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The impact of green space on nonaccidental and cause-specific mortality in the Adventist Health Study-2 population

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Background: There is growing interest in evaluating the long-term health effects of neighborhood environments, particularly green space. However, only a limited body of research further incorporates multiple ambient air pollutants.

Methods: This study looked at the relationship between green space, as measured by the Normalized Difference Vegetation Index, and mortality adjusted by key confounders in the Adventist Health Study-2, a longitudinal cohort study from 2002 to 2015, across the contiguous United States (N = 67,400). We used Cox proportional hazard regression models to assess the risk of nonaccidental, cardiovascular disease (CVD), ischemic heart disease (IHD), and respiratory disease mortality from green space around subjects' home address under multiple covariate and pollutant adjustments.

Results: We found a 0.1 unit increase in the Normalized Difference Vegetation Index was associated with nonaccidental (hazard ratio [HR]: 0.96 [95% confidence interval (CI): 0.93, 0.99]), CVD (HR: 0.94 [95% CI: 0.90, 0.98]), and IHD (HR: 0.87 [95% CI: 0.81, 0.94]) mortality, with the greatest precision in fully adjusted three-pollutant models using the 1000-m buffer. Effect estimates were strengthened in urban areas, when incorporating seasons, and for females. However, all associations between green space and respiratory mortality were null.

Conclusion: This study supports evidence that increased neighborhood green space is inversely associated with nonaccidental, CVD, and IHD mortality, where the inclusion of multiple environmental covariates had a greater impact on effect estimate magnitude and precision than adjustment by individual lifestyle and health factors.

Keywords: Green space; Normalized difference vegetation index; Air pollution; Mortality; Cohort study

Introduction

There is growing evidence that increasing neighborhood-level green space can reduce mortality risk, with the Normalized Difference Vegetation Index (NDVI) serving as a popular method of estimating green space exposure.[1–7] The mechanism behind the health benefits of surrounding greenery is thought to be multifactorial and summarized by Markevych et al[8] as relating to its ability to reduce other harmful exposures and restore and promote healthy activities, in support of both mental and physical health. Such effects manifest through interactions with other environmental determinants of health, such as air pollutants,[9–11] temperature,[12,13] and noise,[14] as well as through individual determinants of health, including physical activity,[15] social cohesion,[16] mental health,[15] and sleep.[17]

The connection between green space and ambient air pollution is of particular interest. Air pollution has been widely studied for its harmful effects on human health.[18] While green space has been associated with reduced mortality regardless of ambient $PM_{2.5}$ concentrations,[3] more recent literature suggests that the higher mortality associated with ambient $PM_{2.5}$ may only exist in areas of low greenness.[10] Others have found inverse correlations between green space and ambient air pollution,[1,19] as well as looked at air pollutants as a mediator,[3,5,19,20] such that the beneficial effects of green space are through reducing harmful air pollutants. Despite these noted interactions, of the multitude of studies that looked at the NDVI with nonaccidental,[1–6,11,19–24] cardiovascular disease (CVD),[2,5,11,19–24] ischemic heart disease (IHD),[2,3,5,19,20] and respiratory disease[2,3,5,6,11,19–24] mortality, only one adjusted for $PM_{2.5}$, NO_2, and O_3, simultaneously,[2] where most either did not include any air pollutants or adjusted for a single pollutant at a time.

Surrounding green space and ambient air pollution can also change over time. However, when assigning NDVI exposure, few studies incorporated time-dependent methodologies,[1,3,4,23] and to

What this study adds:
This research expands upon the relationship between green space and cause-specific mortality risk. While many results were in line with previously published work, the strengthening of estimate precision and magnitude after simultaneously adjusting for multiple air pollutants supports greater exploration into multienvironmental models. In addition, our null findings between green space and respiratory mortality and the observed effect modification suggest that there may be more nuanced environmental and disease characteristics needed to understand this relationship. Overall, we believe this research provides new insight into improving methods for studying the association between green space and health.

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This study used confidential data from the Adventist Health Study-2 cohort that cannot be published publicly.

