Supplemental Digital Content

The Association between Neighborhood Greenness and Incidence of Lethal Prostate Cancer: A Prospective Cohort Study

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eMethods S1. Methods for Covariate Selection, Causal Mediation Analysis, and Sensitivity Analysis

Covariate Selection

We selected individual confounding variables *a priori* based on previous studies that assessed the association between greenness and cancer, greenness and physical activity, and physical activity and cancer. Studies of physical activity and cancer have been conducted previously in HPFS, and adjusted models included prostate cancer risk factors that could be associated with neighborhood greenness, including age, BMI at age 21, height, family history of prostate cancer, smoking, diabetes mellitus, and race (S1, S2). Since prostate cancer screening using prostate specific antigen (PSA) testing is associated with diagnosis of lethal prostate cancer and urbanicity (S3) and thus could be associated with neighborhood greenness, we considered it to be a confounder.

Greenness is a contextual covariate and so adjustment must be made for other contextual environmental factors that may also be associated with greenness and lethal prostate cancer. Our selection of contextual covariates was guided by Krieger's ecosocial theory of epidemiology (S4). We assumed that participants living in different geographic areas would be exposed to different social contexts, urban environments, and healthcare access that would impact their risk of prostate cancer. Contextual socioeconomic status was estimated using data from the 1990 US decennial census at tract level. We used median income and median home value to capture income and wealth of study participants' neighborhoods.

Use of green spaces varies between urban and rural areas (S5), so we examined effect modification by population density at census tract level, using a cutpoint of 1000 people/mi^2 to group people into high compared to low population density areas. We further examined effect modification by greenness exposure at home compared to work address among those participants for whom address type was documented in 1988 (N=35,474).

Mediation Analysis

We used causal mediation analysis to evaluate the importance of vigorous physical activity as a mediating pathway. Briefly, causal mediation analysis differs from traditional mediation analysis by specifying counterfactual targets that correspond to a decomposition of the total effect into a "direct" effect (effect of exposure independent of a mediator) and "indirect" effect (effect of exposure due to mediator) (S6, S7). In addition, a controlled direct effect can be estimated under slightly weaker assumptions of (1) no exposure-outcome confounding and (2) no mediator-outcome confounding (S7, S8).

To evaluate the importance of vigorous physical activity as a mediating pathway, we fit multinomial logistic regression models at baseline with our mediator (categories of vigorous physical activity) as the dependent variable and our exposure (NDVI, continuous and using quintiles) as our independent variable to determine the strength of the exposure-mediator association in our analysis (S7). We fit a multiplicative interaction term between continuous NDVI and population density to evaluate possible differences in the association between NDVI and vigorous physical activity in high compared to low population density areas. To estimate the unbiased effect of NDVI on vigorous physical activity, we adjusted for the covariates described above, as well as additional confounders of the hypothesized exposure-mediator effect (1986 measures of non-vigorous physical activity, current BMI).

Next, we estimated the controlled direct effect of greenness on lethal prostate cancer, fixing vigorous physical activity across levels of NDVI (S7, S8). Valid estimation of controlled direct effects requires the assumption of no unmeasured mediator-outcome confounding along with the assumption of no exposure-outcome confounding, so we further adjusted for non-vigorous physical activity and current BMI as confounders of the effect of vigorous physical activity on lethal prostate cancer. Finally, to ensure correct model specification, we additionally tested for exposure-mediator interaction by fitting multiplicative interaction terms between NDVI (continuous) and quintiles of vigorous physical activity.

