belt (Alabama, Arkansas, Georgia, Louisiana, Mississippi, Tennessee, North Carolina, and South Carolina), and the Stroke Buckle (coastal plains of Georgia, North Carolina, and South Carolina). These regions historically have had much higher stroke mortality

than the rest of the United States.[37] Covariates included self-reported age, sex, race (Black, White), education (< high school, high school graduate, some college, college graduate), annual household income (<$20,000, $20,000-$40,000, $35,000-$74,000, ≥$75,000), and current smoking status (current, former, never). Diabetes was defined as use of hypoglycemic medications or fasting blood glucose ≥ 126 mg/dL or non-fasting glucose ≥ 200 mg/dL. Hypertension was defined as systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 or self-reported current medication use to control blood pressure. Atrial fibrillation was defined by self-report or ECG evidence. Previous cardiovascular disease was defined as self-reported MI, CABG, bypass, angioplasty, or stenting, or evidence of MI via ECG.

In the current analysis, participants were excluded for data anomalies (n=56), if they had a stroke at baseline (n=1,930), missing data on stroke (n=102), missing geocoded data (n=11), lack of follow-up (n=529), missing greenness exposure data (n=44), or missing covariate information (n=198). The final sample size consisted of 27,369 participants.

Stroke ascertainment

Incident stroke is defined as focal neurologic deficit lasting more than 24 hours or imaging consistent with ischemia or hemorrhage. Participants were contacted at 6-month intervals by telephone to collect data on events that require hospitalization, and physician evaluation of stroke-like symptoms. Death certificates and associated hospital records are retrieved if a death is reported. A two-member Events Committee independently reviews the records to validate

stroke occurrence and classifies events by stroke subtype and severity. Details of the stroke adjudication process are available elsewhere.[122] Incident strokes occurring up to September 30, 2020 were included in the analysis.

Greenness

Exposure to neighborhood greenness was assessed using the Normalized Difference Vegetation Index (NDVI) and Enhanced Vegetation Index (EVI) (Figure 2.1 and Supplemental Figure 2.3). NDVI and EVI varies from -1 to 1, with higher values indicating greater vegetation, and negative values corresponding to open water. NDVI is estimated as the ratio of near-infrared and red reflectance bands, whereas EVI additionally uses a blue light band, which corrects for aerosol effects and has greater sensitivity in areas of dense vegetation. Average NDVI and EVI values were calculated were from Moderate Resolution Imaging Spectroradiometer (MODIS), generated every 16 days at a spatial resolution of 250 meters via Google Earth Engine.[124,150] We obtained cloud free images for the summer season (June-August) from 2003 to 2007 to capture vegetation at its maximum height and variation during the 5-year window of all addresses at the enrollment period. A single raster image was obtained by removing water and averaging across summer months and baseline years using Google Earth Engine. We examined the average NDVI and EVI in 250-m, 500-m, and 1,250-m buffers around each geocoded address to evaluate the immediate area around residences and the larger neighborhood level scale. We utilized R software (version 4.1.1) for geographic information systems (GIS) analysis.

Ecoregions

Ecoregions are areas where the type, quality, and quantity of environmental resources are generally similar. EPA ecoregions are identified using the framework developed by Omernik,[151] by analyzing patterns and composition of biotic and abiotic phenomena. Level I ecoregions represent broad, major ecological areas in the United States, while level II ecoregions are nested within level I, and represent a more detailed description of ecological areas (Figure 1.1 and Supplemental Figure 1.1). We classified participants to EPA Level I and Level II ecoregions using their geocoded baseline address data. Level I ecoregions consisted of the Eastern Temperate Forests (n=22,699), Great Plains (n=1,714), and Mediterranean California (n=2,056). We classified all remaining participants into one region, labeled “Other” (n=900), which was comprised of Northern Forests, Northwestern Forested Mountains, and North American Deserts. Because a large percentage of our participants were located within the Eastern Temperate Forests, we focused on this region for the more detailed level II analysis. Within the Eastern Temperate Forests, level II ecoregions consisted of Mixed Wood Plains (n=2,004), Central USA Plains (n=2,289), Southeastern USA Plains (n=11,994), Ozark/Ouachita-Appalachian Forests (n=1,840), and Mississippi Alluvial and Southeast USA Coastal Plains (n=4,572).

Neighborhood level covariates

Participants were assigned neighborhood level covariates by their geocoded address. Covariate data were aggregated to the block group level, when

possible, because of the relatively small size of block groups representing a more homogeneous characterization of neighborhoods. Neighborhood level disadvantage was estimated using the 2015 area deprivation index (ADI) at the block group level.[152] Higher ADI rank indicates a more disadvantage neighborhood. Fine particulate matter ($PM_{2.5}$) was assigned to each participant at the block group level for the year prior to recruitment. $PM_{2.5}$ was obtained from the Center for Air, Climate & Energy Solutions (https://www.caces.us/). Full details of the exposure modeling and performance have been published.[123] Briefly, this approach uses universal kriging and partial least squares from ~350 geographic characteristics to construct exposure estimates from monitored pollutant data from the EPA Air Quality System data repository. Participants were classified by urbanicity as the percentage of urbanicity within their census tract, using data from the 2010 census.[153] Urbanicity was categorized into three levels as rural (≤ 25% urban), mixed (25-75% urban), and urban (≥ 75% urban). Measures of land cover (percent forest, percent agriculture, percent developed) from the National Land Cover Database and aggregated by U.S. census tract.[154]

Publicly available high spatial resolution (4-km) temperature, precipitation, and specific humidity data, derived from PRISM and the National Land Data Assimilation System (NLDAS),[125] were obtained via Google Earth Engine (https://earthengine.google.com/). These data were aggregated to the census block group level, and yearly averages were assigned to each participant for the year prior to baseline enrollment (Supplemental Figure 2.2).

Statistical Analysis

We summarized baseline characteristics of the REGARDS cohort and neighborhood level characteristics by tertiles of 250m NDVI, reported as mean ± SD for continuous variables and frequency (percentage) for categorical variables. Correlations between NDVI and EVI at various radii were estimated using Pearson correlations. Cox Proportional Hazards models were used to estimate the associations between greenness metrics and the incidence of stroke. Follow-up time was calculated in days as the difference between visit data in incidence of stroke. Proportionality was verified by checking the slope of the Schoenfeld residuals, and by including interaction terms of each exposure and calendar time to determine statistically significant violations. We considered all greenness exposure variables as continuous variables for the main analysis but were also modeled as tertiles. We modeled associations for each greenness factor as follows: a) Model 1, adjusted for age, sex, race, age*race interaction, education, urbanicity, and ADI; b) Model 2, Model 1 plus smoking status and yearly average $PM_{2.5}$ for the year prior to baseline. We included an age-race interaction term because it is known that the difference in stroke risk by race varies with age. Models were not adjusted BMI, previous CVD, hypertension, diabetes, or atrial fibrillation because these were considered in the causal pathway between exposure to greenness and risk of stroke. However, we performed a sensitivity analysis additionally adjusting for these variables to estimate the direct effect of greenness on risk of stroke. We examined effect modification by factors that may be associated with stroke disparities and/or that may be associated with differential effects of greenness. We assessed effect modification by race, sex, and

geographic variables (ecoregion, urbanicity, region, and tertiles of: ADI, temperature, precipitation, specific humidity) with likelihood ratio tests. Cox Proportional Hazards models were stratified by level I and level II ecoregions to obtain ecoregion specific hazard ratios. All analyses were performed using SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina), and R software (version 4.1.1).

RESULTS

Participants were 44.6% male, 59.7% White, with an average age of 64.6 years at baseline (Table 2.1). There were 1,581 total stroke events during the study period. The majority of participants lived in urban areas (78.0%), with 10.5% in mixed areas, and 11.5% in rural areas. Those living in areas with higher levels of greenness were more likely to be White adults, have higher income, be college graduates, and lower prevalence of hypertension and diabetes.

Table 2.2 shows summary statistics and correlation coefficients for NDVI and EVI at multiple radii. The mean NDV at 250m radius was 0.50, while the mean EVI was 0.30, with similar values at larger radii. NDVI and EVI were strongly positively correlated within the same radius, with slightly decreasing correlations found for discordant pairs.

Table 2.3 shows hazard ratios and 95% confidence intervals for the relationship between greenness exposure (continuous and tertiles) and risk of stroke. We present only 250-meter and 1,250-meter radii because we found similar results at all radii, thus 500-m radius results are presented in the supplemental

tables. We did not observe strong evidence of associations between greenness metrics and risk of stroke in the full study cohort, with our confidence intervals containing the null. For example, in our continuous analysis we observed a 1.1% lower risk of stroke (95% CI: 0.946, 1.033) for a 0.1 increase in NDVI within a 250-meter radius around participants' homes. Results were consistent for the 1,250-meter radius, with a 1.4% lower risk of stroke (95% CI: 0.942, 1.033) associated with a 0.1 increase in NDVI. In our categorical analysis, those living in the highest tertile of NDVI within a 250-m radius had a 6.7% lower risk of stroke (95% CI: 0.816, 1.068) than those living in the lowest quartile. While in a 1,250-m radius, those living in the highest tertile of NDVI had a 11.8% lower risk of stroke (95% CI: 0.769, 1.011) than those living in the lowest tertile. Results for EVI were generally similar to NDVI results. Results from models additionally adjusting for smoking status and neighborhood $PM_{2.5}$ levels were slightly attenuated but showed similar hazard ratios.

To determine whether the effects of greenness on risk of stroke varied by regions with known geographic differences in stroke mortality, we stratified our analysis by participants living within the stroke belt, stroke buckle, and non-belt regions (Table 2.4). The average NDVI within a 250-m radius was similar for participants living in the stroke belt and stroke buckle (0.57), but lower for those living in the non-belt region (0.42). A similar pattern was observed for EVI, and within a 1,250-m radius. Stratified analysis revealed negative associations between greenness metrics and risk of stroke for participants living in the stroke belt, while those living in the non-belt region had positive but non-significant

associations. For participants residing in the stroke belt, we estimated a 11.7% lower risk of stroke (95% CI: 0.796, 0.980) for a 0.1 increase in NDVI within 250-m, and a 17.0% lower risk (95% CI: 0.693, 0.995) for a 0.1 increase in EVI within 250-m. Similarly, within a 1,250-m radius we found a 13.6% and 17.0% lower risk of stroke for a 0.1 increase in NDVI and EVI, respectively. Although we found negative associations for individuals residing in the stroke belt, we did not find significant associations for those residing in the stroke buckle, the region with the historically highest rates of stroke mortality in the US.

Ecoregion Analyses

We observed statistical evidence of a difference in associations across level I ecoregions (Figure 2.2, Table 2.5). We found negative associations between greenness and stroke risk for participants residing in the Eastern Temperate Forests, but positive associations for participants in the Great Plains and Mediterranean California. Within the Eastern Temperate Forests, we estimated a 5% lower risk of stroke (95% CI: 0.901, 1.002) for a 0.1 increase in NDVI within 250-m, but a 40.5% and 30.9% higher risk of stroke within the Great Plains, and Mediterranean California regions, respectively (interaction p-value= 0.002). The associations between greenness and stroke risk were slightly strengthened at 1,250m radius around the participants' residence. In our sensitivity analysis, additionally adjusting for BMI, previous CVD, hypertension, diabetes, and atrial fibrillation did not significantly alter our results (Supplemental Table 2.7).

We further stratified our analysis within the Eastern Temperate Forests by level II ecoregions (Table 2.6 and Figure 2.3). We found the strongest evidence of negative relationships between greenness and stroke within the Central USA Plains region. Participants within this region had an average NDVI of 0.40 and an average EVI of 0.25 within a 250-m radius. We estimated a 19.1% lower risk of stroke (95% CI: 0.65, 1.00) for a 0.1 increase in NDVI within a 250-m radius, and a 31.3% lower risk of stroke (95% CI: 0.50, 0.94) for a 0.1 increase in EVI within a 250-m radius. These associations were slightly attenuated at larger radii (Supplemental Table 2.4).

Stratified Analyses

We observed no statistically significant differences in the association between greenness and stroke risk by race, sex, urbanicity, ADI, or temperature. Stratified analysis for precipitation and specific humidity are shown in Table 2.7. We observed a stronger association between greenness and stroke risk among participants living in areas of higher specific humidity and higher precipitation levels. This was most evident at 1,250-m NDVI. Participants residing in the highest tertile of specific humidity had an 8.6% lower risk of stroke (95% CI: 0.837, 0.998) for a 0.1 increase in NDVI within 1,250m, while those in the lowest tertile had a 5.2% increase (95% CI: 0.973, 1.137) in risk of stroke (interaction p-value=0.055). Similarly, participants residing in the highest tertile of precipitation had an 8.2% lower risk of stroke (95% CI: 0.852, 0.990) for a 0.1 increase in NDVI, while those in the lowest tertile had a 5.5% increase in stroke (95% CI: 0.979, 1.136) for a 0.1 increase in NDVI (interaction p-value= 0.021).

DISCUSSION

In this nationwide study of adults, we found significant geographic variation in the association between greenness around each participant's home address and incidence of stroke. We found significantly stronger negative associations between greenness and risk of stroke in the Eastern Temperate Forests region of the United States, but positive associations in the Great Plains and Mediterranean California regions. Further stratifying our analysis by the more detailed level II ecoregions, the strongest negative associations between greenness and risk of stroke were found in the Central USA Plains, which is nested within the Eastern Temperate Forests. Associations between greenness and risk of stroke were substantially stronger in areas with high specific humidity, and high precipitation, and in the stroke belt, a region with historically higher stroke mortality. The associations between greenness and risk of stroke were not statistically significantly different by race, sex, individual SES, area level deprivation, or urbanicity. Our overall results were consistent when using NDVI versus EVI, and when focusing on greenness immediately around each residence (250-m buffer) versus larger radii (500-m, 1,250-m) around each participant's home.

Available evidence on the association between greenness and stroke is still scarce, and have predominantly focused on stroke mortality, not incidence. An ecological study in northwest Florida found high stroke mortality in areas with low income levels, high air pollution, and low levels of greenness.[155] Several meta-analysis and reviews have also found a decreased risk of stroke mortality associated with higher greenness.[72,156] Fewer studies have investigated the

relationship between greenness and incidence of stroke. A recent study of 1,254,030 participants in Rome found a 2.4% lower risk of stroke (95% CI: 0.960, 0.993) for a 0.1 increase in NDVI values in a 300-m buffer.[146] While a study in Spain of 3,521,274 participants estimated a hazard ratio of 0.84 for a 0.1 increase in NDVI values within a 300-m buffer.[157] Greenspace exposure has also been related to milder initial stroke,[149] and higher survival after ischemic stroke.[74] In our full study cohort, we found small, but suggestive evidence of a negative association between greenness and stroke, with a 1.1% lower risk (95% CI: 0.946, 1.033) associated with a 0.1 increase in NDVI values in a 250-m buffer. Our findings were similar at larger radii (500-m, 1,250-m), and when using EVI versus NDVI. Our smaller effect sizes compared with other studies could be explained by the older age of our participants (mean age 64.6 years). Previous studies have reported different associations by age group, with null or reduced associations in the oldest age groups.[146,158] This may be due to different uses of green spaces by people of different ages, for example, younger people may be more likely to use green space for physical activity. Exposure to greenspace is postulated to provide health benefits through several mechanisms. Greenness could benefit health through stress reduction,[159] promote social interactions,[160] reduced exposure to pollutants,[90] and promotion of physical activity.[161] Additionally, exposure to green space may lead to vegetation-produce microbial antigens that educate the immune system and prevent disease.[162] Greenness could also benefit health by slowing down vascular aging.[163] A large population-based cohort study in Ontario, Canada found that residential green space was associated with reduced incidence of

dementia and stroke, risks that typically grow with age.[164] Previous studies have also found that greenness was associated with lower arterial stiffness.[20,165] Further, there is evidence that exposure to higher greenness is related to a better angiogenic profile, suggesting individuals living in greener areas have a better wound healing response and higher capacity to repair blood vessels.[75]

Stratifying our analysis by level I ecoregions, we found negative associations between greenness and stroke incidence in the Eastern Temperate Forests ecoregion, but positive associations in the Great Plains and Mediterranean California ecoregions. Level I ecoregions represent the major ecological areas of the United States, allowing for comparisons at the global and intercontinental scale. Vegetation in the Eastern Temperate Forests ecoregion is dominated by deciduous forest, though with many coniferous trees and a high level of plant biodiversity. These findings are consistent with previous studies highlighting the potential benefits of forests. An ecological study of land cover types across Great Britain found positive associations between good health prevalence and density of broadleaf woodlands and coniferous woodlands.[78] These forest types have also been shown to have greater benefits to air quality.[76] Further, compared with other types of vegetation, trees may better promote physical activity, stress reduction, reductions in noise, and lower temperatures. Because a majority of our participants resided in the Eastern Temperate Forests region, we were able to further stratify our analysis by the five nested level II ecoregions. These ecoregions provide a more detailed description of the large level I ecoregions. We found the strongest negative associations between greenness and stroke incidence in the Central USA

Plains ecoregion, located in the northwestern part of the Eastern Temperate Forests. This region has a humid continental climate, with vegetation consisting of hardwood forests. It is unclear why we found positive associations in the Great Plains and Mediterranean California ecoregions. However, our results align with a previous study, which investigated the relationship between greenness and cardiopulmonary mortality in cancer survivors. They found a positive association between NDVI and cardiopulmonary mortality for participants predominantly located within the Great Plains, but a negative association for participants predominantly located in the Eastern Temperate Forests.[87] The Great Plains ecoregion is largely covered by natural grasslands, and because of the suitability for agriculture productions, agriculture is the dominant land use for this ecological region. Few studies have distinguished between agricultural green space and natural green space, however, a study in France found an increased risk of cancer and proximity to agricultural lands, but a protective role of greenspace for breast cancer.[166] While, the Mediterranean California ecoregion is characterized by low growth evergreen shrubs, called chaparral, with some grasslands and coniferous forests at higher elevations. Thus, it is likely that our positive findings could be due to the different types of vegetation in these regions, consisting largely of grasslands, shrubs, and agriculture related greenness, which may not provide the same benefits as trees or forests.