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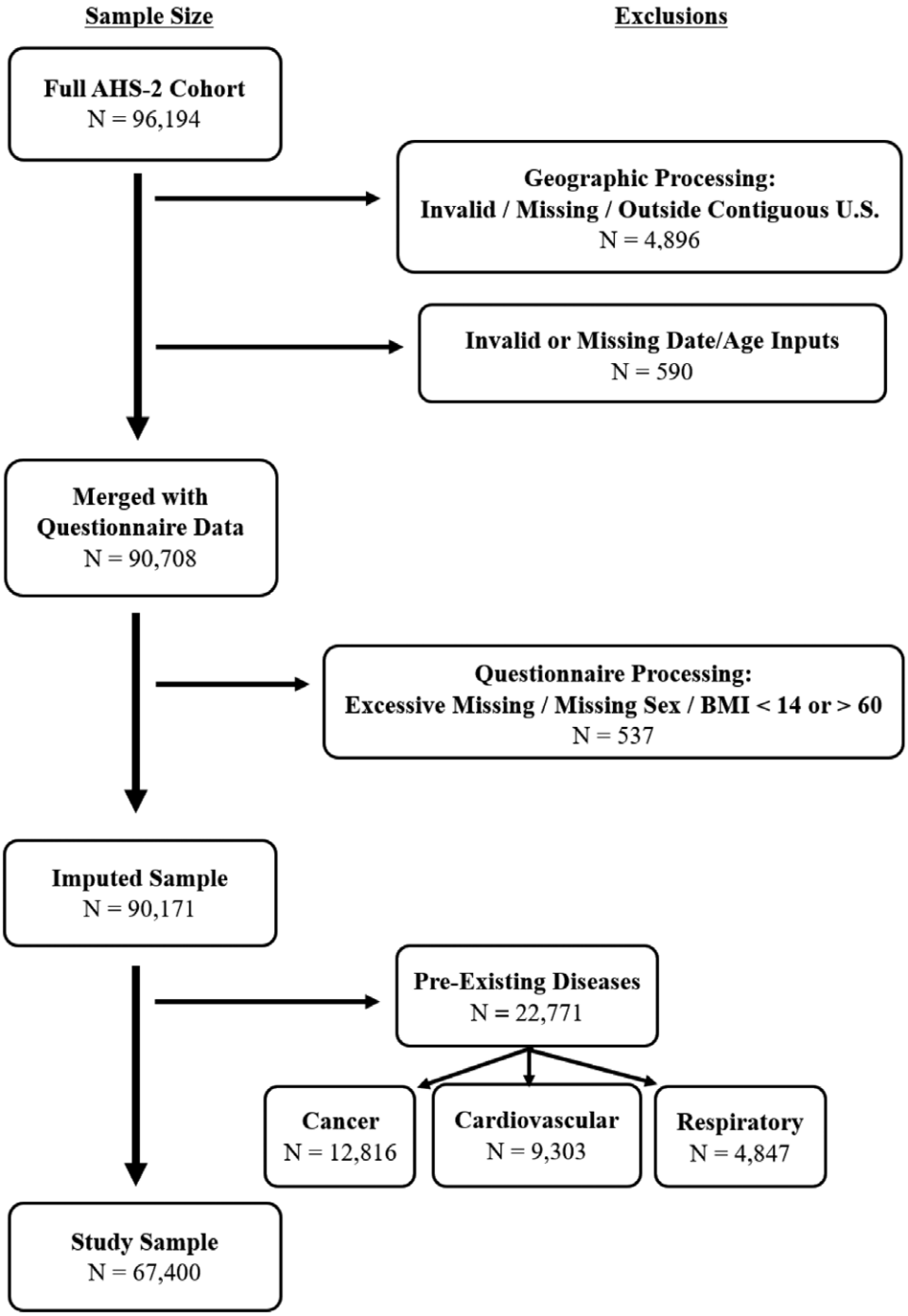

Figure 1. Flowchart depicting AHS-2 subject exclusions for study sample selection.

our knowledge, none did so with a time-changing window that moved across the entire follow-up period. For these reasons, this study sought to quantify the relationship between green space and mortality and the confounding effect of multiple ambient air pollutants, across the contiguous United States (U.S.), using a moving exposure window that was updated for each age risk set.

Methods

Study population

Our study included data from the Adventist Health Study-2 (AHS-2), a prospective longitudinal cohort study of members of the Seventh Day Adventist church, with participants located across the United States and Canada (N = 96,194).[25] Enrollment occurred between 2002 and 2007 with a detailed and validated questionnaire that included many factors related to lifestyle, health, and demographics, described in detail, previously.[25]

We included AHS-2 participants with nonmissing data on sex and year of birth with a valid address in the contiguous U.S. at baseline (Figure 1). Participants residing in Canada, Alaska, and Hawaii were excluded because environmental data did not incorporate these regions. Subjects internally flagged for excessive missing questionnaire responses or with a body mass index (BMI) <14 or >60 were also excluded, leaving 90,171 subjects in the available baseline sample. All other variables in the model with missing data were addressed with multiple imputations using the MICE function in R, version 4.2.1 (The R Foundation, Vienna, Austria).[26] Key dietary variables were assisted with a guided multiple imputation process.[27] We ran three separate

imputation models, one for each NDVI buffer region, with 10 imputations each.

Subjects were tracked for address changes and mortality from the date they entered the study to 31 December 2015. Address updates included the location and date of recording, to optimize matching exposures in space and time. All recorded addresses were geocoded using ArcGIS Pro 2.7 (ESRI, Redlands, CA)[28] and merged with spatial and environmental exposures.

After imputations, we further excluded those with pre-existing cancer, CVD, and respiratory diseases available from the AHS-2 baseline questionnaire. Pre-existing CVD included prior stroke, transient ischemic attack, myocardial infarction, congestive heart failure, angina, or having had any of the following surgeries: coronary bypass, stent, or carotid artery surgery. Pre-existing respiratory diseases were defined as chronic bronchitis or emphysema. All pre-existing conditions were self-reported.

This study was a secondary analysis using existing AHS-2 data with no additional participant contact. Subjects provided written and informed consent at enrollment. This research was approved by the Loma Linda University Institutional Review Board.