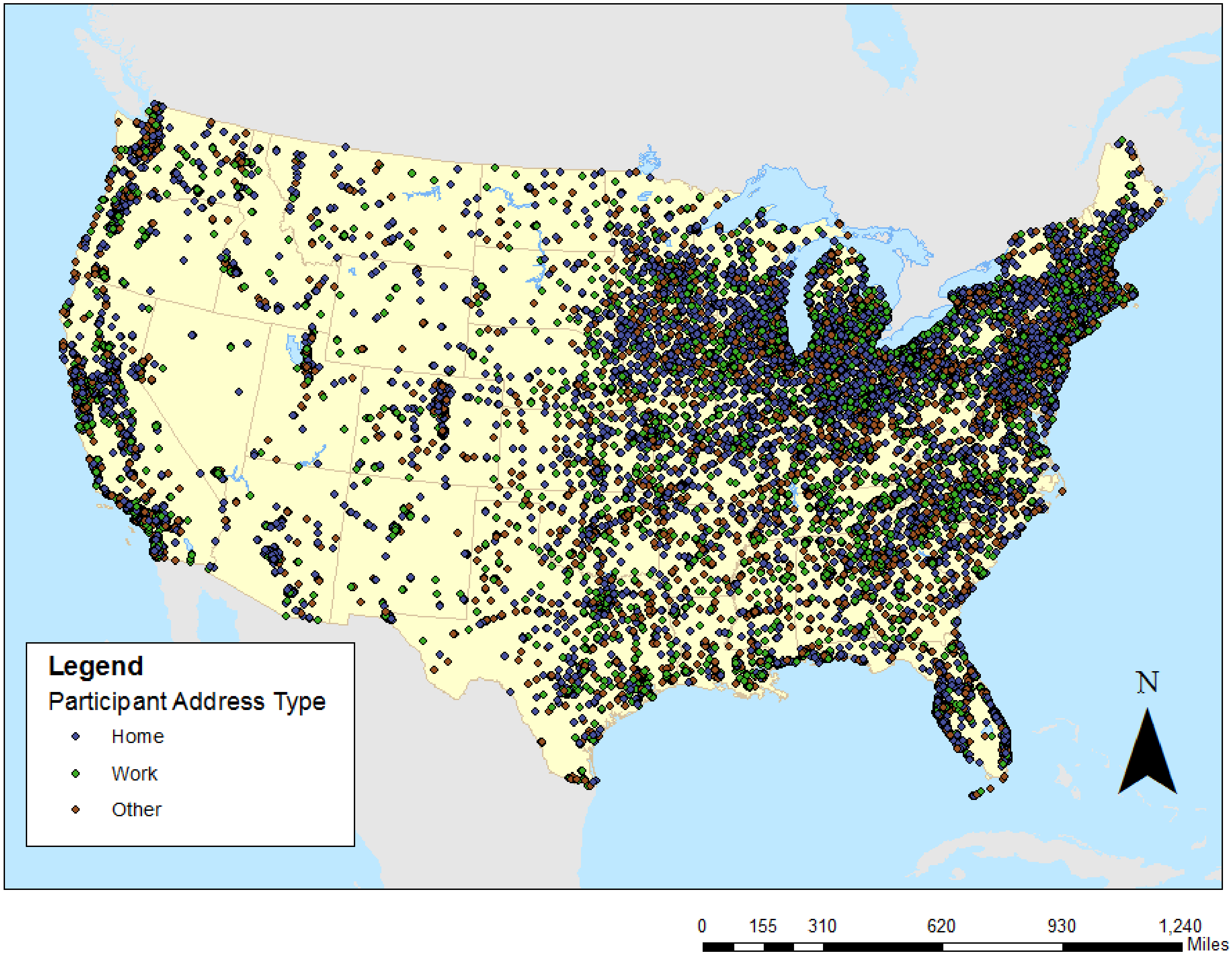
Cumulative Updated Average NDVI Exposure

As a sensitivity analysis, we evaluated the association between NDVI and rate of lethal prostate cancer using cumulative updated average, rather than baseline, exposure. This exposure metric was calculated by updating NDVI exposure at each follow-up point (every two years) with the average across four seasonal images per year (January, April, July, September). We analyzed the data by fitting time-varying Cox proportional hazards models, sequentially adjusting for the same variable sets as described in the primary analysis. However, for regression models using cumulative updated average NDVI, we included time-varying covariates (NDVI, smoking, vigorous physical activity, non-vigorous physical activity, current BMI, every two years; census socioeconomic status measures every 10 years, PSA screening prior to diagnosis, and PSA screening intensity). Since population density patterns were most strongly pronounced, we provided stratified estimates by high and low population density.