In our study, we found evidence that the association between greenness and incidence of stroke was significantly stronger in the Stroke Belt region of the United States. The Stroke Belt is a region in the Southeastern United States with

historically higher stroke mortality.[37] The higher stroke mortality in this region is primarily related to a higher stroke incidence. The major contributors are thought to be a higher risk factor burden, higher levels of inflammation and infection, lower SES, environmental exposures, and lifestyle choices.[37] Thus it seems likely that greenness has a greater protective benefit in population with higher susceptibility to stroke. In fact, previous studies have found a greater protective effect of greenness in disadvantaged groups,[167] and linked green space to less stress in deprived communities.[168] However, we did not find strong evidence of a negative association between greenness and stroke in the Stroke Buckle region of the United States. This region is in the coastal plains of North Carolina, South Carolina, and Georgia, and with higher stroke mortality than the Stroke Belt region. Thus, our findings are likely due to a combination of individual level susceptibilities and environmental features. The Stroke Belt region is predominantly located within the Eastern Temperate Forests level I ecoregion, where we found the strongest evidence of a negative association between greenness and stroke incidence.

We did not find evidence of effect modification by urbanicity. Previous studies have found that greenspace tends to have a stronger protective association with health in urban areas, with greater evidence for specific health outcomes, such as cardiovascular related and mortality endpoints.[169] The benefits of greenness are thought to be strengthened in urban areas due to several pathways, which may be more prevalent in urban areas. Greenness can reduce harmful environmental exposures, alleviate attentional demands, reduce chronic stressors, and promote healthy behaviors.[169] However, we did find evidence of

effect modification by census tract level specific humidity, and precipitation. It is unclear how high humidity could increase the benefits of greenness on risk of stroke. Increasing air humidity is known to increase tree size,[170] similar to the effects of precipitation, consequently increasing the benefits of trees. Likewise, a shortage of water reduces tree growth due to suppression of photosynthesis, to avoid water loss through transpiration, and impeded nutrient uptake.[171] Vegetation thrives only when in a compatible environment. The types of vegetation found in areas of high humidity or higher rainfall may be better suited to benefiting human health.

Our study had several limitations. We used satellite based NDVI and EVI to assess greenspace surrounding participants' homes, however, these measures do not distinguish between different types of vegetation. Further, residential greenness estimates do not take into account the amount of exposure to greenness at other places during daily life or visiting green spaces during leisure time, but this is expected to be non-differential exposure misclassification. Moreover, greenness was assigned to participants' baseline residence which does not account for changes in residence during the study period and could result in misclassification bias. Because of the geographic distribution of our sample, we had limited sample size in several of the geographically smaller level I ecoregions which restricted our analysis to using three ecoregions. Thus, it is unclear how the ecoregions not included in our analysis may have modified our findings.

This study also had some unique strengths. To our knowledge, this is the first prospective examination of the relationship between exposure to greenness

and stroke incidence classifying participants into major ecological regions of the United States. Using the REGARDS study, a national prospective study across the United States, offered the opportunity to estimate ecoregion specific associations of greenness on risk of stroke. Additionally, we were able to control for important confounders, such as individual level SES, area level deprivation and fine particulate matter, urbanicity, and smoking status.

Conclusions

Residential surrounding greenness was inversely associated with stroke incidence in the Eastern Temperate Forests region of the United States. Our results add to the current evidence that residential greenness could promote health. The findings presented here suggest that different vegetation types and their surrounding natural environment could be differentially important in their influence on stroke. Further studies should take into consideration the complexities of the natural environment to improve our understanding of how greenness is related to human health.

V. DISCUSSION

Summary

The purpose of this study was to investigate the relationships between long-term exposure to ambient air pollution, greenness, and incidence of stroke, and whether these relationships change with the surrounding ecology. In the full cohort, we found positive associations of long-term exposure to PM_{10} with stroke. This association was robust when controlling for other pollutants, as well as NDVI, temperature, and specific humidity. We also found evidence of a protective effect for long-term exposure to O_3 on stroke. In analysis of level I ecoregions, there was a higher risk of stroke associated with PM_{10} in the Eastern Temperate Forests than other ecoregions, and a higher risk of stroke associated with $PM_{2.5}$ in the Great Plains. Further stratifying our analysis by more detailed level II ecoregions within the Eastern Temperate Forests, we found stronger effects for $PM_{2.5}$ and PM_{10} within the Mississippi Alluvial and Southeast USA Coastal Plains ecoregion. We also found evidence that the risk of stroke associated with gaseous pollutants (NO_2, SO_2, CO) was higher in areas with high specific humidity.

Further, we found significant geographic variation in the association between greenness around each participant's home address and incidence of stroke. We found significantly stronger negative associations between greenness

and risk of stroke in the Eastern Temperate Forests region of the United States, but positive associations in the Great Plains and Mediterranean California regions. Further stratifying our analysis by the more detailed level II ecoregions, the strongest negative associations between greenness and risk of stroke were found in the Central USA Plains, which is nested within the Eastern Temperate Forests. Associations between greenness and risk of stroke were substantially stronger in areas with high specific humidity, and high precipitation, and in the stroke belt, a region with historically higher stroke mortality. The associations between greenness and risk of stroke were not statistically significantly different by race, sex, individual SES, area level deprivation, or urbanicity. Our overall results were consistent when using NDVI versus EVI, and when focusing on greenness immediately around each residence (250-m buffer) versus larger radii (500-m, 1,250-m) around each participant's home. The major findings specific to each aim are presented below.

Aim 1: Characterize the REGARDS cohort, ambient air pollution, vegetation, and environmental characteristics by EPA ecoregions.

To better understand how characteristics of the REGARDS cohort, ambient air pollution levels, and residential greenness differed by the major ecological regions in the United States we stratified our data by EPA level I ecoregions and assessed summary statistics and distributions. The majority of our participants (~80%) were located in the Eastern Temperate Forests, followed by the Mediterranean California (~7.5%) and Great Plains (~6%) ecoregions. Participants residing in the Eastern Temperate Forests were more likely to have diabetes and

hypertension, and less likely to be college graduates than participants in other regions. Participants located within the Mediterranean California ecoregion were predominantly in urban neighborhoods (96.2%), more likely to be college graduates and have higher income, and less likely to be male (40.2%) or White (51.7%) than participants in other ecoregions. $PM_{2.5}$ levels were highest for participants in the Mediterranean California region, followed by the Eastern Temperate Forests. We observed multimodal distributions for many of the pollutants within the Mediterranean California region. Participants in the Mediterranean California region also experienced the highest levels of PM_{10}, O_3, NO_2, and CO, while participants in the Eastern Temperate Forests experienced the highest levels of SO_2. The average levels of residential greenness were highest for participants located in the Eastern Temperate Forests regions, followed by the Great Plains, and Mediterranean California regions.

Aim 2: Characterize the relationship between long-term ambient air pollution and risk of stroke in the REGARDS cohort.

We found a significant positive association between 1-year PM_{10} levels and risk of stroke in the full study population. This association was robust to adjustment for other pollutants, climate characteristics, and ecoregion. We also found small but suggestive evidence of a negative association between 3-year O_3 levels and incidence of stroke. We did not find evidence of associations for long-term exposure to $PM_{2.5}$, NO_2, SO_2, and CO with stroke incidence. Our associations were largely similar when using 1-year pollution estimates or 3-year pollution estimates.

Overall, these results suggest that long-term exposure to PM_{10} may increase the risk of stroke, independent of the surrounding ecology.

Aim 3: Determine the extent to which the effects of long-term ambient air pollution exposure on risk of stroke are modified by the surrounding ecosystem.

Our results supported the hypothesis that the relationship between long-term exposure to ambient air pollution and risk of stroke would vary by ecoregion. We found evidence of effect modification by level I ecoregions on the associations of $PM_{2.5}$, PM_{10}, and NO_2 with stroke risk. The association between PM_{10} and incident stroke was significantly stronger in the Eastern Temperate Forests, while the association between $PM_{2.5}$ and incident stroke were significantly stronger in the Great Plains.

Aim 4: Characterize the relationship between residential greenness and risk of stroke in the REGARDS cohort.

In the full study populations, we found weak but suggestive evidence of a negative association between greenness and incidence of stroke. This relationship was slightly attenuated when adjusting for smoking status and long term ambient $PM_{2.5}$ levels. The relationship between greenness and stroke was consistent when using NDVI versus EVI, and at different radii around participant's homes (250-m, 500-m, 1,250-m). Categorizing our greenness exposure estimates by tertiles, we observed a small nonsignificant positive association in the middle tertile, followed

by a negative association in the highest tertile, compared with the lowest tertile as the reference.

Aim 5: Determine the extent to which the effects of surrounding greenness on risk of stroke are modified by the surrounding ecosystem.

Our results support the hypothesis that the relationship between residential greenness and risk of stroke varies by ecoregions. We found significant effect modification by level I ecoregions on the association of all greenness metrics with stroke risk. Our results indicated a negative association between greenness and stroke risk in the Eastern Temperate Forests, but positive associations in the Great Plains, and Mediterranean California regions. Further stratifying our analysis by level II ecoregions within the Eastern Temperate Forests, we found the strongest negative associations between greenness and stroke risk in the Central USA Plains ecoregion. These findings suggest that the beneficial effects of greenspace on risk of stroke could be greater in forested areas.

Broader Conclusions

Our results add to the current evidence that long-term exposure to air pollution is associated with increased risk of stroke, and that higher residential greenness could lower the risk of stroke. However, the key finding of this study is that the relationships between air pollution, greenness, and incident stroke vary with the surrounding natural environment. There could be several explanations for why the effects of exposure to air pollution on incident stroke varies by ecoregion. Air pollution could be more harmful when accompanied by certain features of the

natural environment, such as extreme temperatures.[22,23] Our pollution data from monitors may be overestimating individuals' pollution exposure in forested areas, or areas of high vegetation. There is mounting evidence that vegetation filters pollutants by varying degrees,[172,173] and thus ambient pollution estimates may not be representative of individual exposure. Further, the composition of pollution mixtures is likely to be different in geographic regions, due to unique sources in the region and by features of the natural environment, such as altitude, temperature, and humidity, which can affect characteristics such as particle size and deposition. Particulate matter is measured based on particle size ($PM_{2.5}$, fine particles with diameters ≤2.5 micrometers), but ambient PM is not a static variable, its chemical composition can change based on the emission source and environmental features. For example, a study in Beijing found that urban trees reduced PM_{10} more than other pollutants.[173] Likewise, the potential toxicity of ambient PM is driven by the chemical composition, and recent studies have begun to focus on contributions of individual components,[174] and oxidative potential of pollution compositions.[175]

Strengths and Limitations

This study has several strengths. A major strength is the geographically heterogeneous REGARDS study with over 1,500 stroke events, offering the opportunity to estimate ecoregion specific effects of greenness and pollution exposure on stroke risk. This analysis of ecoregions across the United States allows us to reduce the likelihood of confounding due to features of the natural environment. Ecoregions transcend state and political boundaries. Although we

cannot rule out sociopolitical influence in our results, the findings likely represent ecosystem related variations in the associations between air pollution and stroke risk. We included multiple pollutants in our models to estimate associations for each exposure while accounting for other exposures. Our exposures were assigned at the census block group level, which are relatively small geographic areas, which minimizes exposure misclassification. To our knowledge, this is the first prospective examination of the relationship between exposure to greenness and stroke incidence classifying participants into major ecological regions of the United States. Ecoregions are partly characterized by areas of similar types of vegetation, allowing us a method to infer whether our associations are due to differences in vegetations types. Additionally, we were able to control for important confounders, such as individual level SES, area level deprivation and fine particulate matter, urbanicity, and smoking status.

Our study also has some limitations. Air pollution and environmental covariates were assigned to participants' baseline residence. This does not account for changes in residence during the study period and could result in misclassification bias. Exposure was assigned at the census block group level which may result in some measurement error depending on the amount of time the individual spends in the block group. We also had limited sample size in several of the geographically smaller level I ecoregions. Although we combined these participants in our analysis, this approach did not allow for a homogenous ecoregion consistent with the criteria of ecoregions created by the EPA, making interpretation of this combined region difficult. Further, because of the geographic

distribution of our participants, we were only able to analyze level II ecoregions located within the Eastern Temperate Forests. We used satellite based NDVI and EVI to assess greenspace surrounding participants' homes, however, these measures do not distinguish between different types of vegetation. Further, residential greenness estimates do not take into account the amount of exposure to greenness at other places during daily life or visiting green spaces during leisure time, but this is expected to be non-differential exposure misclassification because all participants were assigned using the same approach. Moreover, greenness was assigned to participants' baseline residence which does not account for changes in residence during the study period and could result in misclassification bias.

Public Health Significance

The natural environment is an often-overlooked area in public health. The findings presented in this dissertation suggest that the harmful effects of air pollution on incident stroke, and possibly other health related outcomes, depends on the surrounding natural environment. Thus, policies on safe levels of exposure may need to focus on evidence of detrimental effects specific to the ecological region of interest and consider that the same level of pollution in one ecoregion may be more harmful than a similar level in a different ecoregion. Similarly, our findings that greenspace may lower the risk of stroke in certain ecoregions has public health implications. Green environments might be an important way to reduce socioeconomic health inequalities. In fact, a previous study found that the inequality in all-cause and circulatory disease mortality related to income deprivation is lower for populations living in higher greenness areas, than those

with less exposure to green space.[176] Further, a systematic review concluded that green space could be a tool to advance health equity.[167] Increasing green space provides a way for urban planners, parks manager, and public health professionals a new way to address health disparities. However, they type of greenness, and the complexity of the natural environment should be taken into consideration when using vegetation to address health disparities.

Recommendations for Further Studies

Further studies of environmental health should take into consideration the complexities of the natural environment to improve our understanding of how exposures are related to human health. We have provided a meaningful way of accounting for this complexity by characterizing participants into ecoregions, which are areas of generally similar type, quality, and quantity of environmental resources. However, there could be alternative approaches to account for the natural environment, such as a systems or exposome approaches.[177,178] Not only should the natural environment be accounted for but features of the natural environment can also directly affect human health, and more work is needed in this area.

The relationship between the natural environment and human health is of increasing interest because of global climate change. Rising temperatures will result in changes to our ecosystems, and potentially increasingly detrimental effects of air pollution. Thus, it is of great importance to understand how these relationships change with the natural environment.

TABLES

Table 1.1 Baseline characteristics of participants in the cohort by EPA level I ecoregions.