Outcomes

Outcomes were defined by the International Classification of Diseases and Related Health Problems (ICD-10) listed as the underlying cause of mortality on death records from the National Death Index. We looked at the relationship between green space and nonaccidental (ICD-10: A00–R99), CVD (ICD-10: I00–I99), IHD (ICD-10: I20–I25), and respiratory disease (ICD-10: J00–J99) mortality.

Environmental exposures

Exposure to green space was measured through the NDVI, using satellites, which calculate the reflectiveness of visible and near-infrared light off the surface of the Earth.[29] While the NDVI ranges from –1 to 1, this study only used land-based estimates spanning zero to one (low to high vegetation, respectively), excluding negative water-based values.[29]

We used NDVI data from the National Aeronautics and Space Administration's (NASA) Moderate Resolution Imaging Spectrometer (MODIS) Terra and Aqua satellites that were processed using NASA's Stennis Time Series Product Tool.[30] Data were collected at a 250-m resolution and averaged for every 8 days across the contiguous U.S.[30] We aggregated raster files into meteorological seasonal averages from 2001 to 2015 and used the focal statistics tool in ArcGIS Desktop 10.8 (ESRI, Redlands, CA)[31] to recalculate cells to the average within a 250, 500, and 1000-m radius. All AHS-2 addresses were assigned a respective 250, 500, and 1000-m NDVI average (buffer zone) from these focal statistics grids, for each season across follow-up. Subjects were then assigned a time-changing average NDVI based on the preceding four seasons, with exposures updated based on a quarterly unit change for each age risk set in the survival model. For example, an event in the Summer of 2008 would be assigned an average of the Summer and Fall of 2007 and Winter and Spring of 2008, while nonevents were assigned the average of the preceding four-quarters relative to their exposure at the same age as the event.

Ambient air pollution data also spanned the follow-up period and included annual estimates of fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2), and tropospheric ozone (O_3) by Census Block centroids across the contiguous U.S. Air pollution estimates were created by Kim et al[32] via Integrated Empirical Geographic regression models. $PM_{2.5}$ and NO_2 annual estimates were averaged from daily 24-hour pollutant concentrations, while O_3 annual estimates were averaged from a moving 8-hour daily maximum concentration between the warmer months of the year (May–September).[32] Pollutant exposure was assigned to AHS-2 participants based on the nearest Census Block centroid to each subject's home address from 2001 to 2015. Annual air pollution estimates were weighted to mimic the seasonal changes within NDVI data and exposures were assigned for each age risk set based on a similar moving four-quarter average.

Addresses were merged with environmental predictors using ArcGIS Desktop 10.8,[31] which were further collapsed into moving seasonal averages using both R, version 4.2.1[26] and SAS/STAT software, version 9.4 (SAS Institution, Cary, NC).[33]

Covariates

We adjusted for many self-reported individual-level covariates obtained from AHS-2 questionnaire data, as well as external spatial covariates, based on participants' home address. Covariate data was selected a priori, and all variables were kept regardless of individual significance.

Person-level demographic data included sex (male/female), race (White, Black, other), marital status (currently married including common law marriages, and not currently married), educational attainment (≤high school diploma, some college/trade school/associates degree, and ≥bachelor's degree), born in the United States or Canada (yes/no), and household income (≤$30,000, $31,000–$50,000, $51,000–$100,000, >$100,000). Lifestyle variables included: frequency of consuming red/processed meat (never to <monthly, ≥once a month but <weekly, 1–2 per week, and ≥3 per week) and tree nuts (<weekly, 1–2 per week, 3–6 per week, and ≥daily),[34,35] current alcohol consumption (beer/liquor and wine; <monthly/never and ≥monthly), frequency of vigorous exercise (never, ≤1 per week, 2–3 per week, and ≥4 per week), and smoking status (never, past, current). Red and processed meats included: beef, lamb, pork, ground beef, other processed red meats, and processed poultry. Tree nuts included: almonds, walnuts, and cashews.

We also included additional spatial and temporal data: 5-year 2006–2010 census-tract median household income and median home value, 2010 rural/urban classifications,[36] and the year subjects entered the study (2002–2003, 2004–2005, and 2006–2007). These spatial estimates were based on the subjects' baseline address. Urban status was defined as urban (population ≥50,000), urban cluster (population 2,500–49,999), and rural (population <2,500).[37] Additional effect modification analyses incorporated meteorological season of event (another time-changing estimate quantifying a seasonal age risk set) and baseline region of the United States, based on the four National Weather Service Regions: West, Central, South, and East.[38]

Covariates related to health and medication use included BMI, being treated for diabetes within the past year, ever diagnosed with high blood pressure or cholesterol, and took aspirin, blood pressure, or cholesterol-lowering medications for at least 2 consecutive years in the past 5 years (yes/no variables). Females were also adjusted for menopause status and if hormone replacement therapy (HRT) was used after menopause (premenopause, postmenopause without HRT, and postmenopause with HRT). Unless otherwise specified, all models included the same covariate adjustments, except for respiratory mortality models, which were further adjusted by self-reported pre-existing asthma (yes/no).