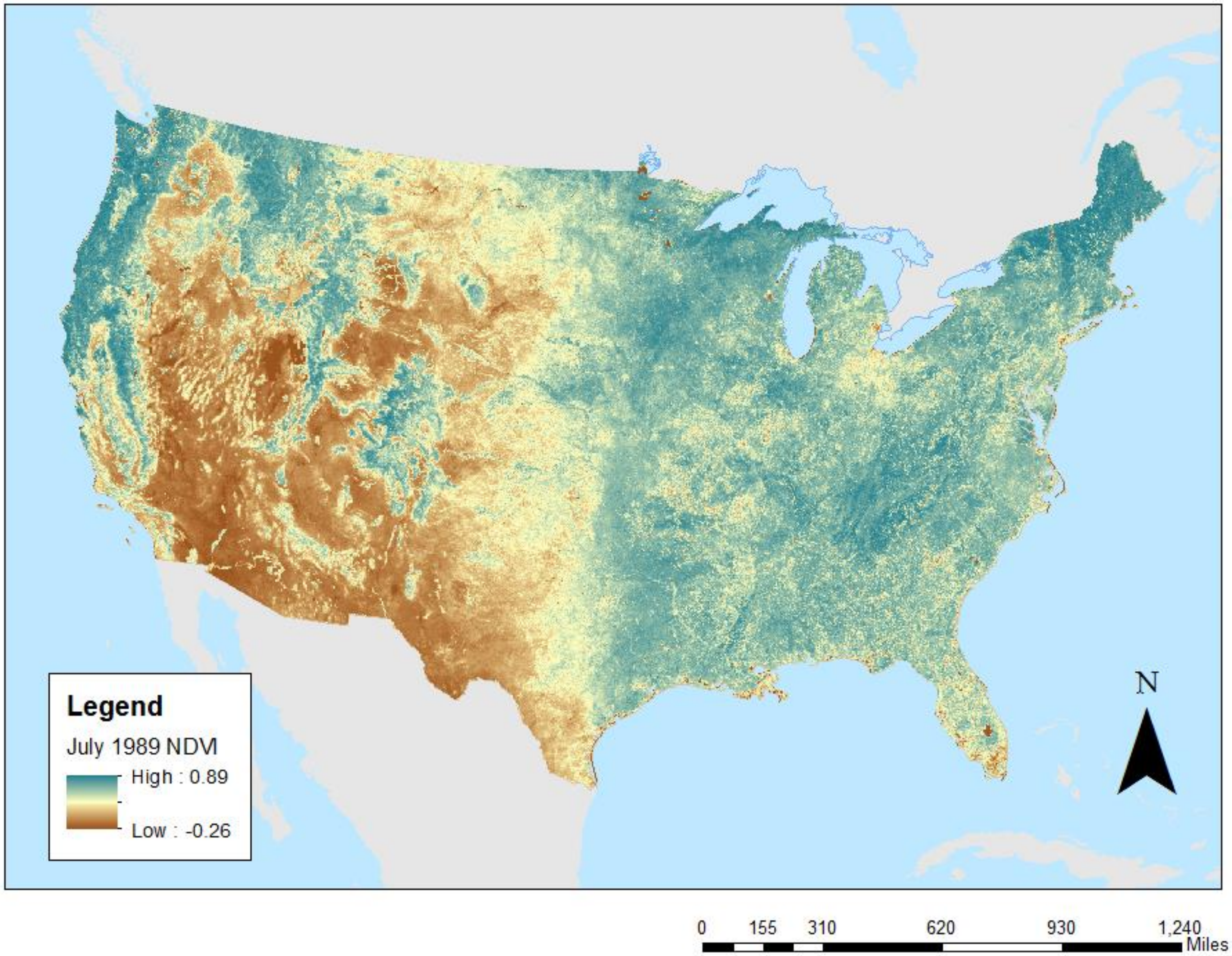
Sensitivity Analysis for Unmeasured Confounding

To determine robustness of our analyses to assumptions regarding unmeasured confounding, we calculated e-values corresponding to fully adjusted hazard ratios and confidence intervals for baseline NDVI and lethal prostate cancer in the full population and among non-movers (S9). The e-value reflects the minimum strength of the ratio effect measure describing 1) the association between an unmeasured confounder and outcome and 2) confounder and exposure, conditional on covariates, required to attenuate a reported association to the null. For confidence intervals, the e-value can be interpreted as the minimum bias required to shift the closer bound such that it includes the null. Stated another way, e-values provide bounds on potential bias arising from failure to adjust for unmeasured confounding. Larger e-values (farther from 1) provide stronger evidence that reported estimates are unlikely to be explained by unmeasured confounding; smaller e-values (closer to 1) provide weaker evidence.