Characteristic	Total	EPA-8	EPA-9	EPA-11	EPA-0
n	26,792	22,222	1,675	2,014	881
Stroke event	1,537 (5.7)	1,292 (5.8)	98 (5.9)	99 (4.9)	48 (5.5)
Person-years	284,405.3	235,211.2	17,731.1	21,765.8	9,697.2
Age (yr)	64.6 (9.4)	64.4 (9.3)	65.4 (9.0)	65.1 (10.1)	66.3 (9.5)
Sex, Male (%)	11,925 (44.5)	9,832 (44.2)	838 (50.0)	810 (40.2)	445 (50.5)
BMI (kg/m^2)	29.3 (6.2)	29.3 (6.2)	29.3 (6.0)	29.3 (6.3)	28.8 (6.0)
Race, White (%)	16,003 (59.7)	13,187 (59.3)	1,035 (61.8)	1,042 (51.7)	739 (83.9)
Income					
<$20,000	4,539 (16.9)	3,940 (17.7)	296 (17.7)	197 (9.8)	106 (12.0)
$20,000 to $34,000	6,414 (23.9)	5,391 (24.3)	418 (25.0)	397 (19.7)	208 (23.6)
$35,000 to $74,000	8,186 (30.6)	6,692 (30.1)	544 (32.5)	661 (32.8)	289 (32.8)
≥$75,000	4,467 (16.7)	3,547 (16.0)	230 (13.7)	520 (25.8)	170 (19.3)
Refused	3,186 (11.9)	2,652 (11.9)	187 (11.2)	239 (11.9)	108 (12.3)
Education (%)					
Less than H.S.	3,096 (11.6)	2,756 (12.4)	190 (11.3)	90 (4.5)	60 (6.8)
H.S. graduate	6,865 (25.6)	5,888 (26.5)	459 (27.4)	316 (15.7)	202 (22.9)
Some College	7,239 (27.0)	5,929 (26.7)	431 (25.7)	636 (31.6)	243 (27.6)
College graduate	9,592 (35.8)	7,649 (34.4)	595 (35.5)	972 (48.3)	376 (42.7)
Diabetes (%)*	5,354 (20.7)	4,567 (21.3)	305 (18.8)	363 (18.8)	119 (13.9)
Hypertension (%)*	15,422 (57.6)	12,967 (58.5)	948 (56.6)	1,077 (53.5)	430 (48.8)
Current Smoker (%)	3,778 (14.1)	3,248 (14.6)	248 (14.8)	204 (10.1)	78 (8.9)
Alcohol Use					
Current	14,141 (52.8)	11,434 (51.5)	885 (52.8)	1,264 (62.8)	558 (63.3)
Never	8,012 (29.9)	6,894 (31.0)	474 (28.3)	450 (22.3)	194 (22.0)
Past	4,639 (17.3)	3,894 (17.5)	316 (18.9)	300 (14.9)	129 (14.6)
Exercise (%)					
None	8,918 (33.3)	7,466 (33.6)	533 (31.8)	655 (32.5)	264 (30.0)
1-3 times/wk	9,833 (36.7)	8,169 (36.8)	610 (36.4)	752 (37.3)	302 (34.3)
≥ 4 times/wk	8,041 (30.0)	6,587 (29.6)	532 (31.8)	607 (30.1)	315 (35.8)
Urbanicity					
Rural (≤25%)	3,070 (11.5)	2,782 (12.5)	135 (8.1)	36 (1.8)	117 (13.3)
Mixed (25-75%)	2,813 (10.5)	2,590 (11.7)	94 (5.6)	40 (10.1)	89 (10.1)
Urban (≥75%)	20,909 (78.0)	16,850 (75.8)	1,446 (86.3)	1,938 (96.2)	675 (76.6)

EPA-8, Eastern Temperate Forests; EPA-9, Great Plains; EPA-11, Mediterranean California, EPA-0, “Other” (EPA-5, Northern Forests; EPA-6, Northwestern Forested Mountains; EPA-10, North American Deserts). * Missing participants (diabetes =917 participants; hypertension=38 participants; previous CVD= 452 participants; Atrial fibrillation= 555 participants).

Table 1.2. Summary Statistics and Pearson correlations between pollutants.

Pollutant 1-year	**Mean (SD)**	**Median (IQR)**	**$PM_{2.5}$**	**PM_{10}**	**O_3**	**NO_2**	**SO_2**	**CO**
$PM_{2.5}$ ($\mu g/m^3$)	12.63 (2.35)	12.70 (2.91)	1	0.58	0.38	0.56	0.46	0.42
PM_{10} ($\mu g/m^3$)	20.90 (4.96)	20.29 (5.38)	0.58	1	0.15	0.63	0.15	0.56
O_3 (ppb)	48.81 (5.15)	49.08 (6.35)	0.38	0.15	1	0.12	0.20	0.03
NO_2 (ppb)	11.22 (5.97)	9.94 (7.42)	0.56	0.63	0.12	1	0.53	0.75
SO_2 (ppb)	2.95 (1.33)	2.62 (1.44)	0.46	0.15	0.20	0.53	1	0.30
CO (ppm)	0.41 (0.11)	0.39 (0.11)	0.42	0.56	0.03	0.75	0.30	1
Pollutant 3-year	**Mean (SD)**	**Median (IQR)**	**$PM_{2.5}$**	**PM_{10}**	**O_3**	**NO_2**	**SO_2**	**CO**
$PM_{2.5}$ ($\mu g/m^3$)	12.83 (2.44)	12.82 (2.88)	1	0.65	0.42	0.64	0.46	0.52
PM_{10} ($\mu g/m^3$)	20.93 (5.00)	20.29 (5.03)	0.65	1	0.12	0.69	0.16	0.68
O_3 (ppb)	49.42 (4.81)	49.82 (6.64)	0.42	0.12	1	0.13	0.29	0.02
NO_2 (ppb)	11.63 (6.11)	10.36 (7.76)	0.64	0.69	0.13	1	0.52	0.84
SO_2 (ppb)	3.03 (1.32)	2.68 (1.45)	0.46	0.16	0.29	0.52	1	0.30
CO (ppm)	0.41 (0.12)	0.39 (0.11)	0.52	0.68	0.02	0.84	0.30	1

Table 1.3. Single pollutant and multipollutant estimated HRs 95% and 95% CIs for stroke associated with an IQR increase in 1-year pollutant levels for the full model (n=26,792).

1-year	$PM_{2.5}$	PM_{10}	O_3	NO_2	SO_2	CO
Single Pollutant	0.99 (0.92, 1.07)	**1.07(1.003,1.15)**	0.97 (0.91, 1.03)	1.00 (0.92, 1.08)	0.99 (0.93, 1.05)	0.97 (0.92, 1.03)
+NDVI, 1250m	0.99 (0.92, 1.07)	**1.08 (1.00, 1.16)**	0.97 (0.91, 1.03)	0.97 (0.88, 1.08)	0.98 (0.92, 1.05)	0.97 (0.91, 1.03)
+Temperature	1.00 (0.92, 1.08)	**1.07 (1.00, 1.15)**	0.97 (0.91, 1.04)	1.01 (0.92, 1.11)	1.00 (0.93, 1.07)	0.98 (0.92, 1.04)
+Sp. Humidity	1.00 (0.92, 1.08)	**1.08 (1.01, 1.15)**	0.98 (0.92, 1.05)	1.02 (0.93, 1.12)	1.01 (0.94, 1.08)	0.98 (0.92, 1.04)
+$PM_{2.5}$	-	**1.12 (1.03, 1.22)**	0.97 (0.90, 1.04)	1.00 (0.91, 1.10)	0.99 (0.93, 1.06)	0.97 (0.91, 1.04)
+PM_{10}	0.92 (0.84, 1.01)	-	0.96 (0.90, 1.02)	0.94 (0.85, 1.03)	0.98 (0.92, 1.04)	0.94 (0.88, 1.00)
+ O_3	1.01 (0.93, 1.10)	**1.08 (1.01, 1.15)**	-	1.00 (0.92, 1.09)	1.00 (0.94, 1.06)	0.98 (0.92, 1.04)
+NO_2	0.99 (0.91, 1.08)	**1.10 (1.02,1.19)**	0.97 (0.91, 1.03)	-	0.99 (0.92, 1.07)	0.96 (0.89, 1.04)
+SO_2	1.00 (0.92, 1.08)	**1.08 (1.01, 1.16)**	0.97 (0.91, 1.04)	1.01 (0.90, 1.12)	-	0.97 (0.91, 1.04)
+CO	1.01 (0.92, 1.09)	**1.10 (1.03, 1.19)**	0.97 (0.91, 1.03)	1.03 (0.93, 1.15)	1.00 (0.94, 1.07)	-

Models adjusted for age, sex, race, age*race, education, BMI, alcohol use, smoking status, exercise, year of baseline, urbanicity, and ecoregion. Additional pollutants and environmental characteristics were added one at a time.

Table 1.4. Estimated HRs and 95% CIs for stroke associated with an IQR increase in 1-year pollutant levels, stratified by EPA level I ecoregions.

Exposure (IQR)	EPA-8	EPA-9	EPA-11	Interaction p-value
n No. of cases	22,222 1,292	1,675 98	2,014 99	
$PM_{2.5}$ 1-year (2.91)	1.02 (0.93, 1.12)	1.44 (0.97, 2.15)	0.88 (0.74, 1.05)	0.021
PM_{10} 1-year (5.38)	**1.15 (1.05, 1.25)**	1.00 (0.70, 1.44)	0.96 (0.84, 1.10)	0.028
O_3 1-year (6.35)	0.98 (0.91, 1.05)	0.83 (0.64, 1.08)	0.99 (0.68, 1.45)	0.556
NO_2 1-year (7.42)	1.02 (0.93, 1.12)	1.06 (0.68, 1.65)	0.88 (0.69, 1.12)	0.087
SO_2 1-year (1.44)	0.99 (0.93, 1.05)	1.19 (0.74, 1.94)	0.87 (0.53, 1.43)	0.344
CO 1-year (0.11)	0.99 (0.92, 1.06)	0.89 (0.65, 1.22)	0.96 (0.82, 1.13)	0.490

Models adjusted for age, sex, race, age*race, education, BMI, alcohol use, smoking status, exercise, year of baseline, and urbanicity. EPA-8, Eastern Temperate Forests; EPA-9, Great Plains; EPA-11, Mediterranean California.

Table 1.5. Estimated HRs and 95% CIs for stroke associated with an IQR increase in 1-year pollutant levels, stratified by EPA level II ecoregions located within the Level I Eastern Temperate Forests.

Exposure	EPA-8.1	EPA-8.2	EPA-8.3	EPA-8.4	EPA-8.5
n	1,967	2,239	11,745	1,812	4,459
No. of cases	125	139	679	91	258
$PM_{2.5}$	1.11 (0.82, 1.51)	1.05 (0.73, 1.50)	1.06 (0.89, 1.27)	0.90 (0.61, 1.32)	**1.28 (1.02, 1.62)**
PM_{10}	1.18 (0.92, 1.50)	1.24 (0.94, 1.65)	1.14 (0.98, 1.32)	0.98 (0.66, 1.46)	**1.23 (1.05, 1.45)**
O_3	1.07 (0.83, 1.39)	0.77 (0.58, 1.03)	1.04 (0.93, 1.17)	0.96 (0.66, 1.39)	0.93 (0.78, 1.10)
NO_2	1.02 (0.78, 1.32)	1.22 (0.84, 1.77)	1.06 (0.91, 1.25)	0.84 (0.45, 1.56)	1.13 (0.89, 1.45)
SO_2	0.97 (0.83, 1.13)	1.21 (0.94, 1.57)	1.08 (0.97, 1.20)	**0.78 (0.62, 0.98)**	1.15 (0.94, 1.40)
CO	0.97 (0.84, 1.12)	1.13 (0.89, 1.43)	1.08 (0.95, 1.23)	0.78 (0.59, 1.04)	0.95 (0.78, 1.15)

Models adjusted for age, sex, race, age*race, education, BMI, alcohol use, smoking status, exercise, year of baseline, and urbanicity. EPA-8.1, Mixed Wood Plains; EPA-8.2, Central USA Plains; EPA-8.3, Southeastern USA Plains, EPA-8.4, Ozark/Ouachita-Appalachian Forests; EPA-8.5, Mississippi Alluvial and Southeast USA Coastal Plains.

Table 1.6. Estimated HRs and 95% CIs for stroke associated with an IQR increase in 1-year pollutant levels by stratified variable.

Characteristic	**$PM_{2.5}$**	**PM_{10}**	**O_3**	**NO_2**	**SO_2**	**CO**
Urbanicity						
Rural	1.01 (0.79, 1.30)	1.06 (0.83, 1.36)	0.97 (0.80, 1.18)	1.11 (0.57, 2.20)	0.88 (0.66, 1.17)	0.91 (0.70, 1.17)
Mixed	**1.35 (1.04, 1.76)**	**1.30 (1.04, 1.62)**	**1.24 (1.02, 1.52)**	**2.49 (1.41, 4.42)**	1.17 (0.93, 1.48)	1.25 (0.96, 1.61)
Urban	0.96 (0.89, 1.05)	1.05 (0.98, 1.13)	0.94 (0.88, 1.01)	0.98 (0.90, 1.07)	0.99 (0.93, 1.05)	0.97 (0.91, 1.03)
p-value for interaction	0.047	0.206	0.037	0.006	0.269	0.145
NDVI 1250m						
Tertile 1	1.01 (0.91, 1.11)	1.01 (0.93, 1.11)	0.96 (0.87, 1.06)	0.97 (0.87, 1.08)	0.99 (0.91, 1.07)	0.95 (0.89, 1.03)
Tertile 2	0.94 (0.83, 1.08)	1.11 (0.97, 1.28)	0.92 (0.83, 1.03)	0.96 (0.80, 1.16)	0.97 (0.87, 1.08)	1.01 (0.88, 1.16)
Tertile 3	1.00 (0.86, 1.16)	**1.19 (1.00, 1.42)**	1.05 (0.93, 1.18)	0.93 (0.71, 1.22)	0.97 (0.84, 1.13)	0.99 (0.85, 1.15)
p-value for interaction	0.714	0.197	0.266	0.971	0.965	0.742
Temperature						
Tertile 1	1.02 (0.90, 1.16)	1.07 (0.96, 1.20)	1.02 (0.91, 1.15)	1.02 (0.90, 1.15)	0.98 (0.91, 1.07)	0.94 (0.86, 1.03)
Tertile 2	1.00 (0.89, 1.13)	1.08 (0.98, 1.20)	1.00 (0.87, 1.14)	1.00 (0.86, 1.16)	0.97 (0.81, 1.16)	1.00 (0.91, 1.10)
Tertile 3	0.98 (0.86, 1.12)	1.05 (0.95, 1.16)	0.95 (0.86, 1.05)	1.01 (0.85, 1.21)	**1.22 (1.00, 1.48)**	1.04 (0.92, 1.18)
p-value for interaction	0.897	0.874	0.632	0.984	0.112	0.390
Sp. Humidity						
Tertile 1	0.99 (0.88, 1.11)	1.03 (0.93, 1.13)	1.00 (0.89, 1.12)	0.97 (0.86, 1.09)	0.98 (0.91, 1.07)	0.94 (0.86, 1.02)
Tertile 2	1.02 (0.88, 1.17)	1.05 (0.94, 1.18)	0.99 (0.84, 1.17)	0.99 (0.85, 1.15)	0.93 (0.77, 1.12)	0.98 (0.89, 1.08)
Tertile 3	1.07 (0.93, 1.23)	**1.19 (1.06, 1.34)**	1.02 (0.91, 1.14)	**1.32 (1.08, 1.61)**	**1.21 (1.01, 1.43)**	1.13 (0.99, 1.28)
p-value for interaction	0.659	0.122	0.964	0.013	0.069	0.045

Models adjusted for age, sex, race, age*race, education, BMI, alcohol use, smoking status, exercise, year of baseline, and urbanicity

Supplemental Table 1.1. Baseline characteristics of participants in the cohort by stroke event.

Characteristic	Total	Stroke	No Stroke
n	26,792	1,537	25,255
Age (yr)	64.6 (9.4)	68.8 (8.8)	64.4 (9.4)
Sex, Male (%)	11,925 (44.5)	757 (49.3)	11,168 (44.2)
BMI (kg/m^2)	29.3 (6.2)	29.2 (5.9)	29.3 (6.2)
Race, White (%)	16,003 (59.7)	898 (58.4)	15,105 (59.8)
Income			
<$20,000	4,539 (16.9)	312 (20.3)	4,227 (16.7)
$20,000 to $34,000	6,414 (23.9)	439 (28.6)	5,975 (23.7)
$35,000 to $74,000	8,186 (30.6)	442 (28.8)	7,744 (30.7)
≥$75,000	4,467 (16.7)	145 (9.4)	4,322 (17.1)
Refused	3,186 (11.9)	199 (13.0)	2,987 (11.8)
Education (%)			
Less than H.S.	3,096 (11.6)	222 (14.4)	2,874 (11.4)
H.S. graduate	6,865 (25.6)	440 (28.6)	6,425 (25.4)
Some College	7,239 (27.0)	405 (26.4)	6,834 (27.1)
College graduate	9,592 (35.8)	470 (30.6)	9,122 (36.1)
Diabetes (%)*	5,354 (20.7)	431 (28.8)	4,923 (20.2)
Hypertension (%)*	15,422 (57.6)	1,097 (71.5)	14,325 (56.8)
Previous CVD (%)*	4,428 (16.8)	395 (26.1)	4,033 (16.2)
Atrial fibrillation (%)*	2,153 (8.2)	198 (13.1)	1,955 (7.9)
Current Smoker (%)	3,778 (14.1)	221 (14.4)	3,557 (14.1)
Alcohol Use			
Current	14,141 (52.8)	729 (47.4)	13,412 (53.1)
Never	8,012 (29.9)	498 (32.4)	7,514 (29.8)
Past	4,639 (17.3)	310 (20.2)	4,329 (17.1)
Exercise (%)			
None	8,918 (33.3)	531 (34.6)	8,387 (33.2)
1-3 times/wk	9,833 (36.7)	542 (35.3)	9,291 (36.8)
≥ 4 times/wk	8,041 (30.0)	464 (30.2)	7,577 (30.0)
Urbanicity			
Rural (≤25%)	3,070 (11.5)	172 (11.2)	2,898 (11.5)
Mixed (25-75%)	2,813 (10.5)	170 (11.1)	2,643 (10.5)
Urban (≥75%)	20,909 (78.0)	1,195 (77.8)	19,714 (78.1)

* Missing participants (diabetes =917 participants; hypertension=38 participants; previous CVD= 452 participants; Atrial fibrillation= 555 participants).