Statistical analysis

We looked at the relationship between green space and mortality adjusted by key demographic, lifestyle, health, and spatial factors using attained age Cox proportional hazard regression models with time-changing environmental exposures. We calculated hazard ratios (HRs) from surrounding neighborhood green space for nonaccidental, CVD, IHD, and respiratory mortality and compared effect estimates under different covariate

Table 1.

Summary statistics for key descriptor variables in the full AHS-2 sample (N = 67,400) and across 1000-m NDVI quintiles

		NDVI quintiles				
Variable list	**Full cohort**	**1 (lowest)**	**2**	**3**	**4**	**5 (highest)**
Continuous (mean ± SD)						
Baseline NDVI	0.5 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.7 ± 0.1
Baseline $PM_{2.5}$ (μg/m^3)	11.6 ± 3.7	13.3 ± 5.2	11.3 ± 3.6	11.4 ± 2.8	11.5 ± 2.7	10.5 ± 2.9
Baseline NO_2 (ppb)	11.9 ± 6.7	18.8 ± 8.0	13.0 ± 5.9	10.9 ± 4.7	9.4 ± 3.7	7.2 ± 3.0
Baseline peak O^3 (ppb)	48.9 ± 6.3	51.5 ± 5.7	48.4 ± 6.9	48.2 ± 6.0	48.7 ± 5.9	47.6 ± 6.2
Baseline age (years)	55.5 ± 13.6	55.6 ± 13.7	55.0 ± 13.5	55.3 ± 13.7	55.1 ± 13.6	56.3 ± 13.4
Categorical, n (%)						
Mortality outcome						
Nonaccidental	5,953 (8.8)	1,316 (9.8)	1,160 (8.6)	1,196 (8.9)	1,075 (8.0)	1,206 (8.9)
CVD	2,147 (3.2)	483 (3.6)	409 (3.0)	456 (3.4)	365 (2.7)	434 (3.2)
IHD	787 (1.2)	200 (1.5)	157 (1.2)	167 (1.2)	117 (0.9)	146 (1.1)
Respiratory	387 (0.6)	83 (0.6)	73 (0.5)	78 (0.6)	67 (0.5)	86 (0.6)
Sex						
Female	44,455 (66.0)	9,154 (67.9)	8,886 (65.9)	8,934 (66.3)	8,795 (65.3)	8,686 (64.4)
Male	22,945 (34.0)	4,326 (32.1)	4,596 (34.1)	4,547 (33.7)	4,683 (34.7)	4,793 (35.6)
Race						
White	40,391 (59.9)	6,329 (47.0)	7,843 (58.2)	7,827 (58.1)	8,313 (61.7)	10,079 (74.8)
Black	20,653 (30.6)	4,845 (35.9)	4,293 (31.8)	4,615 (34.2)	4,260 (31.6)	2,640 (19.6)
Other[a]	6,356 (9.4)	2,306 (17.1)	1,346 (10.0)	1,039 (7.7)	905 (6.7)	760 (5.6)
Born in United States/Canada	53,531 (79.4)	9,119 (67.6)	10,521 (78.0)	10,872 (80.6)	11,072 (82.1)	11,947 (88.6)
Currently married[b]	48,541 (72.0)	8,851 (65.7)	9,385 (69.6)	9,394 (69.7)	10,061 (74.6)	10,850 (80.5)
Educational attainment						
≤High school	13,758 (20.4)	2,794 (20.7)	2,790 (20.7)	2,789 (20.7)	2,619 (19.4)	2,766 (20.5)
Some college[c]	26,522 (39.4)	5,413 (40.2)	5,420 (40.2)	5,355 (39.7)	5,161 (38.3)	5,173 (38.4)
≥Bachelor's degree	27,120 (40.2)	5,273 (39.1)	5,272 (39.1)	5,337 (39.6)	5,698 (42.3)	5,540 (41.1)
Household income						
≤$30,000	22,874 (33.9)	4,878 (36.2)	4,767 (35.4)	4,739 (35.2)	4,225 (31.3)	4,265 (31.6)
$31,000–$50,000	16,150 (24.0)	3,164 (23.5)	3,210 (23.8)	3,285 (24.4)	3,304 (24.5)	3,187 (23.6)
$51,000–$100,000	19,997 (29.7)	3,884 (28.8)	3,770 (28.0)	3,965 (29.4)	4,231 (31.4)	4,147 (30.8)
>$100,000	8,379 (12.4)	1,554 (11.5)	1,735 (12.9)	1,492 (11.1)	1,718 (12.7)	1,880 (13.9)
Urbanicity[d]						
Urban	42,541 (63.1)	11,032 (81.8)	9,908 (73.5)	8,967 (66.5)	7,940 (58.9)	4,694 (34.8)
Urban cluster	7,283 (10.8)	1,234 (9.2)	1,365 (10.1)	1,795 (13.3)	1,645 (12.2)	1,244 (9.2)
Rural	17,576 (26.1)	1,214 (9.0)	2,209 (16.4)	2,719 (20.2)	3,893 (28.9)	7,541 (55.9)

[a]Includes mixed races.

[b]Includes common law marriage.

[c]Includes trade school and associate degree.