eFigure S1. Health Professionals Follow-up Study geocoded locations (Home, Work, Other) at baseline (1988)



eFigure S2. NDVI 1989 values at Health Professionals Follow-up Study geocoded locations (Home, Work, Other)



eTable S1. Odds Ratios for the Association Between Normalized Difference Vegetation Index (NDVI) and Quintiles of Vigorous Physical Activity (PA)*, Health Professionals Follow-up Study, 1986 (N=47,958)

	Baseline Normalized Difference Vegetation Index (NDVI)												
	Continuous†		**Quintile 1**		**Quintile 2**		**Quintile 3**		**Quintile 4**		**Quintile 5**		
Model	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	P_{trend}
Vigorous Physical Activity Level‡													
L1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	
L2	0.94	0.91, 0.98	1.00	Referent	0.99	0.90, 1.08	0.90	0.82, 0.98	0.91	0.83, 0.99	0.89	0.81, 0.97	0.0023
L3	0.91	0.88, 0.94	1.00	Referent	0.92	0.85, 1.01	0.89	0.81, 0.97	0.85	0.78, 0.93	0.81	0.74, 0.89	<.0001
L4	0.91	0.88, 0.94	1.00	Referent	0.93	0.85, 1.01	0.85	0.78, 0.93	0.83	0.76, 0.90	0.79	0.72, 0.87	<.0001
L5	0.89	0.85, 0.92	1.00	Referent	0.95	0.86, 1.06	0.83	0.75, 0.93	0.81	0.72, 0.90	0.75	0.67, 0.84	<.0001

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; IQR, interquartile range; L, level; NDVI, normalized difference vegetation index, USD, United States Dollars

*Adjusted for age in months and calendar time as baseline strata, race (categorical), diabetes mellitus (yes or no), height (categorical), family history of prostate cancer (yes or no), BMI at age 21 (categorical), smoking status in 1986 (categorical), 1990 census tract median income (USD), and 1990 census tract median home value (USD), population density (binary: ≥1000, <1000 people/mi^2), non-vigorous physical activity in 1986 (quintiles), current BMI in 1986 (categorical)

†Estimate corresponds to an IQR increase in continuous NDVI of 0.11 units.

‡Interpretation of model: In a multinomial logistic regression model, odds ratios are calculated for multiple binary outcomes, in which nominal categories are compared to the referent (vigorous physical activity quintile 1). Results are provided for outcomes defined using vigorous physical activity levels (L) 2-5, where Level 1 (referent) corresponds to 0 MET-hours/week, and Levels 2-5 correspond to quartiles among participants who reported any vigorous physical activity.

eTable S2. Hazard Ratios for the Association Between Baseline Normalized Difference Vegetation Index (NDVI) and Lethal Prostate Cancer Incidence in the Health Professionals Follow-up Study, United States, 1986-2014

Model	Baseline Normalized Difference Vegetation Index (NDVI)												
	Continuous§		Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5		
	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	P_{trend}
Total population (N=47,958)													
Age and Calendar-time*	0.96	0.89, 1.03	1.00	Referent	0.87	0.71, 1.07	0.90	0.73, 1.10	0.78	0.63, 0.96	0.93	0.76, 1.14	0.25
Confounding†	0.95	0.88, 1.03	1.00	Referent	0.88	0.72, 1.09	0.92	0.75, 1.13	0.79	0.63, 0.98	0.91	0.73, 1.13	0.23
Controlled Direct Effects‡	0.95	0.88, 1.03	1.00	Referent	0.88	0.71, 1.08	0.92	0.74, 1.13	0.78	0.63, 0.97	0.91	0.73, 1.13	0.21
Men who did not move during follow-up (N=42,492)													
Age and Calendar-time*	0.92	0.85, 1.00	1.00	Referent	0.85	0.69, 1.05	0.88	0.71, 1.09	0.74	0.59, 0.92	0.85	0.69, 1.06	0.057
Confounding†	0.92	0.85, 1.01	1.00	Referent	0.86	0.70, 1.07	0.90	0.73, 1.12	0.75	0.60, 0.95	0.84	0.67, 1.06	0.068
Controlled Direct Effects‡	0.92	0.85, 1.01	1.00	Referent	0.86	0.70, 1.07	0.90	0.73, 1.12	0.75	0.60, 0.94	0.84	0.67, 1.06	0.067

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval, IQR, interquartile range; NDVI, normalized difference vegetation index; USD, United States Dollars.