Supplemental Table 1.2. Baseline characteristics of participants in the cohort by all EPA level I ecoregions.

Characteristic	EPA-5	EPA-6	EPA-7	EPA-8	EPA-9
n	114	81	171	22,222	1,675
Stroke event	5 (4.4)	5 (6.2)	6 (3.5)	1,292 (5.8)	98 (5.9)
Age (yr)	65.7 (9.8)	65.1 (9.4)	66.4 (9.6)	64.4 (9.3)	65.4 (9.0)
Sex, Male (%)	66 (57.9)	42 (51.9)	90 (52.6)	9,832 (44.2)	838 (50.0)
BMI (kg/m^2)	27.8 (5.2)	28.9 (5.9)	27.9 (4.8)	29.3 (6.2)	29.3 (6.0)
Race, White (%)	114 (100.0)	81 (100.0)	170 (99.4)	13,187 (59.3)	1,035 (61.8)
Income					
<$20,000	16 (14.0)	10 (12.4)	11 (6.4)	3,940 (17.7)	296 (17.7)
$20,000 to $34,000	37 (32.5)	15 (18.5)	35 (20.5)	5,391 (24.3)	418 (25.0)
$35,000 to $74,000	27 (23.7)	32 (39.5)	57 (33.3)	6,692 (30.1)	544 (32.5)
≥$75,000	18 (15.8)	16 (19.8)	52 (30.4)	3,547 (16.0)	230 (13.7)
Refused	16 (14.0)	8 (9.9)	16 (9.4)	2,652 (11.9)	187 (11.2)
Education (%)					
Less than H.S.	7 (6.1)	3 (3.7)	5 (2.9)	2,756 (12.4)	190 (11.3)
H.S. graduate	38 (33.3)	20 (24.7)	30 (17.5)	5,888 (26.5)	459 (27.4)
Some College	31 (27.2)	20 (24.7)	47 (27.5)	5,929 (26.7)	431 (25.7)
College graduate	38 (33.3)	38 (46.9)	89 (52.1)	7,649 (34.4)	595 (35.5)
Diabetes (%)*	7 (6.4)	6 (7.7)	17 (10.3)	4,567 (21.3)	305 (18.8)
Hypertension (%)*	58 (50.9)	34 (42.0)	70 (40.9)	12,967 (58.5)	948 (56.6)
Previous CVD (%)*	30 (26.8)	7 (8.6)	31 (18.6)	3,732 (17.1)	280 (17.0)
Atrial fibrillation (%)*	10 (8.9)	8 (9.9)	21 (12.7)	1,812 (8.3)	125 (7.6)
Current Smoker (%)	9 (7.9)	6 (7.4)	10 (5.9)	3,248 (14.6)	248 (14.8)
Alcohol Use					
Current	84 (73.7)	54 (66.7)	128 (74.9)	11,434 (51.5)	885 (52.8)
Never	16 (14.0)	20 (24.7)	28 (16.4)	6,894 (31.0)	474 (28.3)
Past	14 (12.3)	7 (8.6)	15 (8.8)	3,894 (17.5)	316 (18.9)
Exercise (%)					
None	33 (29.0)	17 (21.0)	50 (29.2)	7,466 (33.6)	533 (31.8)
1-3 times/wk	39 (34.2)	30 (37.0)	63 (36.8)	8,169 (36.8)	610 (36.4)
≥ 4 times/wk	42 (36.8)	34 (42.0)	58 (33.9)	6,587 (29.6)	532 (31.8)
Urbanicity					
Rural (≤25%)	58 (50.9)	25 (30.9)	11 (6.4)	2,782 (12.5)	135 (8.1)
Mixed (25-75%)	26 (22.8)	20 (24.7)	20 (11.7)	2,590 (11.7)	94 (5.6)
Urban (≥75%)	30 (26.3)	36 (44.4)	140 (81.9)	16,850 (75.8)	1,446 (86.3)

EPA-5, Northern Forests; EPA-6, Northwestern Forested Mountains; EPA-7, Marine West Coast Forest, EPA-8, Eastern Temperate Forests; EPA-9, Great Plains; EPA-10, North American Deserts; EPA-11, Mediterranean California, EPA; EPA-12, Southern Semiarid Highlands (n=1, not shown); EPA-13, Temperate Sierras; EPA-15, Tropical Wet Forests. * Missing participants (diabetes =917 participants; hypertension=38 participants; previous CVD= 452 participants; Atrial fibrillation= 555 participants).

Supplemental Table 1.2 continued. Baseline characteristics of participants in the cohort by EPA level I ecoregions.

Characteristic	EPA-10	EPA-11	EPA-13	EPA-15
n	262	2,014	7	245
Stroke event	13 (5.0)	99 (4.9)	0 (0.0)	18 (7.4)
Age (yr)	66.6 (9.4)	65.1 (10.1)	68.1 (6.7)	66.6 (9.7)
Sex, Male (%)	129 (49.2)	810 (40.2)	3 (42.9)	114 (46.5)
BMI (kg/m^2)	29.0 (6.3)	29.3 (6.3)	27.7 (4.5)	29.8 (6.8)
Race, White (%)	249 (95.0)	1,042 (51.7)	7 (100.0)	117 (47.8)
Income				
<$20,000	21 (8.0)	197 (9.8)	0 (0.0)	48 (19.6)
$20,000 to $34,000	46 (17.6)	397 (19.7)	3 (42.9)	72 (29.4)
$35,000 to $74,000	107 (40.8)	661 (32.8)	2 (28.6)	63 (25.7)
≥$75,000	55 (21.0)	520 (25.8)	1 (14.3)	28 (11.4)
Refused	33 (12.6)	239 (11.9)	1 (14.3)	34 (13.9)
Education (%)				
Less than H.S.	9 (3.4)	90 (4.5)	0 (0.0)	36 (14.7)
H.S. graduate	48 (18.3)	316 (15.7)	2 (28.6)	64 (26.1)
Some College	79 (30.2)	636 (31.6)	2 (28.6)	64 (26.1)
College graduate	126 (48.1)	972 (48.3)	3 (42.9)	81 (33.1)
Diabetes (%)	29 (11.3)	363 (18.8)	1 (14.3)	59 (24.8)
Hypertension (%)	122 (46.6)	1,077 (53.5)	3 (42.9)	143 (58.4)
Previous CVD (%)	45 (17.3)	262 (13.2)	1 (14.3)	39 (16.0)
Atrial fibrillation (%)	23 (8.9)	133 (6.7)	0 (0.0)	21 (8.6)
Current Smoker (%)	26 (9.9)	204 (10.1)	0 (0.0)	27 (11.0)
Alcohol Use				
Current	153 (58.4)	1,264 (62.8)	5 (71.4)	133 (54.3)
Never	72 (27.5)	450 (22.3)	2 (28.6)	56 (22.9)
Past	37 (14.1)	300 (14.9)	0 (0.0)	56 (22.9)
Exercise (%)				
None	76 (29.0)	655 (32.5)	1 (14.3)	87 (35.5)
1-3 times/wk	89 (34.0)	752 (37.3)	3 (42.9)	77 (31.4)
≥ 4 times/wk	97 (37.0)	607 (30.1)	3 (42.9)	81 (33.1)
Urbanicity				
Rural (≤25%)	21 (8.0)	36 (1.8)	2 (28.6)	0 (0.0)
Mixed (25-75%)	21 (8.0)	40 (10.1)	2 (28.6)	0 (0.0)
Urban (≥75%)	220 (84.0)	1,938 (96.2)	3 (42.9)	245 (100.0)

EPA-5, Northern Forests; EPA-6, Northwestern Forested Mountains; EPA-7, Marine West Coast Forest, EPA-8, Eastern Temperate Forests; EPA-9, Great Plains; EPA-10, North American Deserts; EPA-11, Mediterranean California, EPA; EPA-12, Southern Semiarid Highlands (n=1, not shown); EPA-13, Temperate Sierras; EPA-15, Tropical Wet Forests.

Supplemental Table 1.3. Baseline characteristics of participants in the cohort by EPA level II ecoregions located within the Level I Eastern Temperate Forests.

Characteristic	EPA-8.1	EPA-8.2	EPA-8.3	EPA-8.4	EPA-8.5
n	1,967	2,239	11,745	1,812	4,459
Stroke event	125 (6.4)	139 (6.2)	679 (5.8)	91 (5.0)	258 (5.8)
Age (yr)	65.0 (9.3)	64.7 (9.4)	64.1 (9.3)	65.0 (9.3)	64.7 (9.4)
Sex, Male (%)	934 (47.5)	1,033 (46.1)	5,102 (43.4)	802 (44.3)	1,961 (44.0)
BMI (kg/m^2)	29.1 (6.2)	29.7 (6.3)	29.4 (6.2)	28.8 (5.7)	29.4 (6.2)
Race, White (%)	1,157 (58.8)	874 (39.0)	6,924 (59.0)	1,345 (74.2)	2,887 (64.8)
Income					
<$20,000	321 (16.3)	405 (18.1)	2,069 (17.6)	326 (18.0)	819 (18.4)
$20,000 to $34,000	477 (24.3)	588 (26.3)	2,802 (23.9)	477 (26.3)	1,047 (23.5)
$35,000 to $74,000	602 (30.6)	649 (29.0)	3,582 (30.5)	542 (29.9)	1,317 (29.5)
≥$75,000	322 (16.4)	333 (14.9)	1,904 (16.2)	250 (13.8)	738 (16.6)
Refused	245 (12.5)	264 (11.8)	1,388 (11.8)	217 (12.0)	538 (12.1)
Education (%)					
Less than H.S.	196 (10.0)	282 (12.6)	1,489 (12.7)	190 (10.5)	599 (13.4)
H.S. graduate	535 (27.2)	619 (27.7)	3,060 (26.1)	528 (29.1)	1,146 (25.7)
Some College	508 (25.8)	654 (29.2)	3,141 (26.7)	491 (27.1)	1,135 (25.5)
College graduate	728 (37.0)	684 (30.6)	4,055 (34.5)	603 (33.3)	1,579 (35.4)
Diabetes (%)*	375 (19.8)	450 (20.8)	2,471 (21.8)	336 (19.2)	935 (21.7)
Hypertension (%)*	1,120 (57.1)	1,353 (60.6)	6,898 (58.8)	1,000 (55.2)	2,596 (58.3)
Previous CVD (%)*	319 (16.5)	385 (17.5)	1,911 (16.6)	304 (17.0)	813 (18.5)
Atrial fibrillation (%)*	157 (8.1)	170 (7.8)	949 (8.3)	142 (8.0)	394 (9.0)
Current Smoker (%)	294 (15.0)	374 (16.7)	1,704 (14.5)	268 (14.8)	608 (13.6)
Alcohol Use					
Current	1,209 (61.5)	1,282 (57.3)	5,678 (48.3)	853 (47.1)	2,412 (54.1)
Never	410 (20.8)	548 (24.5)	4,004 (34.1)	635 (35.0)	1,297 (29.1)
Past	348 (17.7)	409 (18.3)	2,063 (17.6)	324 (17.9)	750 (16.8)
Exercise (%)					
None	671 (34.1)	827 (36.9)	3,969 (33.8)	565 (31.2)	1,434 (32.2)
1-3 times/wk	715 (36.4)	839 (37.5)	4,268 (36.3)	715 (39.5)	1,632 (36.6)
≥ 4 times/wk	581 (29.5)	573 (25.6)	3,508 (29.9)	532 (29.4)	1,393 (31.2)
Urbanicity					
Rural (≤25%)	145 (7.4)	51 (2.3)	1,619 (13.8)	281 (15.5)	686 (15.4)
Mixed (25-75%)	129 (6.6)	51 (2.3)	1,617 (13.8)	259 (14.3)	534 (12.0)
Urban (≥75%)	1,693 (86.1)	2,137 (95.4)	8,509 (72.5)	1,272 (70.2)	3,239 (72.6)

EPA-8.1, Mixed Wood Plains; EPA-8.2, Central USA Plains; EPA-8.3, Southeastern USA Plains, EPA-8.4, Ozark/Ouachita-Appalachian Forests; EPA-8.5, Mississippi Alluvial and Southeast USA Coastal Plains. * Missing participants (diabetes =917 participants; hypertension=38 participants; previous CVD= 452 participants; Atrial fibrillation= 555 participants).

Supplemental Table 1.4**.** Mean and standard deviations of pollutants by EPA level I ecoregion.

Pollutant, 1-year	**Total (n=26,792)**	**EPA-8 (n=22,223)**	**EPA-9 (n=1,675)**	**EPA-11 (n=2,014)**	**EPA-0 (n=881)**
$PM_{2.5}$ (μg/m^3)	12.63 (2.35)	12.84 (1.92)	10.85 (1.84)	13.84 (3.88)	8.04 (1.63)
PM_{10} (μg/m^3)	20.90 (4.96)	20.13 (3.76)	23.15 (3.25)	28.25 (8.57)	19.22 (7.21)
O_3 (ppb)	48.81 (5.15)	48.92 (4.77)	48.58 (4.83)	50.41 (3.37)	42.91 (11.00)
NO_2 (ppb)	11.22 (5.97)	10.60 (5.51)	10.83 (3.81)	18.63 (7.65)	10.69 (4.49)
SO_2 (ppb)	2.95 (1.33)	3.13 (1.36)	2.24 (0.59)	2.07 (0.62)	1.76 (0.74)
CO (ppm)	0.41 (0.11)	0.39 (0.09)	0.39 (0.08)	0.56 (0.18)	0.46 (0.12)
Pollutant, 3-year	**Total**	**EPA-8**	**EPA-9**	**EPA-11**	**EPA-0**
$PM_{2.5}$ (μg/m^3)	12.83 (2.44)	12.99 (1.91)	10.79 (1.68)	14.86 (4.30)	8.17 (1.59)
PM_{10} (μg/m^3)	20.93 (5.00)	20.09 (3.60)	23.03 (2.81)	29.06 (9.10)	19.39 (7.06)
O_3 (ppb)	49.42 (4.81)	49.64 (4.34)	48.51 (4.71)	50.58 (2.85)	42.83 (10.88)
NO_2 (ppb)	11.63 (6.11)	10.96 (5.57)	11.17 (3.88)	19.62 (7.94)	11.23 (4.52)
SO_2 (ppb)	3.03 (1.32)	3.23 (1.35)	2.28 (0.55)	2.07 (0.53)	1.85 (0.74)
CO (ppm)	0.41 (0.12)	0.39 (0.09)	0.41 (0.07)	0.61 (0.21)	0.47 (0.11)

Supplemental Table 1.5. Estimated HRs and 95% CIs for stroke by quartiles of pollutant levels in the REGARDS cohort (n=26,792).

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
$PM_{2.5}$, range (μg/m^3)					-
1-year	1 (ref)	0.97 (0.83, 1.12)	0.97 (0.83, 1.14)	0.96 (0.81, 1.13)	0.670
3-year	1 (ref)	0.99 (0.85, 1.15)	1.02 (0.87, 1.19)	0.98 (0.83, 1.16)	0.908
PM_{10}, range (μg/m^3)					-
1-year	1 (ref)	1.04 (0.90, 1.21)	**1.21 (1.04, 1.41)**	**1.21 (1.03, 1.43)**	0.005
3-year	1 (ref)	1.03 (0.88, 1.19)	1.10 (0.95, 1.29)	1.14 (0.97, 1.34)	0.072
O_3, range (ppb)					-
1-year	1 (ref)	1.04 (0.90, 1.20)	1.05 (0.91, 1.21)	0.97 (0.84, 1.13)	0.749
3-year	1 (ref)	0.97 (0.84, 1.12)	0.91 (0.79, 1.06)	0.87 (0.75, 1.01)	0.047
NO_2, range (ppb)					-
1-year	1 (ref)	1.17 (0.99, 1.38)	1.13 (0.94, 1.36)	1.11 (0.91, 1.36)	0.552
3-year	1 (ref)	1.14 (0.97, 1.35)	1.04 (0.86, 1.26)	1.10 (0.90, 1.34)	0.673
SO_2, range (ppb)					-
1-year	1 (ref)	1.13 (0.97, 1.31)	1.16 (0.99, 1.35)	1.13 (0.96, 1.33)	0.159
3-year	1 (ref)	1.10 (0.94, 1.27)	1.06 (0.90, 1.24)	1.13 (0.96, 1.33)	0.233
CO, range (ppm)					-
1-year	1 (ref)	0.99 (0.86, 1.15)	1.02 (0.88, 1.19)	1.01 (0.86, 1.18)	0.831
3-year	1 (ref)	1.02 (0.87, 1.18)	1.02 (0.87, 1.20)	1.03 (0.86, 1.22)	0.763

Models adjusted for age, sex, race, age*race, education, BMI, alcohol use, smoking status, exercise, year of baseline, urbanicity, and ecoregion.