[d]Population definitions based on: urban (≥50,000); urban cluster (2,500–49,999); rural (<2,500).

and pollutant adjustments. Models were clustered on baseline county. Main analyses were conducted using the 1000-m NDVI buffer around the home, with supplemental analyses comparing results from the 250-m and 500-m buffers. Individuals who moved outside the contiguous U.S., were lost to follow-up, or died during the study were censored at the time of event.

We used restricted cubic splines with four knots placed at the 5th, 35th, 65th, and 95th percentiles to model all nonenvironmental continuous variables (BMI, census-tract median household income, and census-tract median home value). These variables were also log-transformed. Due to the complexity of time-changing environmental exposures, we tested the linearity of the NDVI, $PM_{2.5}$, NO_2, and O_3 with restricted cubic splines and only maintained the spline term if there was a significant difference in the log-likelihood ratio tests between splined and linear models. We evaluated the proportional hazards assumption for all variables with time interaction terms, addressing nonproportionality by keeping significant interactions in the model. There was no evidence of nonlinearity or nonproportionality in the NDVI.

HRs were reported for a 0.1 unit increase in the NDVI for each mortality outcome under different covariate adjustments. We also looked at effect modification between the NDVI and urbanicity, region of the U.S., and season of event. For nonaccidental mortality, we further conducted subgroup analyses that separated the population by sex and those who ended the study at <80 and ≥80 years of age. Supplemental analyses included effect modification between green space and self-reported asthma, with and without adjustment by season of event, within respiratory mortality models. Finally, we tested the sensitivity of our estimates by expanding the exposure window to 2 years prior to the event and adjusting for, rather than excluding, pre-existing conditions, for all mortality outcomes. Statistical analyses were performed in the SAS/STAT software, version 9.4.[33]

Results

After excluding key self-reported pre-existing conditions related to cancer (n = 12,816), CVD (n = 9,303), and respiratory diseases (n = 4,847), there were 67,400 subjects remaining in the study sample (Figure 1). Mean follow-up time for study participants was 11.3 years, totaling 763,798 person-years. Table 1 shows the distribution of key variables within the full sample and across NDVI quintiles for the 1000-m buffer. Summary statistics for all other variables are provided in eTable 1; http://links.lww.com/EE/A297. Quintile cutoffs for the 20th, 40th, 60th, and 80th percentiles were 0.38, 0.47, 0.54, and 0.61, respectively. The average baseline NDVI exposure for the entire cohort was 0.5 ± 0.1 and ranged from an average of 0.3 ± 0.1 in the lowest quintile to 0.7 ± 0.1 in the highest quintile. There were 5953 deaths from nonaccidental causes, 2,147 from CVD, 787 specific to IHD, and 387 deaths

from respiratory diseases. The majority of the sample were female (66%), identified as non-Hispanic White (59.9%), were born in the United States or Canada (79.4%), and lived in an urban area (population ≥50,000) at baseline (63.1%). In addition, 34% of the baseline population resided in the West, 18% in Central states, 24% in the South, and 24% in the East. The average ambient concentrations for $PM_{2.5}$, NO_2, and O_3 at baseline were highest in the lowest NDVI quintile at 13.3 μg/m^3, 18.8 ppb, and 51.5 ppb, respectively, with statistically significant inverse Pearson correlation coefficients between green space and all three ambient air pollutants (eTable 2; http://links.lww.com/EE/A297).

Table 2 displays HRs for a 0.1 unit increase in the NDVI within the 1000-m buffer for each mortality outcome with different covariate adjustments, from crude to fully adjusted three-pollutant models. There were negligible differences in the magnitude of the HRs between unadjusted base models (nonaccidental HR: 0.98 [95% confidence interval (CI): 0.96, 1.00], CVD HR: 0.98 [95% CI: 0.95, 1.01], IHD HR: 0.91 [95% CI: 0.86, 0.96], and respiratory HR: 1.01 [95% CI: 0.94, 1.09]) to models adjusted by $PM_{2.5}$ and all demographic, lifestyle, spatial, and health covariates (Model 5: nonaccidental HR: 0.97 [95% CI: 0.95, 0.99], CVD HR: 0.97 [95% CI: 0.93, 1.00], IHD HR: 0.91 [95% CI: 0.86, 0.97], and respiratory HR: 1.00 [95% CI: 0.93, 1.09], see Table 2). In fully adjusted models (Table 2, Model 6), which included all three air pollutants, a 0.1 unit increase in the NDVI resulted in a 4% reduction in nonaccidental (HR: 0.96 [95% CI: 0.93, 0.99]), a 6% reduction in CVD (HR: 0.94 [95% CI: 0.90, 0.98]), and a 13% reduction in IHD (HR: 0.87 [95% CI: 0.81, 0.94]) mortality. HRs in the single- and three-pollutant models using the 250-m and 500-m NDVI buffers were similar in magnitude (eTable 3; http://links.lww.com/EE/A297).

