The association between neighborhood greenness and incidence of lethal prostate cancer

A prospective cohort study

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Background: Growing evidence suggests that neighborhood contextual environment could influence risk factors and, therefore, incidence of lethal prostate cancer. We studied the association between neighborhood greenness and lethal prostate cancer incidence and assessed mediation by vigorous physical activity.

Methods: A total of 47,958 participants were followed in the Health Professionals Follow-up Study from 1986 to 2014. Neighborhood greenness exposure was estimated using normalized difference vegetation index (NDVI) with 1 km resolution, assigned to home or work addresses at start of follow-up. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were estimated using sequentially adjusted Cox models with individual and contextual prostate cancer risk factors as covariates. Analyses were compared among those whose addresses were constant over follow-up and stratified by population density and address type.

Results: We observed 898 cases over 1,054,745 person-years. An interquartile range increase in NDVI was associated with 5% lower rate of lethal prostate cancer (aHR = 0.95, 95% CI = 0.88, 1.03), with stronger associations in non-movers (aHR = 0.92, 95% CI = 0.85, 1.01). Inverse associations were observed among men in high (aHR = 0.90, 95% CI = 0.82, 0.99) but not low (aHR = 1.11, 95% CI = 0.95, 1.29, Phet = 0.086) population density areas, and those reporting from work (aHR = 0.87, 95% CI = 0.75, 1.01) but not home (aHR = 1.04, 95% CI = 0.91, 1.17, Prural = 0.10) addresses. There was no evidence of mediation by vigorous physical activity.

Conclusion: We report inverse associations between neighborhood greenness and lethal prostate cancer when restricting to non-movers and in high population density areas. Replication could confirm findings and clarify mechanisms.

Key Words: Green space; Prostate cancer; Built environment; Physical activity; Cohort studies; Causal mediation

Introduction

Prostate cancer is the most common noncutaneous malignancy among men in the United States, with an estimated 174,650 new cases and 31,620 deaths in 2019.1 Prostate cancer is considered to be a heterogeneous disease, contrasting indolent, screen-detected cancer with advanced or lethal prostate cancer defined by clinical stage and grade.2-3 Most risk factors for total prostate cancer (age, family history, African American race, height, genetic risk loci) are not modifiable. However, modifiable risk factors, including smoking, obesity, and physical activity, have been identified for lethal prostate cancer.4-5 Focusing purely on individual-level risk factors ignores the broader societal and environmental context in which the individual is embedded.4 Therefore, studying contextual environmental risk factors could help develop a multilevel model of lethal prostate cancer risk,7 as well as identify geographic predictors that can be used to improve prostate cancer risk stratification.10

Natural vegetation in a given area (referred to hereafter as “neighborhood greenness”) is increasingly considered to be a

What this study adds

Few effective strategies exist for prostate cancer prevention. Neighborhood greenness could promote higher physical activity, thereby preventing lethal prostate cancer. Using 28 years of prospective cohort data, we linked satellite-derived measures of neighborhood greenness to participants’ home or work addresses. While neighborhood greenness was not associated with lower lethal prostate cancer incidence overall, inverse associations were stronger among those men who remained at the same address over follow-up, among those in high compared with low population density areas, and among those with neighborhood greenness assessed at work compared with home. There was no evidence of mediation by vigorous physical activity.
health-promoting contextual environmental factor. Large observational studies have reported beneficial associations between greenness and health, including all-cause mortality, depression, physical activity, and obesity. Neighborhood greenness exposure could offer psychological benefits that increase adherence to healthy lifestyles or spaces to exercise which increase physical activity. In addition, neighborhood greenness is associated with stronger community cohesion and greater social capital, which are associated with increased use of preventive health care services. Together, these pathways could reduce risk of lethal prostate cancer.

There are few empirical studies of the association between neighborhood greenness and prostate cancer incidence or mortality. Demoury and colleagues reported an inverse association between residential greenness and risk of total prostate cancer risk in an urban setting using a case-control design. Our group reported inverse associations between residential greenness and cause-specific mortality in a US registry-based cohort of Black and White men with prostate cancer. Given that neighborhood greenness could be associated with higher levels of physical activity, an established correlate of lethal prostate cancer, use of a prospective design with a lethal prostate cancer endpoint could reveal stronger associations between hypothesized exposure and endpoints and enable exploration of possible mechanisms.