Supplemental Table 1.6. Single pollutant and multipollutant estimated HRs 95% and 95% CIs for stroke associated with an IQR increase in 3-year pollutant levels for the full model (n=26,792).

3-year	$PM_{2.5}$	PM_{10}	O_3	NO_2	SO_2	CO
Single Pollutant	0.99 (0.91, 1.07)	1.05 (0.98, 1.12)	**0.93 (0.87, 1.00)**	0.98 (0.90, 1.07)	0.99 (0.93, 1.06)	0.97 (0.91, 1.03)
+NDVI, 1250m	0.98 (0.91, 1.06)	1.05 (0.98, 1.13)	0.93 (0.87, 1.00)	0.96 (0.86, 1.07)	0.99 (0.92, 1.06)	0.96 (0.90, 1.02)
+Temperature	0.99 (0.92, 1.07)	1.05 (0.98, 1.12)	0.93 (0.87, 1.00)	1.00 (0.90, 1.10)	1.01 (0.94, 1.08)	0.97 (0.91, 1.03)
+Sp. Humidity	1.00 (0.92, 1.08)	1.05 (0.98, 1.12)	0.94 (0.87, 1.02)	1.01 (0.92, 1.12)	1.02 (0.95, 1.09)	0.97 (0.92, 1.03)
+$PM_{2.5}$	-	**1.10 (1.01, 1.19)**	**0.92 (0.85, 1.00)**	0.99 (0.89, 1.10)	1.00 (0.93, 1.07)	0.96 (0.90, 1.03)
+PM_{10}	0.92 (0.83, 1.02)	-	**0.93 (0.86, 1.00)**	0.93 (0.84, 1.03)	0.98 (0.92, 1.05)	0.93 (0.87, 0.99)
+ O_3	1.02 (0.94, 1.11)	1.05 (0.99, 1.12)	-	0.99 (0.91, 1.08)	1.01 (0.95, 1.08)	0.97 (0.91, 1.02)
+NO_2	0.99 (0.91, 1.09)	1.08 (1.00, 1.16)	0.93 (0.87, 1.00)	-	1.00 (0.93, 1.08)	0.94 (0.87, 1.03)
+SO_2	0.99 (0.91, 1.07)	1.05 (0.98, 1.12)	**0.93 (0.86, 1.00)**	0.98 (0.88, 1.10)	-	0.96 (0.90, 1.03)
+CO	1.01 (0.93, 1.10)	**1.09 (1.01, 1.17)**	**0.93 (0.86, 1.00)**	1.05 (0.92, 1.19)	1.01 (0.94, 1.08)	-

Models adjusted for age, sex, race, age*race, education, BMI, alcohol use, smoking status, exercise, year of baseline, urbanicity, and ecoregion.

Supplemental Table 1.7. Estimated HRs and 95% CIs for stroke associated with an IQR increase in 3-year pollutant levels, stratified by EPA level I ecoregions.

Exposure (IQR)	EPA-8	EPA-9	EPA-11	Interaction p-value
n	22,222	1,675	2,014	
No. of cases	1,292	98	99	
$PM_{2.5}$				
3-year (2.88)	1.02 (0.93, 1.13)	**1.61 (1.03, 2.53)**	0.89 (0.75, 1.05)	0.009
PM_{10}				
3-year (5.03)	**1.13 (1.04, 1.23)**	0.97 (0.66, 1.41)	0.94 (0.83, 1.06)	0.012
O_3				
3-year (6.64)	0.95 (0.87, 1.04)	0.82 (0.62, 1.08)	0.59 (0.34, 1.01)	0.157
NO_2				
3-year (7.76)	1.01 (0.91, 1.11)	0.96 (0.60, 1.54)	0.88 (0.69, 1.13)	0.160
SO_2				
3-year (1.45)	0.99 (0.93, 1.06)	1.30 (0.79, 2.15)	0.72 (0.40, 1.31)	0.115
CO				
3-year (0.11)	0.98 (0.91, 1.06)	0.72 (0.51, 1.01)	0.97 (0.85, 1.11)	0.437

Models adjusted for age, sex, race, age*race, education, BMI, alcohol use, smoking status, exercise, year of baseline, and urbanicity. EPA-8, Eastern Temperate Forests; EPA-9, Great Plains; EPA-11, Mediterranean California.

Table 2.1. Baseline characteristics of participants in the cohort by tertiles of average NDVI within 250-m buffers from 2003 to 2008 (n=27,369).

Characteristic	Total	NDVI Tertile 1 (0.04-0.46)	NDVI Tertile 2 (0.46-0.57)	NDVI Tertile 3 (0.57-0.85)
n	27,369	9,123	9,123	9,123
Stroke event	1,581 (5.8)	521 (5.7)	582 (6.4)	478 (5.2)
Median Follow-up (yr)	12.02	11.78	11.87	12.34
Age (yr)	64.6 (9.4)	65.3 (9.6)	64.6 (9.4)	64.1 (9.1)
Sex, Male (%)	12,195 (44.6)	3,968 (43.5)	4,098 (44.9)	4,129 (45.3)
BMI (kg/m^2)	29.3 (6.2)	29.6 (6.4)	29.5 (6.2)	28.9 (6.0)
Race, White (%)	16,332 (59.7)	4,390 (48.1)	5,395 (59.1)	6,547 (71.8)
Income (%)				
<$20,000	4,670 (17.1)	1,751 (19.2)	1,608 (17.6)	1,311 (14.4)
$20,000 to $34,000	6,555 (24.0)	2,246 (24.6)	2,230 (24.4)	2,079 (22.8)
$35,000 to $74,000	8,316 (30.4)	2,671 (29.3)	2,830 (31.0)	2,815 (30.9)
≥$75,000	4,530 (16.6)	1,378 (15.1)	1,391 (15.3)	1,761 (19.3)
Refused	3,298 (12.1)	1,077 (11.8)	1,064 (11.7)	1,157 (12.7)
Education (%)				
Less than H.S.	3,195 (11.7)	1,088 (11.9)	1,136 (12.5)	971 (10.6)
H.S. graduate	7,033 (25.7)	2,310 (25.3)	2,389 (26.2)	2,334 (25.6)
Some College	7,373 (26.9)	2,587 (28.4)	2,426 (26.6)	2,360 (25.9)
College graduate	9,768 (35.7)	3,138 (34.4)	3,172 (34.8)	3,458 (37.9)
Diabetes (%)	5,512 (20.9)	1,888 (21.6)	1,878 (21.3)	1,746 (19.8)
Hypertension (%)	15,765 (57.8)	5,381 (59.1)	5,318 (58.5)	5,066 (55.7)
Previous CVD (%)	4,529 (16.8)	1,470 (16.4)	1,539 (17.2)	1,520 (17.0)
Atrial fibrillation (%)	2,211 (8.3)	725 (8.1)	733 (8.2)	753 (8.4)
Current Smoker (%)	3,860 (14.1)	1,391 (15.3)	1,269 (13.9)	1,200 (13.2)
Exercise (%)				
None	9,011 (33.4)	3,225 (35.9)	3,013 (33.5)	2,773 (30.9)
1-3 times/wk	9,888 (36.7)	3,229 (35.9)	3,254 (36.2)	3,405 (37.9)
≥ 4 times/wk	8,080 (30.0)	2,541 (28.3)	2,732 (30.4)	2,807 (31.2)
Area Deprivation Index	61.7 (28.9)	56.3 (32.3)	66.8 (26.7)	62.2 (26.4)
Urbanicity				
Rural (≤25%)	3,139 (11.5)	328 (3.6)	679 (7.4)	2,132 (23.4)
Mixed (25-75%)	2,874 (10.5)	296 (3.2)	949 (10.4)	1,629 (17.9)
Urban (≥75%)	21,356 (78.0)	8,499 (93.2)	7,495 (82.2)	5,362 (58.8)
$PM_{2.5}$ ($\mu g/m^3$)	12.6 (2.3)	13.0 (2.9)	12.7 (2.0)	12.2 (1.9)

Table 2.2. Summary statistics and Pearson correlations between NDVI and EVI at different radii.

Greenness		Mean (SD)	Median (IQR)	NDVI			EVI		
				250m	500m	1250m	250m	500m	1250m
NDVI	250m	0.50 (0.12)	0.52 (0.17)	1	0.987	0.922	0.965	0.952	0.888
	500m	0.50 (0.12)	0.52 (0.17)	0.987	1	0.956	0.956	0.968	0.924
	1,250m	0.49 (0.12)	0.51 (0.17)	0.922	0.956	1	0.893	0.927	0.972
EVI	250m	0.30 (0.07)	0.32 (0.10)	0.965	0.956	0.893	1	0.986	0.915
	500m	0.30 (0.07)	0.31 (0.10)	0.952	0.968	0.927	0.986	1	0.952
	1,250m	0.29 (0.07)	0.31 (0.10)	0.888	0.924	0.972	0.915	0.952	1

250m represents averaged values in a 250m buffer around residence; 500m represents averaged values in a 500m buffer around residence;1,250m represents averaged values in a 1,250m buffer around residence.

Table 2.3. Hazard ratios and 95% confidence intervals for greenness and stroke in the REGARDS study.

Exposure Metric	250-meter buffer		1,250-meter buffer	
	Model 1	**Model 2**	**Model 1**	**Model 2**
NDVI				
Continuous	0.989 (0.946, 1.033)	0.992 (0.949, 1.037)	0.983 (0.939, 1.029)	0.986 (0.942, 1.033)
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	1.112 (0.985, 1.256)	1.122 (0.993, 1.267)	1.018 (0.901, 1.149)	1.026 (0.908, 1.158)
Tertile 3	0.933 (0.816, 1.068)	0.943 (0.824, 1.079)	0.882 (0.769, 1.011)	0.889 (0.775, 1.020)
p for trend	0.352	0.437	0.087	0.114
EVI				
Continuous	0.990 (0.918, 1.068)	0.996 (0.923, 1.075)	0.982 (0.907, 1.063)	0.989 (0.913, 1.070)
Tertile 1	Reference	Reference	Reference	Reference
Tertile 2	1.085 (0.961, 1.225)	1.094 (0.969, 1.236)	1.046 (0.925, 1.183)	1.056 (0.934, 1.194)
Tertile 3	0.897 (0.783, 1.028)	0.908 (0.792, 1.041)	0.934 (0.813, 1.073)	0.941 (0.819, 1.082)
p for trend	0.148	0.203	0.388	0.459

Model 1 was adjusted for age, sex, race, age*race, education, urbanicity, and ADI. Model 2 was adjusted for covariates in model 1 and smoking status, and average 1-year baseline $PM_{2.5}$. Continuous hazard ratios are presented for a 0.1 difference in NDVI or EVI.

Table 2.4. Hazard ratios and 95% confidence intervals for greenness and stroke stratified by stroke region in the REGARDS study.

	Stroke belt (n=9,489)	Stroke buckle (n=5,756)	Non-belt (n=12,124)	p-value for interaction
NDVI 250m, mean (SD)	0.57 (0.08)	0.57 (0.08)	0.42 (0.12)	
Model 1	0.883 (0.796, 0.980)	0.990 (0.856, 1.146)	1.014 (0.948, 1.085)	0.063
Model 2	0.883 (0.796, 0.980)	0.996 (0.858, 1.156)	1.022 (0.954, 1.094)	0.060
NDVI 1250m, mean (SD)	0.56 (0.08)	0.57 (0.08)	0.41 (0.12)	
Model 1	0.865 (0.778, 0.962)	0.940 (0.812, 1.089)	1.021 (0.952, 1.095)	0.026
Model 2	0.864 (0.778, 0.961)	0.948 (0.818, 1.098)	1.028 (0.958, 1.104)	0.026
EVI 250m, mean (SD)	0.34 (0.05)	0.33 (0.05)	0.25 (0.08)	
Model 1	0.842 (0.703, 1.009)	1.006 (0.783, 1.294)	1.018 (0.914, 1.134)	0.182
Model 2	0.830 (0.693, 0.995)	1.020 (0.788, 1.321)	1.031 (0.924, 1.151)	0.171
EVI 1250m, Mean (SD)	0.33 (0.05)	0.33 (0.05)	0.25 (0.07)	
Model 1	0.811 (0.672, 0.979)	0.880 (0.686, 1.127)	1.041 (0.929, 1.166)	0.056
Model 2	0.799 (0.662, 0.963)	0.895 (0.698, 1.149)	1.053 (0.939, 1.181)	0.055

Model 1 was adjusted for age, sex, race, age*race, education, urbanicity, and ADI. Model 2 was adjusted for covariates in model 1 and smoking status, and average 1-year baseline $PM_{2.5}$. Hazard ratios are presented for a 0.1 difference in NDVI or EVI. P-values for interaction were estimated by including a region*greenness interaction term in the model. 250m represents averaged values in a 250m buffer around residence; 1,250m represents averaged values in a 1,250m buffer around residence.

Table 2.5. Estimated HRs 95% and CIs for stroke associated with a 0.1 increase in greenness, stratified by EPA level I ecoregions.

Characteristic	EPA-8	EPA-9	EPA-11	P-value
n	22,699	1,714	2,056	
No. of cases	1,330	100	103	
NDVI 250m, mean (SD)	0.53 (0.11)	0.45 (0.09)	0.32 (0.10)	
Model 1	0.946 (0.898,0.997)	1.442 (1.124,1.849)	1.327 (1.058,1.664)	<0.001
Model 2	0.950 (0.901,1.002)	1.405 (1.083,1.822)	1.309 (1.013,1.692)	<0.001
NDVI 1,250m, mean (SD)	0.52 (0.11)	0.44 (0.08)	0.32 (0.10)	
Model 1	0.937 (0.888,0.989)	1.432 (1.104,1.857)	1.358 (1.085,1.700)	<0.001
Model 2	0.941 (0.891,0.994)	1.387 (1.057,1.822)	1.349 (1.036,1.757)	<0.001
EVI 250m, mean (SD)	0.31 (0.07)	0.29 (0.06)	0.19 (0.06)	
Model 1	0.924 (0.846,1.009)	1.768 (1.200,2.605)	1.766 (1.173,2.659)	<0.001
Model 2	0.931 (0.851,1.018)	1.697 (1.130,2.549)	1.727 (1.123,2.655)	<0.001
EVI 1,250m, mean (SD)	0.31 (0.07)	0.28 (0.05)	0.18 (0.06)	
Model 1	0.909 (0.829,0.996)	1.790 (1.188,2.698)	1.878 (1.229,2.870)	<0.001
Model 2	0.916 (0.835,1.005)	1.707 (1.108,2.630)	1.831 (1.155,2.903)	<0.001

Model 1 was adjusted for age, sex, race, age*race, education, urbanicity, and area deprivation index. Model 2 was adjusted for covariates in model 1 and smoking status, and average 1-year baseline $PM_{2.5}$. EPA-8, Eastern Temperate Forests; EPA-9, Great Plains; EPA-11, Mediterranean California. P-values for interaction were estimated by including an ecoregion*greenness interaction term in the model. 250m represents averaged values in a 250m buffer around residence; 1,250m represents averaged values in a 1,250m buffer around residence.

Table 2.6. Estimated HRs 95% and CIs for stroke associated with a 0.1 increase in greenness, stratified by EPA level II ecoregions located within the level I Eastern Temperate Forests.

Characteristic	EPA-8.1	EPA-8.2	EPA-8.3	EPA-8.4	EPA-8.5
n	2,004	2,289	11,994	1,840	4,572
No. of cases	128	141	702	91	268
NDVI 250m, mean (SD)	0.41 (0.12)	0.40 (0.08)	0.56 (0.09)	0.56 (0.09)	0.54 (0.11)
Model 1	0.981(0.823,1.169)	0.806(0.651,0.999)	0.941(0.862,1.027)	0.911(0.708,1.173)	0.937(0.830,1.059)
Model 2	1.004(0.837,1.204)	0.809(0.653,1.003)	0.944(0.862,1.032)	0.893(0.692,1.153)	0.979(0.861,1.113)
NDVI 1,250m, mean (SD)	0.40 (0.11)	0.39 (0.08)	0.55 (0.09)	0.55 (0.09)	0.52 (0.11)
Model 1	0.970(0.812,1.158)	0.839(0.670,1.050)	0.928(0.843,1.022)	0.818(0.627,1.067)	0.944(0.840,1.061)
Model 2	0.993(0.827,1.192)	0.840(0.671,1.050)	0.929(0.841,1.027)	0.792(0.605,1.036)	0.973(0.863,1.099)
EVI 250m, mean (SD)	0.24 (0.08)	0.25 (0.06)	0.33 (0.05)	0.33 (0.06)	0.32 (0.06)
Model 1	0.999(0.763,1.307)	0.683(0.498,0.936)	0.948(0.815,1.102)	0.814(0.553,1.198)	0.890(0.730,1.086)
Model 2	1.037(0.789,1.369)	0.687(0.500,0.942)	0.957(0.819,1.118)	0.788(0.534,1.163)	0.954(0.774,1.176)
EVI 1,250m, mean (SD)	0.24 (0.08)	0.24 (0.05)	0.33 (0.05)	0.33 (0.05)	0.31 (0.07)
Model 1	0.981(0.743,1.295)	0.744(0.532,1.041)	0.935(0.790,1.107)	0.678(0.447,1.029)	0.889(0.734,1.077)
Model 2	1.018(0.765,1.355)	0.746(0.533,1.042)	0.944(0.791,1.126)	0.635(0.416,0.970)	0.931(0.764,1.134)

Model 1 was adjusted for age, sex, race, age*race, education, urbanicity, and area deprivation index. Model 2 was adjusted for covariates in model 1 and smoking status, and average 1-year baseline $PM_{2.5}$. EPA-8.1, Mixed Wood Plains; EPA-8.2, Central USA Plains; EPA-8.3, Southeastern USA Plains, EPA-8.4, Ozark/Ouachita-Appalachian Forests; EPA-8.5, Mississippi Alluvial and Southeast USA Coastal Plains. 250m represents averaged values in a 250m buffer around residence; 1,250m represents averaged values in a 1,250m buffer around residence.