*Adjusted for age in months and calendar time as strata.

†Adjusted for age in months and calendar time as strata, race (categorical), diabetes mellitus (yes or no), height (categorical), family history of prostate cancer (yes or no), BMI at age 21 (categorical), smoking status in 1986 (categorical), 1990 census tract median income (USD), 1990 census tract median home value (USD), population density, history of prostate-specific antigen testing, and intensity of prostate-specific antigen testing.

‡Adjusted for age in months and calendar time as strata, race (categorical), diabetes mellitus (yes or no), height (categorical), family history of prostate cancer (yes or no), BMI at age 21 (categorical), smoking status in 1986 (categorical), 1990 census tract median income (USD), 1990 census tract median home value (USD), population density, history of prostate-specific antigen testing, intensity of prostate-specific antigen testing, vigorous physical activity (categorical), non-vigorous physical activity (quintiles), and current BMI (categorical).

§Estimate corresponds to an IQR increase in continuous NDVI of 0.11 units.

eTable S3. Age-standardized Characteristics by Quintile of Normalized Difference Vegetation Index (NDVI) Among Men in the Health Professionals Follow-up Study From 1986 to 2014[*,†]

	Address Type	
Characteristics	**Home**	**Work**
Participants, no.	16,732	18,742
Age[‡,§], years	66.7 (11.7)	62.9 (10.7)
Baseline NDVI[§]	0.30 (0.09)	0.27 (0.09)
NDVI[§] (cumulative updated average)	0.32 (0.09)	0.30 (0.09)
Vigorous Activity[§], MET-hours/week	8.0 (16.7)	9.5 (18.0)
Non-vigorous Activity[§], MET-hours/week	17.3 (22.4)	17.6 (22.7)
Total activity[§], MET-hours/week	27.8 (29.9)	30.4 (31.1)
Height[§], inches	70.1 (2.7)	70.3 (2.6)
BMI at age 21[§], kilogram/meter^2	22.9 (2.8)	23.1 (2.8)
Current BMI[§], kilogram/meter^2	25.8 (3.5)	26.0 (3.6)
Race		
White, %	97	96
African American, %	1	1
Asian, %	1	2
Other, %	1	1
Smoking status		
Non-smoker, %	54	56
Past, quit >10 years ago, %	33	30
Current & past, quit ≤10 years ago, %	13	14
Diabetes, %	6	6
Family history of prostate cancer, %	13	13
Prostate Specific Antigen (PSA) screening history		
Had PSA test prior to diagnosis, %	35	42
PSA test on at least half of all questionnaires, 1994-2012, %	31	40
Census Region		
Northeast, %	23	22
Midwest, %	27	27
South, %	28	29
West, %	21	22
Population density[§], 1,000 people/mi^2	3.0 (7.9)	4.4 (10.0)
Census tract median income[§], 1,000 USD	55.1 (26.9)	55.0 (30.1)
Census tract median home value[§], 1000 USD	161.2 (136.0)	167.2 (154.2)
Moved during follow-up, %	14	10
Cases of lethal prostate cancer	390	291
Person-years	348573	436305
Incidence rate per 100,000 person-years	112	67

Abbreviations: BMI, body mass index; MET, metabolic equivalent of task; NDVI, normalized difference vegetation index; USD, United States Dollar.

[*]Values are standardized to the age distribution of the study population

[†]Values of polytomous variables may not sum to 100% due to rounding

[‡]Not age-adjusted

[§]Values are expressed as mean (standard deviation)

eTable S4. Hazard ratios for the Association Between Cumulative Updated Average Normalized Difference Vegetation Index (NDVI) and Lethal Prostate Cancer Incidence in the Health Professionals Follow-up Study, United States, 1986-2014, Stratified by Population Density