We studied the association between baseline neighborhood greenness and lethal prostate cancer incidence in a nationwide prospective cohort of male health professionals in the United States. We hypothesized that neighborhood greenness would be associated with lower rates of lethal prostate cancer and that this protective association would be mediated in part through higher levels of vigorous physical activity among participants in greener neighborhoods. Because prior studies had focused on urban areas using seasonal NDVI to capture possible benefits arising from physical activity.37,38 Geographic differences in seasonal behavioral patterns that could preserving seasonal variability in NDVI allowed us to account for possible mechanisms, such as physical activity.37,38 We modeled baseline neighborhood greenness as our primary exposure,27 we further sought to evaluate whether associations varied by population density or exposure at home compared with work.

Methods

Study population and design

We used data from the Health Professionals Follow-up Study (HPFS), an ongoing prospective cohort study based at the Harvard T. H. Chan School of Public Health. Since 1986, 51,529 participating male health professionals across the United States have completed biennial questionnaires that record information about lifestyle and health-related factors, as well as diagnosis of new illnesses. Cohort participants could choose to mail their questionnaire to a home or work address over follow-up. Geocoded addresses were available from questionnaire mailing records from 1988 to 2012. In 1988, participants indicated if the address was their home, work, or other address. Upon receipt of a new diagnosis, study personnel conduct a detailed review of medical and pathological information for validation purposes. The questionnaire response rate is 90%, with mortality follow-up over 98%. Participants with prior history of prostate cancer or nonmelanoma skin cancer (n = 2,084), missing a geocoded address (n = 1,447) or date of birth (n = 36), or died before returning their first questionnaire (n = 4) were excluded, resulting in a study population of 47,958. The study protocol was approved by the Institutional Review Boards of the Brigham and Women’s Hospital and Harvard T. H. Chan School of Public Health and those of participating registries as required.

Lethal prostate cancer assessment

Lethal rather than total prostate cancer was chosen as the primary endpoint. Using lethal prostate cancer allowed us to distinguish indolent tumors from aggressive, clinically meaningful tumors with greater public health significance. In addition, due to widespread screening in the United States, the overall prostate tumor burden has shifted over time from largely aggressive to largely indolent tumors, which complicates the interpretation of findings if total prostate cancer were used as the endpoint. Finally, indolent tumors and lethal tumors appear to have different metabolic risk factor profiles, with higher body mass index and lower levels of physical activity associated with increased lethal prostate cancer.2,3 Because these were hypothesized mechanisms through which neighborhood greenness could influence prostate cancer incidence, we chose to model lethal prostate cancer as our endpoint.

Incident prostate cancer diagnoses were ascertained from biennial questionnaires. Study personnel and clinical staff reviewed medical records and pathology reports to confirm reported diagnosis. Lethal prostate cancer was defined by the presence of distant metastasis (stage M1) or indication that prostate cancer was the primary cause of death for the study participant, over follow-up. Study staff were notified of cohort deaths from family members, as well as linkages with the National Death Index.

Exposure to neighborhood greenness

Exposure to neighborhood greenness was estimated by linking satellite data on greenness to geocoded participant addresses from the 1988 questionnaire, allowing us to compare greenness exposure measurements at home and work. We used the normalized difference vegetation index (NDVI), calculated by taking a ratio of the difference of near-infrared and visible light divided by the sum of near-infrared and visible light. Longitudinal NDVI data were obtained from images produced by the Advanced Very-High-Resolution Radiometer satellite of the National Oceanic and Atmospheric Administration. Images were taken every 16 days at 1,000 m resolution and began in 1989, earlier than other sources. The NDVI scale ranges from −1 to 1, with 1 representing maximal vegetation; values close to 0 representing barren areas of rock, sand, or snow; and values approaching −1 indicating bodies of water. NDVI values of 0 and below were set to missing to restrict our exposure measure to values corresponding to natural green vegetation.