Green space was not associated with respiratory mortality regardless of buffer size or model adjustments. Effect modification estimates between the NDVI and pre-existing asthma were also not statistically significant, although there was a notable difference in the relationship between green space and respiratory mortality among those with (HR: 1.20 [95% CI: 0.94, 1.53]) and without (HR: 0.99 [95% CI: 0.90, 1.10]) baseline prevalent asthma that continued to diverge when adjusted by season of event (with asthma HR: 1.14 [95% CI: 0.90, 1.45] and without asthma HR: 0.94 [95% CI: 0.85, 1.05], eTable 4; http://links.lww.com/EE/A297). The amount of surrounding vegetation also modified the association between asthma and respiratory mortality, with a 78% (HR: 1.78 [95% CI: 1.08, 2.93]) increased risk in the 10th percentile of the NDVI to a 224% (HR: 3.24 [95% CI: 2.05, 5.13]) increased risk in the 90th percentile.

Table 3 presents the results of effect modification for green space by urbanicity, region, and season of event for each mortality outcome. A 0.1 unit increase in the NDVI significantly reduced the risk of nonaccidental (HR: 0.94 [95% CI: 0.91, 0.98]), CVD (HR: 0.89 [95% CI: 0.84, 0.95]), and IHD (HR: 0.83 [95% CI: 0.76, 0.91]) mortality in urban neighborhoods, with HRs attenuated to the null in urban cluster and rural areas. Across regions, green space had a stronger association with nonaccidental mortality in the West, and with CVD and IHD mortality in the West and South. When incorporating season of event into the risk set, HRs were greatest for CVD (HR: 0.86 [95% CI: 0.81, 0.92]) and IHD (HR: 0.77 [95% CI: 0.69. 0.86]) mortality in the Fall, with lower mortality rates that spanned all seasons, only attenuating from significance in the Summer for CVD and the Spring for IHD. HRs were consistently associated with green space and nonaccidental mortality, ranging from a 7% to 10% reduction across seasons. The association between the NDVI and respiratory mortality remained null for all rural/urban categories, regions, and seasons, although with some variability.

Additional subgroup analyses between green space and nonaccidental mortality (Table 4) showed a stronger association in females (HR: 0.94 [95% CI: 0.90, 0.97]) than males (HR: 0.99 [95% CI: 0.94, 1.04]), but no difference between those <80 or ≥80 years of age. In sensitivity tests, there were also negligible changes in effect after doubling the exposure window for all four mortality outcomes (eTable 5; http://links.lww.com/EE/A297), and when adjusting for, rather than excluding, pre-existing cancers, CVD, and respiratory diseases (eTable 6; http://links.lww.com/EE/A297), there was no change in the interpretation of the results. However, between green space and IHD mortality, there was a slight attenuation, although still a significant association, when including pre-existing conditions. While results remained null for respiratory mortality, adding subjects with pre-existing conditions lowered the mortality rate, with narrower CIs.

Discussion

We found neighborhood green space was associated with nonaccidental, CVD, and IHD mortality, with the strongest effects in fully adjusted three-pollutant models. This association was fairly robust, with little change in HRs from crude models up

Table 2.

Attained age Cox proportional hazard ratios for a 0.1 unit increase in the NDVI within a 1000-m buffer for each mortality outcome (nonaccidental, CVD, IHD, and respiratory), comparing crude to fully adjusted models

	Nonaccidental	CVD	IHD	Respiratory
Models	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Base Model[a]	0.98 (0.96, 1.00)	0.98 (0.95, 1.01)	0.91 (0.86, 0.96)	1.01 (0.94, 1.09)
Model 2[b]	0.98 (0.95, 1.00)	0.97 (0.94, 1.01)	0.91 (0.86, 0.96)	1.01 (0.93, 1.09)
Model 3[c]	0.98 (0.95, 1.00)	0.97 (0.94, 1.01)	0.91 (0.85, 0.96)	1.00 (0.92, 1.09)
Model 4[d]	0.98 (0.95, 1.00)	0.97 (0.93, 1.01)	0.91 (0.85, 0.96)	1.01 (0.93, 1.10)[e]
Model 5[f]	0.97 (0.95, 0.99)	0.97 (0.93, 1.00)	0.91 (0.86, 0.97)	1.00 (0.93, 1.09)[e]
Model 6[g]	0.96 (0.93, 0.99)	0.94 (0.90, 0.98)	0.87 (0.81, 0.94)	1.02 (0.92, 1.12)[e]

[a]Model clustered on baseline county with no covariate adjustments.

[b]Model 2 = base model plus adjustment by sex, race, born in the United States or Canada, educational attainment, marital status, household income, consumption of red/processed meat, tree nuts, wine, beer/liquor, smoking status, baseline neighborhood-level factors of urbanicity, median household income, and median home value.

[c]Model 3 = Model 2 plus adjustment by physical activity and BMI.

[d]Model 4 = Model 3 plus adjusted by diabetes, high blood pressure, blood pressure medication, high cholesterol, cholesterol medication, daily aspirin use, and the use of hormone replacement therapy by menopausal status (females only).

[e]Models additionally adjusted by pre-existing asthma.

[f]Model 5 = Model 4 plus adjustment by $PM_{2.5}$.

[g]Model 6 = Model 5 plus adjustment by NO_2 and O_3.

Table 3.