	Cumulative Updated Average Normalized Difference Vegetation Index (NDVI)												
Model	**Continuous**‖		**Quintile 1**		**Quintile 2**		**Quintile 3**		**Quintile 4**		**Quintile 5**		
	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	P_{trend}
Total population§ (N=47,958)													
Age and Calendar-time*	0.96	0.89, 1.04	1.00	Referent	0.85	0.69, 1.04	0.84	0.68, 1.03	0.86	0.70, 1.05	0.87	0.71, 1.06	0.19
Confounding†	0.96	0.88, 1.05	1.00	Referent	0.85	0.69, 1.05	0.85	0.69, 1.05	0.87	0.71, 1.08	0.86	0.69, 1.07	0.21
Controlled Direct Effects‡	0.96	0.88, 1.05	1.00	Referent	0.85	0.70, 1.06	0.85	0.69, 1.05	0.88	0.71, 1.08	0.86	0.69, 1.07	0.21
High (≥1000 people/mi²) population density (N=34,229)													
Age and Calendar-time*	0.93	0.84, 1.03	1.00	Referent	0.84	0.67, 1.05	0.80	0.63, 1.01	0.79	0.63, 1.00	0.81	0.62, 1.05	0.048
Confounding†	0.93	0.84, 1.04	1.00	Referent	0.84	0.67, 1.05	0.80	0.63, 1.02	0.80	0.63, 1.02	0.81	0.61, 1.06	0.065
Controlled Direct Effects‡	0.93	0.84, 1.04	1.00	Referent	0.84	0.67, 1.06	0.80	0.63, 1.02	0.80	0.63, 1.03	0.80	0.61, 1.05	0.063
Low (<1000 people/mi²) population density (N=13,729)													
Age and Calendar-time*	1.04	0.88, 1.22	1.00	Referent	0.85	0.50, 1.44	1.06	0.64, 1.75	1.11	0.68, 1.80	1.02	0.65, 1.61	0.67
Confounding†	1.05	0.89, 1.24	1.00	Referent	0.91	0.53, 1.56	1.17	0.70, 1.95	1.22	0.74, 1.99	1.10	0.69, 1.75	0.51
Controlled Direct Effects‡	1.06	0.89, 1.25	1.00	Referent	0.90	0.52, 1.55	1.15	0.69, 1.92	1.23	0.75, 2.03	1.11	0.70, 1.77	0.45

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval, IQR, interquartile range; NDVI, normalized difference vegetation index; USD, United States Dollars.

*Adjusted for age in months and calendar time as baseline strata

†Adjusted for age in months and calendar time as baseline strata, race (categorical), diabetes mellitus (yes or no), height (categorical), family history of prostate cancer (yes or no), BMI at age 21 (categorical), history of prostate-specific antigen testing, smoking (categorical), intensity of prostate-specific antigen testing (categorical), census tract median income (USD), and census tract median home value (USD)

‡Adjusted for age in months and calendar time as baseline strata, race (categorical), diabetes mellitus (yes or no), height (categorical), family history of prostate cancer (yes or no), BMI at age 21 (categorical), history of prostate-specific antigen testing, smoking (categorical), intensity of prostate-specific antigen testing (categorical), census tract median income (USD), and census tract median home value (USD), vigorous physical activity (categorical), non-vigorous physical activity (quintiles), and current BMI (categorical)

§For models fit in total population, models 2 and 3 additionally adjusted for population density (binary: ≥1000, <1000 people/mi²)

‖Estimate corresponds to an IQR increase in continuous NDVI of 0.11 units.

eTable S5. Hazard Ratios for the Association Between Maximum Normalized Difference Vegetation Index (NDVI) at Start of Follow-up and Lethal Prostate Cancer Incidence in the Health Professionals Follow-up Study, United States, 1986-2014

	Baseline Normalized Difference Vegetation Index (NDVI)												
Model	**Continuous**[§]		**Quintile 1**		**Quintile 2**		**Quintile 3**		**Quintile 4**		**Quintile 5**		
	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	aHR	95% CI	P_{trend}
Total population (N=47,958)													
Age and Calendar-time[*]	0.97	0.92, 1.03	1.00	Referent	0.85	0.69, 1.05	0.92	0.76, 1.13	0.89	0.72, 1.09	0.87	0.70, 1.07	0.23
Confounding[†]	0.98	0.91, 1.04	1.00	Referent	0.87	0.71, 1.08	0.96	0.78, 1.18	0.91	0.73, 1.14	0.85	0.67, 1.08	0.27
Controlled Direct Effects[‡]	0.97	0.91, 1.04	1.00	Referent	0.87	0.71, 1.08	0.95	0.77, 1.17	0.91	0.73, 1.13	0.85	0.67, 1.07	0.34
Men who did not move during follow-up (N=42,492)													
Age and Calendar-time[*]	0.96	0.90, 1.02	1.00	Referent	0.81	0.65, 1.01	0.86	0.70, 1.06	0.86	0.69, 1.06	0.80	0.64, 1.00	0.07
Confounding[†]	0.96	0.90, 1.03	1.00	Referent	0.83	0.67, 1.04	0.90	0.72, 1.12	0.89	0.71, 1.12	0.81	0.63, 1.03	0.15
Controlled Direct Effects[‡]	0.96	0.90, 1.03	1.00	Referent	0.83	0.67, 1.04	0.89	0.72, 1.11	0.89	0.70, 1.11	0.81	0.63, 1.03	0.14