Table 2.7. Estimated HRs 95% and CIs for stroke associated with a 0.1 increase in greenness by stratified variable.

Characteristic	NDVI		EVI	
	250-m buffer	**1,250-m buffer**	**250-m buffer**	**1,250-m buffer**
Specific Humidity				
Tertile 1	1.056 (0.979, 1.139)	1.052 (0.973, 1.137)	1.084 (0.962, 1.221)	1.088 (0.960, 1.232)
Tertile 2	0.959 (0.887, 1.038)	0.974 (0.897, 1.056)	0.928 (0.810, 1.063)	0.964 (0.836, 1.112)
Tertile 3	0.939 (0.857, 1.028)	0.914 (0.837, 0.998)	0.922 (0.782, 1.088)	0.859 (0.735, 1.004)
p-value for interaction	0.086	0.055	0.138	0.059
Precipitation				
Tertile 1	1.041 (0.968, 1.119)	1.055 (0.979, 1.136)	1.070 (0.947, 1.210)	1.102 (0.971, 1.252)
Tertile 2	0.965 (0.874, 1.065)	0.945 (0.853, 1.046)	0.964 (0.813, 1.143)	0.930 (0.780, 1.110)
Tertile 3	0.937 (0.870, 1.010)	0.918 (0.852, 0.990)	0.917 (0.811, 1.036)	0.886 (0.783, 1.003)
p-value for interaction	0.112	0.021	0.181	0.034

Hazard ratios are adjusted for age, sex, race, age*race, education, urbanicity, and ADI. 250-m represents averaged values in a 250-m buffer around residence; 1,250-m represents averaged values in a 1,250-m buffer around residence.

Supplemental Table 2.1. Baseline characteristics of participants in the cohort by EPA level I ecoregions.

Characteristic	Total	EPA-8	EPA-9	EPA-11	EPA-0
n	27,369	22,699	1,714	2,056	900
Stroke event	1,581 (5.8)	1,330 (5.9)	100 (5.8)	103 (5.0)	48 (5.3)
Age (yr)	64.6 (9.4)	64.5 (9.3)	65.4 (9.0)	65.2 (10.1)	66.3 (9.6)
Sex, Male (%)	12,195 (44.6)	10,048 (44.3)	857 (50.0)	834 (40.6)	456 (50.7)
BMI (kg/m^2)	29.3 (6.2)	29.3 (6.2)	29.4 (6.1)	29.3 (6.3)	28.8 (6.0)
Race, White (%)	16,332 (59.7)	13,458 (59.3)	1,054 (61.5)	1,065 (51.8)	755 (83.9)
Income (%)					
<$20,000	4,670 (17.1)	4,054 (17.9)	305 (17.8)	201 (9.8)	110 (12.2)
$20,000 to $34,000	6,555 (24.0)	5,508 (24.3)	426 (24.9)	407 (19.8)	214 (23.8)
$35,000 to $74,000	8,316 (30.4)	6,798 (30.0)	551 (32.2)	675 (32.8)	292 (32.4)
≥$75,000	4,530 (16.6)	3,592 (15.8)	237 (13.8)	527 (25.6)	174 (19.3)
Refused	3,298 (12.1)	2,747 (12.1)	195 (11.4)	246 (12.0)	110 (12.2)
Education (%)					
Less than H.S.	3,195 (11.7)	2,847 (12.5)	195 (11.4)	90 (4.4)	63 (7.0)
H.S. graduate	7,033 (25.7)	6,028 (26.6)	471 (27.5)	326 (15.9)	208 (23.1)
Some College	7,373 (26.9)	6,036 (26.6)	440 (25.7)	648 (31.5)	249 (27.7)
College graduate	9,768 (35.7)	7,788 (34.3)	608 (35.5)	992 (48.3)	380 (42.2)
Diabetes (%)	5,512 (20.9)	4,698 (21.5)	317 (19.0)	373 (18.9)	124 (14.2)
Hypertension (%)	15,765 (57.8)	13,253 (58.6)	975 (57.0)	1,097 (53.3)	440 (48.9)
Previous CVD (%)	4,529 (16.8)	3,816 (17.1)	290 (17.2)	267 (13.2)	156 (17.5)
Atrial fibrillation (%)	2,211 (8.3)	1,864 (8.4)	129 (7.7)	135 (6.7)	83 (9.3)
Current Smoker (%)	3,860 (14.1)	3,319 (14.6)	256 (14.9)	206 (10.0)	79 (8.8)
Exercise (%)					
None	9,011 (33.4)	7,546 (33.7)	536 (31.8)	662 (32.6)	267 (30.1)
1-3 times/wk	9,888 (36.7)	8,214 (36.7)	613 (36.4)	757 (37.3)	304 (34.3)
≥ 4 times/wk	8,080 (30.0)	6,621 (29.6)	535 (31.8)	609 (30.0)	315 (35.6)
Area Deprivation Index	61.7 (28.9)	65.6 (26.9)	67.8 (25.9)	20.6 (16.3)	46.5 (26.1)
Urbanicity					
Rural (≤25%)	3,139 (11.5)	2,843 (12.5)	138 (8.1)	37 (1.8)	121 (13.4)
Mixed (25-75%)	2,874 (10.5)	2,647 (11.7)	95 (5.5)	42 (2.0)	90 (10.0)
Urban (≥75%)	21,356 (78.0)	17,209 (75.8)	1,481 (86.4)	1,977 (96.2)	689 (76.6)
$PM_{2.5}$ ($\mu g/m^3$)	12.6 (2.3)	12.8 (1.9)	10.9 (1.8)	13.8 (3.9)	8.1 (1.6)

EPA-8, Eastern Temperate Forests; EPA-9, Great Plains; EPA-11, Mediterranean California, EPA-0, "Other" (EPA-5, Northern Forests; EPA-6, Northwestern Forested Mountains; EPA-10, North American Deserts).

Supplemental Table 2.2. Hazard ratios and 95% confidence intervals for greenness within a 500-m buffer and stroke in the REGARDS study.

Exposure Metric	**500-meter buffer**	
	Model 1	**Model 2**
NDVI		
Continuous	0.990 (0.946, 1.035)	0.993 (0.949, 1.039)
Tertile 1	Reference	Reference
Tertile 2	1.155 (1.023, 1.304)	1.165 (1.032, 1.315)
Tertile 3	0.925 (0.808, 1.060)	0.935 (0.816, 1.071)
p for trend	0.317	0.398
EVI		
Continuous	0.990 (0.917, 1.069)	0.997 (0.923, 1.077)
Tertile 1	Reference	Reference
Tertile 2	1.059 (0.937, 1.197)	1.070 (0.947, 1.209)
Tertile 3	0.923 (0.806, 1.058)	0.933 (0.814, 1.069)
p for trend	0.287	0.365

Model 1 was adjusted for age, sex, race, age*race, education, urbanicity, and ADI. Model 2 was adjusted for covariates in model 1 and smoking status, and average 1-year baseline $PM_{2.5}$.

Supplemental Table 2.3. Estimated HRs and 95% CIs for stroke associated with 0.1 increase in greenness within a 500-m buffer, stratified by EPA level I ecoregions.

Characteristic	EPA-8	EPA-9	EPA-11	P-value
n	22,699	1,714	2,056	
No. of cases	1,330	100	103	
NDVI 500-m, mean (SD)	0.52 (0.11)	0.45 (0.08)	0.32 (0.10)	
Model 1	0.948 (0.899,0.999)	1.423 (1.105,1.833)	1.345 (1.072,1.688)	<0.001
Model 2	0.952 (0.902,1.004)	1.384 (1.062,1.803)	1.331 (1.026,1.726)	<0.001
EVI 500-m, mean (SD)	0.31 (0.07)	0.29 (0.06)	0.19 (0.06)	
Model 1	0.924 (0.845,1.010)	1.736 (1.168,2.581)	1.810 (1.199,2.731)	<0.001
Model 2	0.931 (0.851,1.019)	1.660 (1.095,2.519)	1.763 (1.140,2.725)	<0.001

Model 1 was adjusted for age, sex, race, age*race, education, urbanicity, and area deprivation index. Model 2 was adjusted for covariates in model 1 and smoking status, and average 1-year baseline $PM_{2.5}$. EPA-8, Eastern Temperate Forests; EPA-9, Great Plains; EPA-11, Mediterranean California. P-values for interaction were estimated by including an ecoregion*greenness interaction term in the model.

Supplemental Table 2.4. Estimated HRs and 95% CIs for stroke associated with a 0.1 increase in greenness within a 500-m buffer, stratified by EPA level II ecoregions located within the Level I Eastern Temperate Forests.

Characteristic	EPA-8.1	EPA-8.2	EPA-8.3	EPA-8.4	EPA-8.5
n	2,004	2,289	11,994	1,840	4,572
No. of cases	128	141	702	91	268
NDVI 500m, mean (SD)	0.40 (0.12)	0.40 (0.08)	0.56 (0.09)	0.55 (0.09)	0.53 (0.11)
Model 1	0.975(0.819,1.161)	0.824(0.662,1.025)	0.935(0.856,1.022)	0.891(0.694,1.145)	0.963(0.852,1.088)
Model 2	0.998(0.833,1.195)	0.826(0.664,1.028)	0.937(0.855,1.027)	0.876(0.681,1.126)	1.004(0.883,1.141)
EVI 500m, mean (SD)	0.24 (0.08)	0.24 (0.06)	0.33 (0.05)	0.33 (0.06)	0.32 (0.06)
Model 1	0.989(0.756,1.294)	0.712(0.516,0.985)	0.931(0.798,1.086)	0.777(0.529,1.143)	0.928(0.759,1.135)
Model 2	1.027(0.778,1.356)	0.716(0.518,0.990)	0.939(0.800,1.100)	0.753(0.512,1.107)	0.991(0.803,1.223)

Model 1 was adjusted for age, sex, race, age*race, education, urbanicity, and area deprivation index. Model 2 was adjusted for covariates in model 1 and smoking status, and average 1-year baseline $PM_{2.5}$. EPA-8.1, Mixed Wood Plains; EPA-8.2, Central USA Plains; EPA-8.3, Southeastern USA Plains, EPA-8.4, Ozark/Ouachita-Appalachian Forests; EPA-8.5, Mississippi Alluvial and Southeast USA Coastal Plains.

Supplemental Table 2.5. Baseline characteristics of REGARDS participants in the sensitivity analysis.

Characteristic	Total
n	25,471
Stroke event	1,477
Age (yr)	64.6 (9.4)
Sex, Male (%)	11,467 (45.0)
BMI (kg/m^2)	29.3 (6.2)
Race, White (%)	15,329 (60.2)
Income	
<$20,000	4,240 (16.7)
$20,000 to $34,000	6,105 (24.0)
$35,000 to $74,000	7,833 (30.8)
≥$75,000	4,289 (16.8)
Refused	3,004 (11.8)
Education (%)	
Less than H.S.	2,923 (11.5)
H.S. graduate	6,537 (25.7)
Some College	6,852 (26.9)
College graduate	9,159 (36.0)
Diabetes	5,219 (20.5)
Hypertension	14,645 (57.5)
Previous CVD	4,206 (16.5)
Atrial fibrillation	2,060 (8.1)
Current Smoker	3,566 (14.0)
Exercise	
None	8,288 (33.0)
1-3 times/wk	9,254 (36.8)
≥ 4 times/wk	7,576 (30.2)
Area Deprivation Index	61.5 (28.9)
Urbanicity	
Rural (≤25%)	2,944 (11.6)
Mixed (25-75%)	2,681 (10.5)
Urban (≥75%)	19,849 (77.9)
$PM_{2.5}$ ($\mu g/m^3$)	12.6 (2.3)

Supplemental Table 2.6. Sensitivity analysis hazard ratios and 95% confidence intervals for greenness and stroke in the REGARDS study (n=25,471).

	250 m	500 m	1250 m
NDVI			
Continuous	0.988 (0.944, 1.035)	0.990 (0.945, 1.037)	0.985 (0.939, 1.033)
Tertile 1	Reference	Reference	Reference
Tertile 2	1.110 (0.978, 1.259)	1.175 (1.036, 1.332)	1.060 (0.934, 1.202)
Tertile 3	0.937 (0.815, 1.077)	0.926 (0.804, 1.066)	0.882 (0.765, 1.018)
p for trend	0.393	0.342	0.098
EVI			
Continuous	0.994 (0.919, 1.076)	0.995 (0.918, 1.078)	0.989 (0.911, 1.074)
Tertile 1	Reference	Reference	Reference
Tertile 2	1.110 (0.970, 1.248)	1.081 (0.953, 1.227)	1.077 (0.948, 1.222)
Tertile 3	0.906 (0.786, 1.044)	0.927 (0.804, 1.068)	0.918 (0.794, 1.061)
p for trend	0.208	0.337	0.312

Models are adjusted for age, sex, race, age*race, education, urbanicity, ADI, smoking status, average 1-year baseline $PM_{2.5}$, BMI, previous CVD, hypertension, diabetes, and atrial fibrillation.

Supplemental Table 2.7. Sensitivity analysis estimated HRs and 95% CIs for stroke associated with a 0.1 increase in greenness, stratified by EPA level I ecoregions.

Characteristic	EPA-8	EPA-9	EPA-11	P-value
n	21,095	1,613	1,908	
No. of cases	1,242	94	94	
NDVI 250m	0.943 (0.892, 0.997)	1.393 (1.062, 1.827)	1.396 (1.070, 1.822)	<0.001
NDVI 500m	0.945 (0.894, 0.999)	1.375 (1.044, 1.811)	1.421 (1.086, 1.860)	<0.001
NDVI 1250m	0.935 (0.884, 0.990)	1.420 (1.070, 1.885)	1.450 (1.104, 1.904)	<0.001
EVI 250m	0.925 (0.843, 1.015)	1.694 (1.108, 2.589)	1.882 (1.210, 2.926)	<0.001
EVI 500m	0.925 (0.842, 1.015)	1.664 (1.077, 2.571)	1.920 (1.230, 2.998)	<0.001
EVI 1250m	0.911 (0.828, 1.002)	1.795 (1.143, 2.819)	2.043 (1.270, 3.287)	<0.001

Models are adjusted for age, sex, race, age*race, education, urbanicity, ADI, smoking status, average 1-year baseline $PM_{2.5}$, BMI, previous CVD, hypertension, diabetes, and atrial fibrillation. EPA-8, Eastern Temperate Forests; EPA-9, Great Plains; EPA-11, Mediterranean California. P-values for interaction were estimated by including a region*greenness interaction term in the model.

FIGURES

Figure 1.1. Location of all residential addresses reported by REGARDS participants and EPA level I ecoregions.