Hazard ratios for a 0.1 unit increase in the NDVI within a 1000-m buffer looking at effect modification by baseline urbanicity, baseline region of the United States, and season of event for each mortality outcome

	Nonaccidental	CVD	IHD	Respiratory
Effect modifiers	**HR (95% CI)[a]**	**HR (95% CI)[a]**	**HR (95% CI)[a]**	**HR (95% CI)[a,b]**
Urbanicity				
Urban (≥50,000)	0.94 (0.91, 0.98)	0.89 (0.84, 0.95)	0.83 (0.76, 0.91)	0.97 (0.84, 1.12)
Urban cluster (2,500–49,999)	0.98 (0.91, 1.05)	0.92 (0.84, 1.01)	0.87 (0.75, 1.01)	1.17 (0.97, 1.41)
Rural (<2,500)	0.97 (0.93, 1.01)	1.01 (0.95, 1.08)	0.94 (0.84, 1.06)	0.99 (0.85, 1.16)
Region[c]				
Central	0.99 (0.92, 1.07)	1.05 (0.93, 1.18)	1.00 (0.83, 1.21)	0.83 (0.62, 1.12)
East	0.98 (0.93, 1.04)	0.97 (0.87, 1.07)	0.97 (0.79, 1.18)	1.15 (0.91, 1.45)
West	0.94 (0.91, 0.98)	0.92 (0.87, 0.97)	0.85 (0.78, 0.92)	1.06 (0.94, 1.18)
South	0.99 (0.93, 1.05)	0.92 (0.83, 1.00)	0.81 (0.71, 0.93)	0.97 (0.79, 1.18)
Season of event[d]				
Winter	0.90 (0.85, 0.95)	0.91 (0.84, 0.97)	0.84 (0.75, 0.94)	0.93 (0.79, 1.10)
Spring	0.92 (0.88, 0.97)	0.89 (0.82, 0.96)	0.91 (0.81, 1.02)	1.03 (0.86, 1.23)
Summer	0.93 (0.89, 0.98)	0.92 (0.85, 1.01)	0.83 (0.73, 0.95)	0.94 (0.81, 1.10)
Fall	0.91 (0.87, 0.96)	0.86 (0.81, 0.92)	0.77 (0.69, 0.86)	0.98 (0.82, 1.17)

[a]Models clustered on baseline county and adjusted for sex, race, born in the United States or Canada, educational attainment, marital status, household income, physical activity, consumption of red/processed meat, tree nuts, wine, beer/liquor, smoking status, body mass index, baseline neighborhood-level factors of urbanicity, median household income, median home value, diabetes, high blood pressure, blood pressure medication, high cholesterol, cholesterol medication, daily aspirin use, the use of hormone replacement therapy by menopausal status (females only), and $PM_{2.5}$, NO_2, and O_3.
[b]Models also adjusted by pre-existing asthma.
[c]Region based on baseline address and divided into: Western (Arizona, California, Idaho, Montana, Nevada, Oregon, Utah, and Washington), Central (Colorado, Illinois, Indiana, Iowa, Kansas, Kentucky, Michigan, Minnesota, Missouri, Nebraska, North Dakota, South Dakota, Wisconsin, and Wyoming), Southern (Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, New Mexico, Oklahoma, Tennessee, and Texas), and Eastern (Connecticut, Delaware, Massachusetts, Maine, Maryland, New Hampshire, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Rhode Island, South Carolina, Vermont, Virginia, and West Virginia).
[d]Based on meteorological seasons: Winter (December, January, February), Spring (March, April, May), Summer (June, July, August), and Fall (September, October, November).

Table 4.

Subgroup analyses by sex and age subjects ended the study using separate attained age Cox proportional hazard regression models

	Nonaccidental
Subgroup	**HR (95% CI)[a]**
Sex[b]	
Female	0.94 (0.90, 0.97)
Male	0.99 (0.94, 1.04)
Age[c]	
<80 years	0.96 (0.92, 1.00)
≥80 years	0.96 (0.92, 0.99)

HRs reported a 0.1 unit increase in the NDVI within a 1000-m buffer for nonaccidental mortality within each subgroup.
[a]Models clustered on baseline county and adjusted for sex, race, born in the United States or Canada, educational attainment, marital status, household income, physical activity, consumption of red/processed meat, tree nuts, wine, beer/liquor, smoking status, body mass index, baseline neighborhood-level factors of urbanicity, median household income, median home value, diabetes, high blood pressure, blood pressure medication, high cholesterol, cholesterol medication, daily aspirin use, and the use of hormone replacement therapy by menopausal status (females only).
[b]Separate models for males and females.
[c]Separate models for risk sets based on subjects <80 years and subjects ≥80 years of age.

to models adjusted by all covariates other than NO_2 and O_3. Sensitivity analyses also resulted in minimal changes in the magnitude of the association between green space and mortality across different buffer sizes, findings that were consistent with others,[2,3,5,6] and after the inclusion of subjects with pre-existing conditions. There was virtually no change in effect when using a 2-year exposure window, suggesting longer exposure averages are unnecessary.