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval, IQR, interquartile range; NDVI, normalized difference vegetation index; USD, United States Dollars.

[*]Adjusted for age in months and calendar time as strata.

[†]Adjusted for age in months and calendar time as strata, race (categorical), diabetes mellitus (yes or no), height (categorical), family history of prostate cancer (yes or no), BMI at age 21 (categorical), smoking status in 1986 (categorical), 1990 census tract median income (USD), 1990 census tract median home value (USD), population density, history of prostate-specific antigen testing, and intensity of prostate-specific antigen testing.

[‡]Adjusted for age in months and calendar time as strata, race (categorical), diabetes mellitus (yes or no), height (categorical), family history of prostate cancer (yes or no), BMI at age 21 (categorical), smoking status in 1986 (categorical), 1990 census tract median income (USD), 1990 census tract median home value (USD), population density, history of prostate-specific antigen testing, intensity of prostate-specific antigen testing, vigorous physical activity (categorical), non-vigorous physical activity (quintiles), and current BMI (categorical).

[§]Estimate corresponds to an IQR increase in continuous NDVI of 0.11 units.

eTable S6. E-values for Hazard Ratios for the Association Between Baseline Normalized Difference Vegetation Index (NDVI) and Lethal Prostate Cancer*, Total Population and Men who did not Move During Follow-up, Health Professionals Follow-up Study, United States, 1986-2014, stratified by population density

	Baseline Normalized Difference Vegetation Index (NDVI)											
	Continuous†		**Quintile 1**		**Quintile 2**		**Quintile 3**		**Quintile 4**		**Quintile 5**	
E-Value	Estimate	CI	Estimate	CI	Estimate	CI	Estimate	CI	Estimate	CI	Estimate	CI
Total population												
Full cohort‡ (N=47,958)	1.29	1.00	1.00	Referent	1.53	1.00	1.39	1.00	1.85	1.16	1.36	1.00
High (≥1000 people/mi^2) population density (N=34,229)	1.45	1.08	1.00	Referent	1.27	1.00	1.47	1.00	1.67	1.00	1.86	1.00
Low (<1000 people/mi^2) population density (N=13,729)	1.45	1.00	1.00	Referent	1.34	1.00	1.65	1.00	1.72	1.00	2.05	1.00
Participants who did not change addresses												
Full subcohort‡ (N=42,492)	1.39	1.00	1.00	Referent	1.60	1.00	1.45	1.00	2.00	1.29	1.67	1.00
High (≥1000 people/mi^2) population density (N=30,259)	1.53	1.19	1.00	Referent	1.26	1.00	1.55	1.00	1.77	1.00	2.12	1.29
Low (<1000 people/mi^2) population density (N=12,233)	1.34	1.00	1.00	Referent	1.18	1.00	2.00	1.00	1.75	1.00	1.72	1.00

Abbreviations: BMI, body mass index; CI, confidence interval, IQR, interquartile range; NDVI, normalized difference vegetation index; USD, United States Dollars.

*Adjusted for age in months and calendar time as baseline strata, race (categorical), diabetes mellitus (yes or no), height (categorical), family history of prostate cancer (yes or no), BMI at age 21 (categorical), smoking status in 1986 (categorical), 1990 census tract median income (USD), 1990 census tract median home value (USD), history of prostate-specific antigen testing, and intensity of prostate-specific antigen testing

†Estimate corresponds to an IQR increase in continuous NDVI of 0.11 units.

‡For models fit in full cohort and subcohorts, additionally adjusted for population density (binary: ≥1000, <1000 people/mi^2)

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