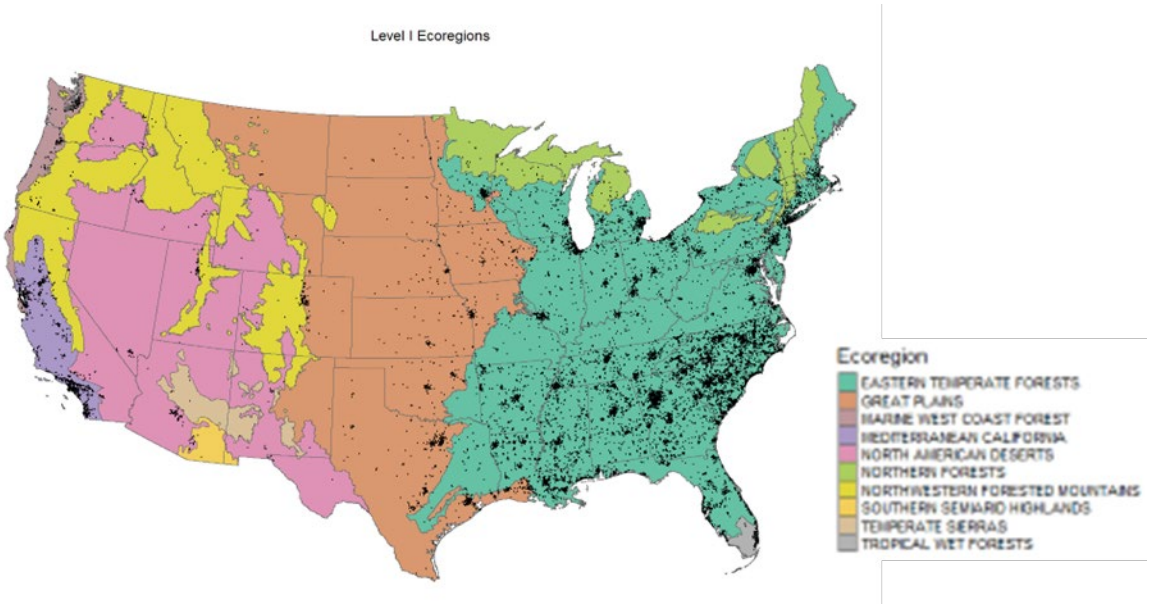
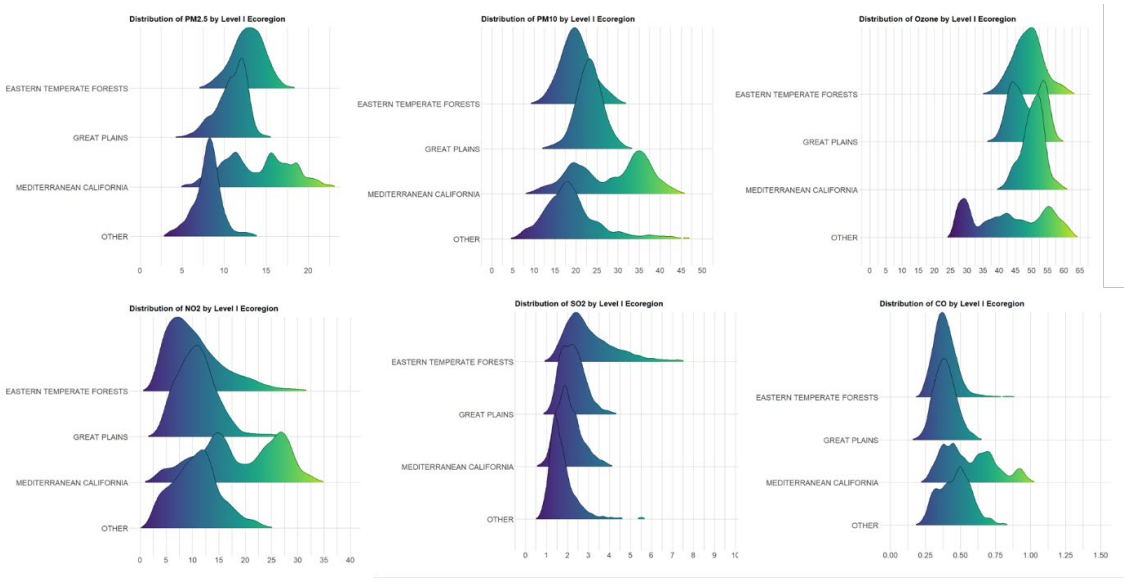
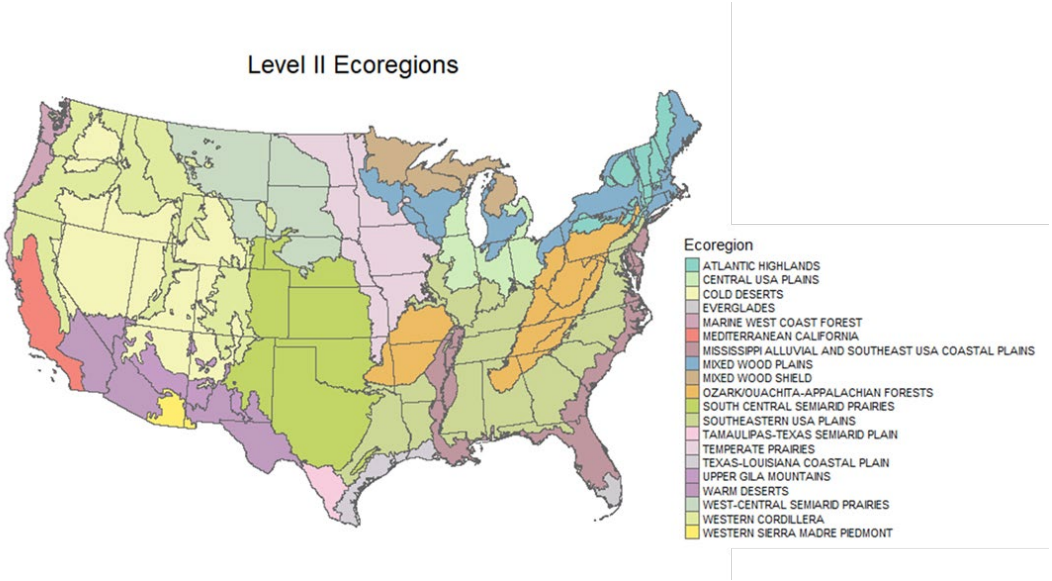


Figure 1.2. Distribution of 1-year pollutant levels by EPA level I ecoregions.



Supplemental Figure 1.1. EPA level II ecoregion boundaries for the contiguous United States.



Supplemental Figure 1.2. Scatter plots, histograms, and Pearson correlations for 1-year pollutants.

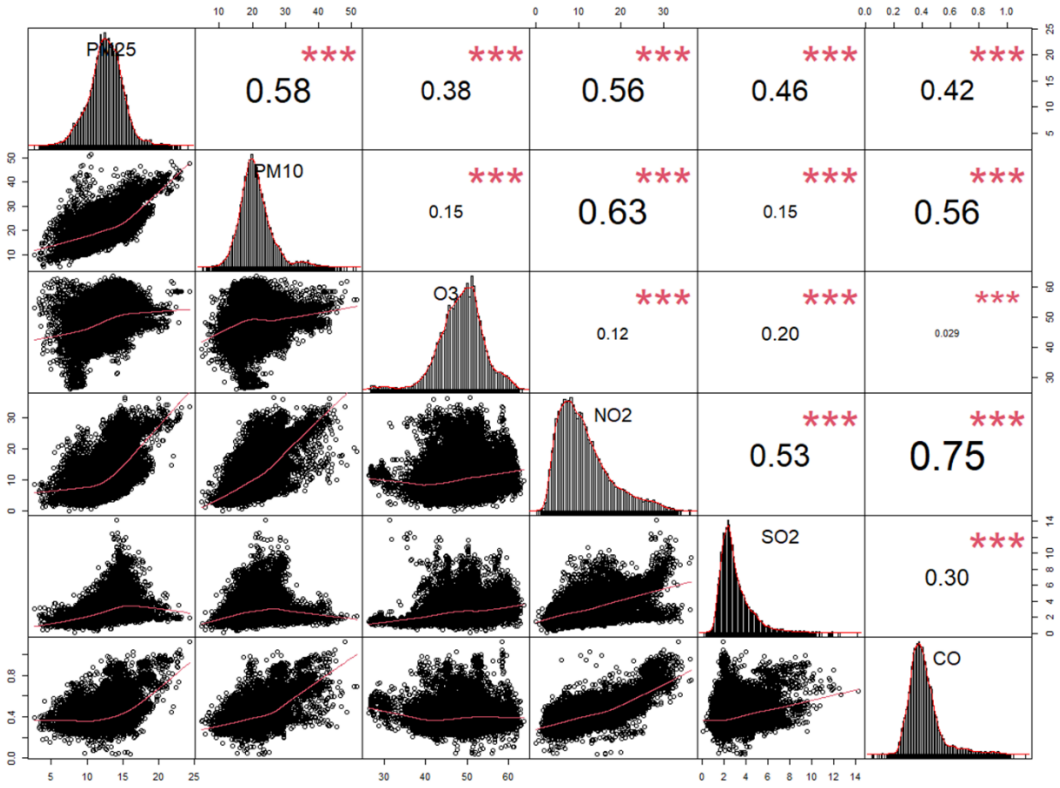


Figure 2.1. Average summer NDVI values for the contiguous United States and location of all residential addresses for REGARDS participants.

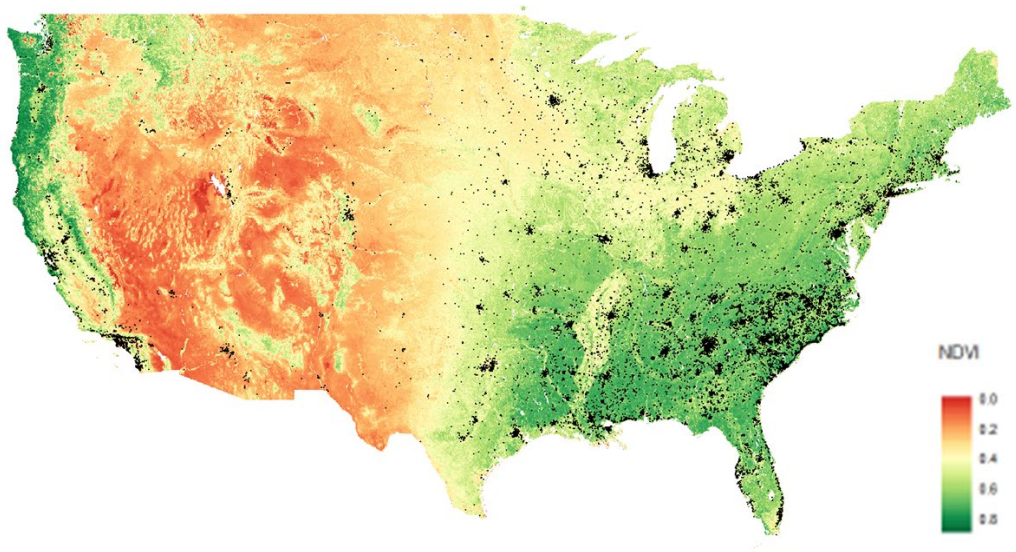


Figure 2.2. Hazard ratios and 95% confidence intervals for a 0.1 unit increase in NDVI or EVI and Stroke in the REGARDS study (n=27,369) stratified by EPA level I ecoregions

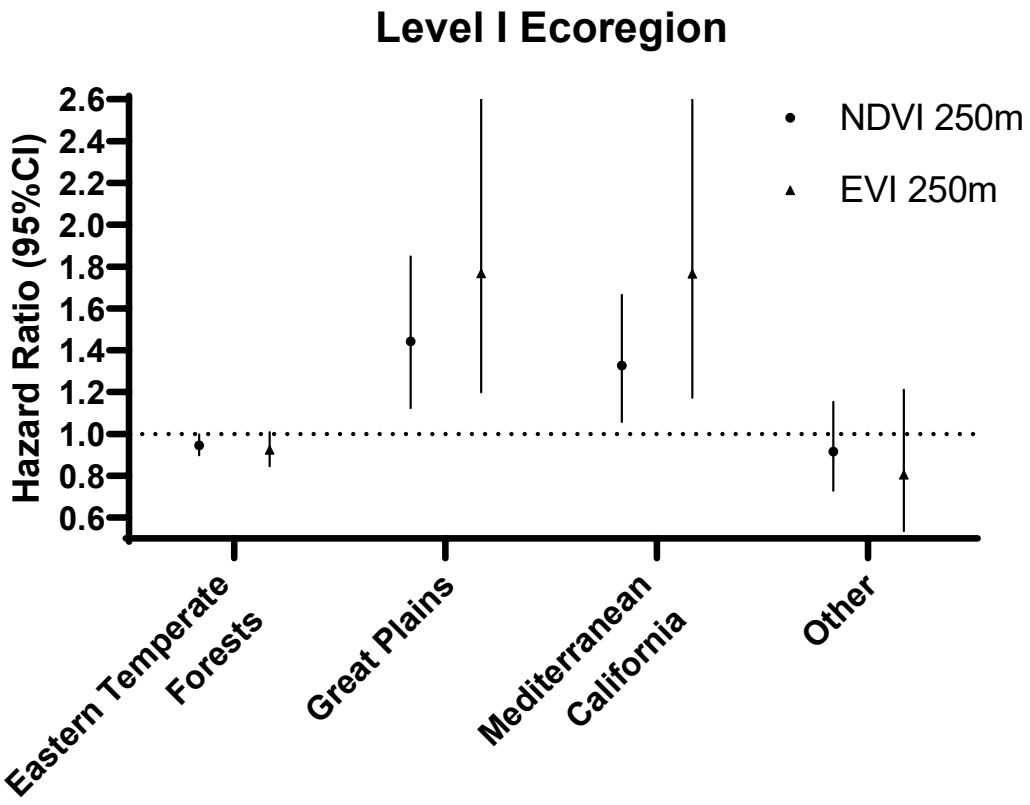
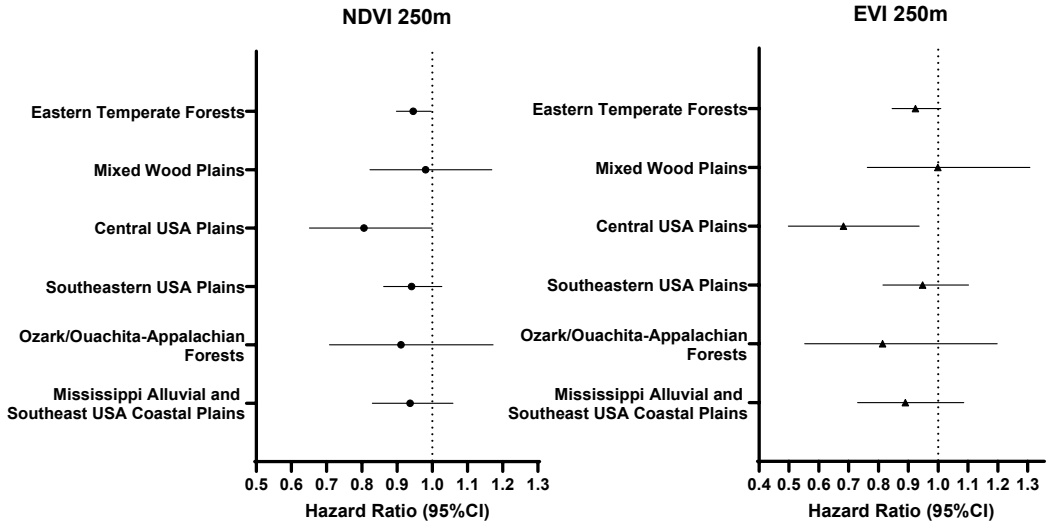
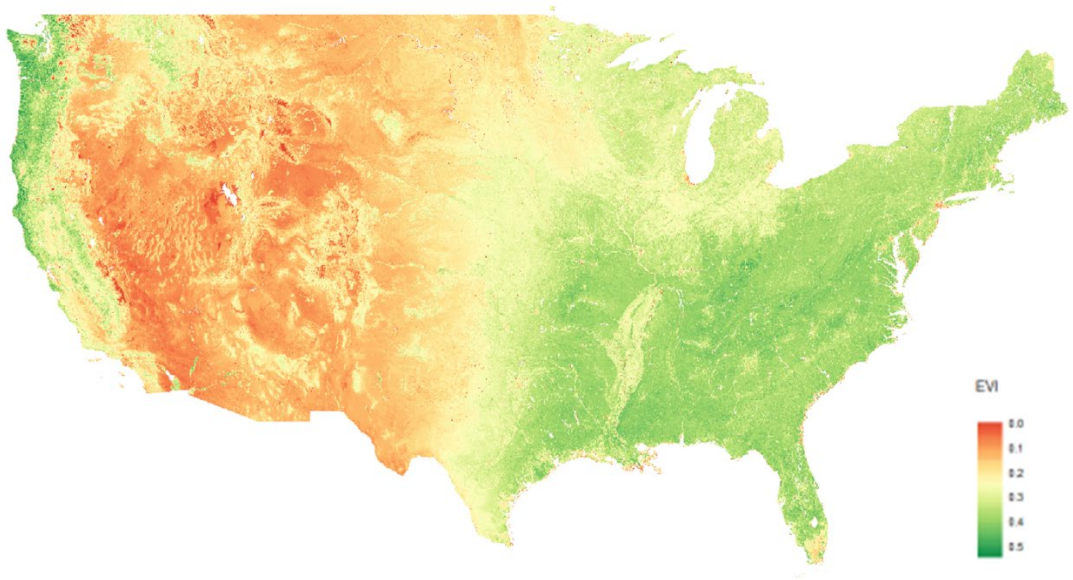


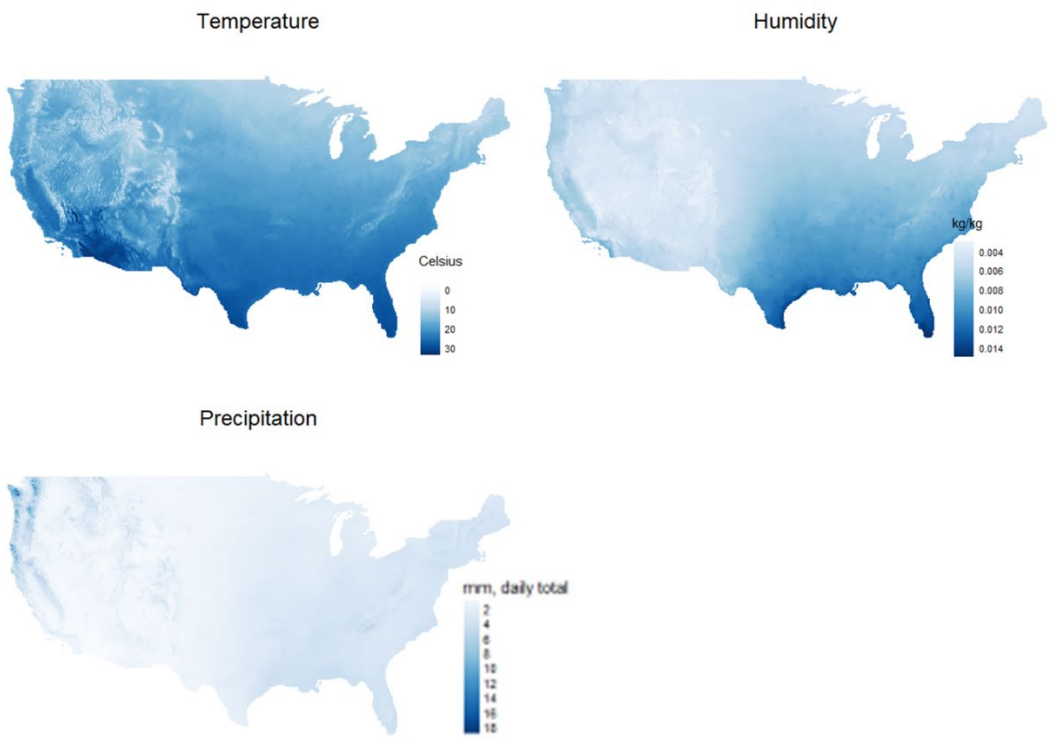
Figure 2.3. Hazard ratios and 95% confidence intervals for a 0.1 unit increase in NDVI or EVI and Stroke in the REGARDS study (n=27,369) stratified by EPA level II ecoregions located within the Eastern Temperate Forests.