Additional adjustment by NO_2 and O_3, however, had the greatest effect on overall estimate precision and magnitude. We only found one study that compared the NDVI with nonaccidental, CVD, IHD, or respiratory mortality while adjusting for $PM_{2.5}$, NO_2, and O_3, individually and combined, and like our findings, the strength of the association was greater in three-pollutant, than single pollutant ($PM_{2.5}$) models.[2] While air pollutants have been regarded as mediators of the association between green space and health, two studies that had broad geographic coverage showed very little mediation,[3,5] and the greater precision and strengthened effect from our study and from Canada[2] suggest mediation had little influence in these areas. Effect modification analyses within the fully adjusted three-pollutant models found additional strengthening of the association between green space and nonaccidental, CVD, and IHD mortality in urban areas, as well as a stronger overall effect across seasons, when incorporating season of event into the model. For example, with CVD mortality, HRs for a 0.1 unit increase in the NDVI between the unadjusted Base Model to Model 5, resulted in a nonsignificant 2%–3% reduction (Table 2). In fully adjusted three-pollutant models, this increased to a significant 6% reduction (Table 2), which was further elevated to an 11% reduction in urban areas and an 8%–14% reduction across seasons (Table 3). Thus, in our study, incorporating more environmental factors that characterized the defined neighborhood, including the season, strengthened associations more than the size of the buffer, exposure window, or adjustment by individual demographic characteristics, lifestyle habits, and health conditions of study subjects.

Region also modified the effect, but unlike season, many regional associations were null. For example, green space was only associated with CVD and IHD mortality in the West and South, and null in Central and Eastern states. While not a perfect surrogate, many areas in Western and Southern states experience smaller seasonal shifts, particularly in Winter, than do states in the Central and Eastern regions. This could have made our estimate of green space, the average of the NDVI across all seasons, less effective in these areas that are more prone to snow during the winter months.

It was also possible that our exposure assignment methods could, at least partially, have explained the unexpected null results between green space and respiratory mortality. While many other studies have found green space inversely associated with respiratory mortality,[2,3,5,6,20,22] five of these six studies used a static single or average estimate of peak NDVI,[2,5,6,20,22] in contrast

to our moving exposure window of all four seasons. These studies were also from countries generally located in higher latitudes[2,5,6,20,22] than the contiguous U.S., impacting the degree of seasonal change, such as temperature, snow, sunlight, and plant life cycles, throughout the year. Respiratory diseases, such as cold, flu, and allergies, also have prominent seasonal variations, with both sickness and weather patterns altering how populations interact with the natural environment. With these seasonal influences in exposure and disease, it is possible that seasonally specific estimates, such as peak greenness, are more predictive of the association between green space and respiratory mortality. In addition, effect modification by season of event found a stronger association between green space and respiratory mortality in the Winter and Summer. Events in Winter, the prominent cold and flu season, could hint towards reduced risk of acute infectious respiratory diseases. This idea is further supported by Coleman et al[11] who found green space was associated with (albeit non-significantly) pneumonia and influenza mortality (HR: 0.90 [95% CI: 0.77, 1.05]), but completely null for chronic lower respiratory disease mortality (HR: 1.00 [95% CI: 0.91, 1.09]). Although the limited number of respiratory events makes these associations difficult to assess.

We observed the strongest association between green space and IHD mortality, with a 13% reduction for every 0.1 unit increase in the NDVI. The weaker association with CVD mortality, which IHD is a subset of, suggested that the relationship between green space and total CVD was not representative of all cardiovascular-type diseases, with the need for further disaggregation of non-IHD CVD events.

Finally, the magnitude of the association between green space and nonaccidental mortality was similar to that of other studies, with generally a small but significant reduction in mortality risk.[1–3,5,6,19–22] We hypothesize that the stronger association between green space and nonaccidental mortality among AHS-2 females may be a result of our green space estimate, neighborhood NDVI, more accurately reflecting our female population's total exposure. While we lacked information on time spent at home and exposure profiles beyond the neighborhood buffer zone, more females had reported being unemployed (41%) or working in the home (20%) on the AHS-2 questionnaire, than males (30% and <1%, respectively).

Strengths and limitations

Our large study was strengthened by time-changing green space and air pollutants, while adjusting for a broad spectrum of risk factors. However, one limitation was the noncongruent granularity of NDVI and air pollution estimates (seasonal and annual, respectively), which could have introduced measurement error. There were also limited mortality events, particularly for respiratory mortality, after removing subjects with pre-existing cancer, CVD, and respiratory diseases. While two studies comprised exclusively of persons with some of these prevalent diseases had null findings,[39,40] sensitivity analyses suggested that only IHD mortality risk was attenuated (although still significant) in our models after including subjects with these prevalent conditions. Even with such limitations, additional sensitivity analysis showed the results to be robust and comparable to other published work.

Conclusion

This study adds to the body of research highlighting the inverse association of green space with nonaccidental, CVD, and IHD mortality, and the precision that can be gained by including multiple environmental neighborhood characteristics in the model. While our study focused on adjusting for multiple ambient air pollutants, with added benefits from including season and specifying urban localities, future studies should continue to broaden the definition of pertinent neighborhood and seasonal characteristics that impact human health, as well as quantify these associations with more granular mortality outcomes (such as cerebrovascular events and infectious versus noninfectious respiratory diseases).

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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