Supplemental Figure 2.1. Average summer EVI values of the contiguous United States. EVI was obtained from MODIS at 250 x 250m resolution.



Supplemental Figure 2.2. Maps of daily average climate features, 2003-2008.



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APPENDIX

REGARDS Study

This dissertation utilized the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study, a national, population-based, prospective cohort study of 30,239 African-American and White adults aged ≥ 45 years.[121] REGARDS was designed to identify factors contributing to the excess stroke mortality in the Southeastern United States and among African Americans. The primary objectives of REGARDS are: 1) Provide national data on stroke incidence and case fatality and assess racial and geographic variations in these measures. 2) Provide national data on prevalence of stroke risk factors and assess their geographic and racial variation. 3) Assess the degree that geographic and racial variations in stroke incidence, case fatality, and mortality are attributed to variations in risk factor prevalence. 4) Assess the magnitude of geographic and racial variations impact on prevalent stroke risk factors. 5) Assess the impact of migration on stroke incidence, case fatality, and mortality. 6) Create a repository of blood, urine, and DNA for future studies.

Study Design

The REGARDS participants were sampled from a commercially available nationwide list, with inclusion criteria including having a name, telephone number,

and address in the database. Sampling was age-race-sex-geographic stratified with oversampling of Black individuals, and individuals living in the stroke belt. The recruitment strategy was designed to include 30% of participants from the Stroke Belt, 20% from the Stroke Buckle, and the remainder of participants from the continental United States. Within each geographic region strata, sampling was designed to select half White and half Black participants, consisting of 50% males, and 50% females within each region-race strata.

Participants were recruited from January 2003 to October 2007 through a combination of mail and telephone contacts. Exclusion criteria included race other than Black or White, current treatment for cancer, medical conditions that would prevent long term participation, cognitive impairment, residence in a nursing home, or inability to communicate in English. Following verbal consent, medical history was collected by computer-assisted telephone interviews. In-home exams were completed to collect physical measurements, resting ECG, medication inventory, and to obtain blood and urine samples. Participants were asked to fast overnight (10-12 hours) prior to the exam, and to have medications available at the time of the visit. Self-administered questionnaires are left with the participant to obtain information on demographic and risk factor characteristics. Specific components of the baseline evaluation are listed below.

REGARDS Data Components

Components of the telephone interview include variables on medical history, personal history, demographic data, socioeconomic status, stroke-free status, physical activity, depression, cognitive screening, perceived health/ quality

of life, social support, social network, and potential caregiver. The in-home examination includes laboratory assays (lipid profiles, glucose, creatinine, C-reactive protein, etc..), urine collection, height, weight, waist circumference, blood pressure, pulse, electrocardiography, and medication use in the past 2 weeks. The self-administered exam component includes data on residential history, dietary intake (Block 98 Food Frequency Questionnaire), and family history.

Incident Stroke

The REGARDS study conducts active surveillance of participants to classify fatal and nonfatal stroke events. Participants are contacted at 6-month intervals by telephone to collect data on events that require hospitalization, and physician evaluation of stroke-like symptoms. Death certificates and associated hospital records are retrieved in the event that a death is reported. A two-member Events Committee independently reviews the records to validate stroke occurrence and classifies events by stroke subtype and severity. Incident stroke is defined as "rapid onset of a persistent neurologic deficit attributable to an obstruction or rupture of the arterial system (including stroke occurring during a procedure such as angiography or surgery); deficit is not known to be secondary to brain trauma, tumor, infection, or other non-ischemic cause; deficit must last more than 24 h, unless death supervenes or there is a demonstrable lesion compatible with acute stroke on computed tomography or magnetic resonance imaging".

Sample Size

The sample size of REGARDS was justified to provide a sufficient number of stroke events and detect associations with risk factors with relatively small hazard ratios.[121] The expected number of events per 1,000 person years used in the calculations was 55 events per year for black males, 52.3 for black females, 36.1 for white males, and 34.6 for white females, based on the Greater Cincinnati/Northern Kentucky Stroke Study.[179] Using the hazard ratio approach by Schoenfeld,[180] the study is expected to be able to detect a hazard ratio of 1.30 with 80% power for common predictors (i.e. predictors with 30% prevalence), and a hazard ratio of 1.74 with 80% power for rare predictors (5% prevalence).

Ecoregions of the United States

The United States possesses a diverse set of ecosystems that contain a vast number of natural resources. These ecosystems can be categorized in an ecologically meaningful way, termed ecoregions. The environmental protection agency (EPA) defines ecoregions as areas where ecosystems (and the type, quality, and quantity of environmental resources) are generally similar. The current EPA ecoregion framework is derived from approximations by Omernik in 1987[181] along with mapping done in collaboration with Federal agencies, designed to serve as a framework for research, assessment, and monitoring of ecosystems. Ecoregions are classified using satellite imagery and natural resource maps, which are used to analyze patterns and composition of biotic (including humans) and abiotic phenomena, including geology, landforms, soils, vegetation, climate, land use, wildlife, and hydrology.[151,181] The classification scheme uses a nested hierarchy, with the most broad region labeled level I, with 3 successively more

detailed levels nested within. Level I ecoregions consist of 12 regions within the continental United States that highlight the major ecological areas, providing context at the global scale (Figure 1.1). There are 25 level II ecological regions, nested within level I, which give a more detailed description of the ecological areas and provide a national/regional perspective of ecological areas (Supplemental Figure 1.1). Within the level II ecoregions are the smaller level III (105 ecoregions in the continental U.S.), and the further nested level IV regions (967 ecoregions). Detailed descriptions of EPA level I and level II ecoregions used in this dissertation are provided below.

The level I **Eastern Temperate Forests** ecoregion represents the largest ecoregion, dominating the eastern half of the United States.[120] The climate is generally warm, humid and temperate, with cooler temperatures in the northern latitudes. Precipitation ranges from 1,000-1,599 mm per year and is evenly distributed throughout the year. The region is covered in large areas of dense forest consisting mostly of broadleaf, deciduous trees, and needle-leaf conifers. There are also forests of beech-maple and maple-basswood. Oak, hickory, and pine are also common in the south and Appalachian regions. The region contains a large diversity of species, including extremely diverse populations of birds, fish, reptiles, and amphibians. The northern part of this region contains the level II **Mixed Wood Plains**, a discontinuous region in the northeastern United States. The climate is humid continental, and warm enough for breakdown and release of organic matter into the soil, leading to richer soils that can be used for agriculture. Forest cover consists of mixed (hardwood and coniferous) and deciduous, which

have been drastically reduced over time due to agriculture, urbanization, and forestry. In the Midwestern U.S. lies the **Central USA Plains** level II ecoregion. This region is mostly flat, with a range of soil types, that transition between treeless great plains, and forested regions to the east. The climate is humid continental, with four well defined seasons. The northwestern part of the region can experience extreme cold, while the climate gets milder to the south and east. The temperatures contribute to nutrient-rich soils and has been heavily altered by agriculture. The **Southeastern USA Plains** are the largest level II ecoregion in the eastern U.S., consisting of two discontinuous areas. The topography ranges from flat to rolling hills. The climate is humid subtropical, with most of the region on the colder end. There are four well defined seasons in the north, but less defined in the south. The absence of mountain regions contributes to large variations in temperatures and humidity. The region averages moderate levels of precipitation but can have prolonged periods of drought or flooding. Most of the region is dominated by hardwood forests, with mixed and coniferous forests in some areas, and pines more common in southern areas. Broadleaf evergreen trees and shrubs are also common in most of the region. There are also areas of significant wetlands. The level II **Ozark/Ouachita-Appalachian Forests** ecoregion contains two discontinuous areas, one located in northern Arkansas/southern Missouri, the other containing the Appalachians. This region is mountainous, but with lower elevations than mountains in the western U.S. Moisture is abundant in the area, and the climate ranges from humid subtropical at lower elevations, to subtropical at higher altitudes. Forest cover is extensive, with hardwood forests at lower

altitudes, and mixed and coniferous forests at higher altitudes. Plant diversity is high due to the range of climates and altitude. The area is thinly populated, mostly rural, and with significant poverty. Agriculture is diverse in the area, though not at large-scale, allowing forest cover to remain high. The level II **Mississippi Alluvial and Southeast USA Coastal Plains** ecoregion extends along the east coast of the United States, and along the Gulf Coast north along the Mississippi river. This region is mostly flat, and low elevation. There are extensive wetlands, river deltas, beaches, and sand along the coast. The climate is subtropical, with the northern region having four well defined seasons. The proximity to the ocean and low altitude moderates the climate. Precipitation is similar year-round, but comes from frontal systems in the cool season, and from thunderstorms, hurricanes, and tropical storms in the warm season. Land cover consists of forest and wetlands, with pines dominating the forests in coastal areas. Hardwood forests are more common in the interior. The area is heavily populated and utilized for agriculture and forestry.

The **Great Plains** level I ecoregion are a flat, open region located in central United States, extending from Mexico into Canada. The region was historically grasslands but has been heavily developed for agriculture. Rainfall increases towards the east. The drier climate along with flat topography can create volatile temperatures swings. There are also periods of short- and long-term drought. The area is less populated and urbanized then the eastern ecoregions.

The **Mediterranean California** level I ecoregion is a relatively small region extending from southern California to Oregon along the western coast of the United

States. The climate is a dry summer Mediterranean, with hot summers and mild winters. The vegetation is mostly evergreen shrubs, called chaparral, with areas of oak woodlands, grasslands, and some coniferous forests.

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Dissertation: Ecological differences in the associations between air pollution, greenness, and risk of stroke: The REGARDS study.

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10/2014-present Biostatistician II
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2014 SAS Certified Base Programmer for SAS 9
2014 SAS Training Course - Statistics 2: ANOVA and Regression. Boston, MA. May 28-30.
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PROFESSIONAL MEMBERSHIPS

2017-present American Heart Association
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2013-2014 Oak Ridge Institute for Science and Education (ORISE) Fellowship
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EDITORIAL WORK

Scientific Review (*ad hoc*)

Environment International
Journal of the American Heart Association (JAHA)
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Journal of Alzheimer's Disease
Journal of Alzheimer's Disease Reports

ABSTRACTS AND PRESENTATIONS

Oral Presentations

1. **02/28/2018**: "Green Heart Study Design: Clustering Strategy." Green Heart Project Annual Scientific Meeting.
2. **2018-2019**: Oral Presentations, Superfund Monthly Meeting, (Regular Presenter).
3. **02/03/2020**: "Molecular Epidemiology for Basic Science Researchers." Diabetes and Obesity Center Weekly Conference.
4. **08/23/2021**: "Associations between Air Pollution and County Level Cardiovascular Mortality in the United States by Ecoregions." International Society for Environmental Epidemiology. Lightning Talk.

Chair/Moderator at National/International Conferences

1. 11/29/2018: Co-Chair: "Connecting Exposures to Health Outcomes." Superfund Research Program Annual Meeting, Sacramento, CA.

Abstracts

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2. Hill BG, Srivastava S, **Riggs DW**, and Bhatnagar A. Metabolism of HNE-modified proteins in vascular smooth muscle cells. Enzymology and Molecular Biology of Carbonyl Metabolism. Nashville, IN, 2006.

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7. DeJarnett N, Conklin D, Myers JA, Hamzeh I, Wagner S, Chugh A, Zahn M, Tollerud DJ, Higdon D, Becher C, Wyatt B, Ciszewski T, **Riggs DW**, Prabhu S, Bhatnagar A. Traditional cardiovascular disease risk factors predict acrolein metabolite level in a population-based study. American Public Health Association. San Francisco, CA, 2012.

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9. Sithu SD, Riggs KA, Gornek MA, **Riggs DW**, Agarwal A, Bhatnagar A, Srivastava S. Deletion of low-density lipoprotein receptor in rats induces hyperlipidemia and atherosclerotic lesion formation. American Heart Association. Los Angeles, CA, 2012.

10. DeJarnett N, Conklin DJ, **Riggs D**, O'Toole TE, Chugh A, Srivastava S, Tollerud DJ, Yeager R, Prabhu SD, Bhatnagar A. Association between benzene exposure, circulating angiogenic cell levels, and cardiovascular disease risk in the Louisville Healthy Heart Study. Ohio Valley Society of Toxicology. Louisville, KY, 2013.

11. DeJarnett N, Conklin DJ, **Riggs D**, Tollerud D, O'Toole T, Ramos K, Srivastava S, Chugh A, Prabhu SD, Bhatnagar A. Association between benzene exposure, circulating angiogenic cell (CAC) levels, and cardiovascular disease risk in the Louisville healthy heart study. Research Louisville. Louisville, KY, 2013.

12. Hamed-Berair R, Sithu S, Riggs K, **Riggs D**, Wickramasinghe N, Agarwal A, Bhatnagar A, Srivastava S. Circulating microRNAs as biomarkers of atherosclerosis in LDL receptor knockout rats. Research Louisville. Louisville, KY, 2013.

13. DeJarnett N, Conklin DJ, **Riggs D**, O'Toole T, McCracken J, Abplanalp W, Haberzettl P, Yeager R, Srivastava S, Hamzeh H, Wagner S, Chugh A, DeFilippis A, Ciszewski T, Wyatt B, Becher C, Xie Z, Ramos K, Tollerud DJ, Myers JA, Rai S, Prabhu SD, Bhatnagar A. Association between benzene exposure, circulating angiogenic cell levels, and cardiovascular disease risk in the Louisville healthy heart study. American Public Health Association. New Orleans, LA, 2014.

14. Yeager R, DeJarnett N, Conklin D, Tollerud DJ, Abplanalp W, O'Toole T, Myers JA, Ramos K, Lee J, McCracken J, Srivastava S, Hamzeh I, Wagner S, Chugh A, DeFilippis A, Becher C, Higdon D, Wyatt B, Ciszewski T, **Riggs D**, Bhatnagar A. Levels of early circulating angiogenic cells associated with geographic metrics of roadway exposure. American Public Health Association. New Orleans, LA, 2014.

15. Hamed-Berair RE, Lorkiewicz P, Sithu SD, Riggs KA, Malovichko M, Winner MG, Agarwal A, **Riggs DW**, Bhatnagar A, Srivastava S. Dyslipidemia, obesity, insulin resistance and atherosclerosis in LDL-receptor deficient rats. Arteriosclerosis, Thrombosis, and Vascular Biology. San Francisco, CA, 2015.

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NM. Electronic cigarette use and vascular health in the cardiovascular injury in tobacco use study. NIH Tobacco Centers of Regulatory Science Conference. Bethesda, MD, 2016.

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33. Konkle SL, **Riggs D**, Bhatnagar A. Associations between volatile organic compound exposures and serum lipids in the national health and nutrition examination survey (NHANES). Society of Toxicology. San Antonio, TX, 2018.

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