The HPFS follows a biennial questionnaire cycle, and cohort participants reside across the United States, reflecting a broad range of regional and seasonal variation in neighborhood greenness. Because prostate cancer has a long natural history, we modeled associations between neighborhood greenness at the start of follow-up and lethal prostate cancer. We took an average of measurements of NDVI corresponding to different seasons (January, April, July, and September) to account for seasonal changes in and geographic differences in duration of greenness. Seasonal average NDVI measurements from 1989, the earliest year that NDVI data were available, were assigned to participants’ geocoded address within a 1,000 m buffer. We chose to use 1 km resolution NDVI to capture possible benefits arising from physical activity, which could occur within a larger area around one’s address, along with more proximal hypothesized mechanisms like mental health and social cohesion. Seasonal NDVI allowed us to preserve the marked variability in climate zones across the United States, which represent different weather patterns. In addition, preserving seasonal variability in NDVI allowed us to account for geographic differences in seasonal behavioral patterns that could be possible mechanisms, such as physical activity.

We modeled baseline neighborhood greenness as our primary exposure rather than cumulative updated average because we felt that earlier exposure to neighborhood greenness, rather than duration and intensity of exposure up to diagnosis, would be more likely to occur during the etiologic window for lethal prostate cancer. As a secondary exposure, we estimated cumulative updated average NDVI incorporating four seasonal images per year over follow-up (eMethods S1; http://links.lww.com/EE/A82). We also performed the analysis using maximum baseline NDVI as a sensitivity analysis to reflect maximal intensity of greenness.
**Longitudinal measures of physical activity**

Physical activity was reported by participants on biennial questionnaires. Participants were asked questions about the average time spent each week engaging in different types of physical activity (walking or hiking outdoors, jogging, running, bicycling, lap swimming, tennis, squash or racquetball, and calisthenics or rowing). In subsequent questionnaire cycles, additional activities were included: heavy outdoor work (from 1988), weightlifting (1990), moderate outdoor work (2004), and lower intensity exercise and other aerobic exercise (2010). Additional activities included flights of stairs traversed daily and usual walking pace. Each activity was assigned a metabolic equivalent of task (MET). Nonvigorous activities were classified as those with MET ≤6, while vigorous activities were classified as MET >6. Total physical activity was reported in MET-hours per week, calculated by summing the product of MET-hours and average hours per week for all physical activity reported by participants. Validation studies comparing MET-hours per week in questionnaires to weekly diaries found generally high correlations.  

**Statistical analysis**

Participant follow-up began with return of the first questionnaire (1986) until diagnosis of lethal prostate cancer, death from another cause, or administrative censoring on 1 January 2014, whichever came first. We used Cox proportional hazards models with study follow-up as the primary time scale to estimate hazard ratios and 95% confidence intervals for the association between rate of lethal prostate cancer and NDVI. We modeled NDVI as quintiles and estimated \( P \) values for linear trend using the median value for each NDVI quintile. We also estimated the change in rate of lethal prostate cancer associated with a linear interquartile range (IQR) unit increase in continuous NDVI (0.11 units). We tested for nonlinearity of continuous NDVI using splines. In addition, to more precisely examine long-term exposure to neighborhood greenness, we repeated the main analysis restricting to participants who did not move during follow-up.  

To assess the impact of covariate adjustment on effect estimates, we fit sequentially adjusted models (model 1: age [continuous], calendar time at 2-year questionnaire cycle [continuous] included as covariates in the baseline hazard; model 2: All covariates included in model 1, plus race [categorical: White, African American, Other], diabetes mellitus, body mass index [BMI] at age 21 [kg/m², <20, 20–<22.5, 22.5–<25, ≥25], height [inches, <66, 66–<68, 68–<70, 70–<72, ≥72], smoking [never, <10 years ago, current, <10 years ago, former smoking], family history of prostate cancer, prostate-specific antigen [PSA] testing over follow-up using two variables: ever had PSA screening before diagnosis [lagged to reflect screened, rather than diagnostic PSA test] and intensity of PSA screening before diagnosis [defined as having reported having PSA screening in over half of prior visits since 1994], census tract median income [USD, continuous], census tract median home value [USD, continuous] and population density; and model 3: All covariates in model 2, plus vigorous physical activity, nonvigorous physical activity [quintiles], and current BMI [kg/m², <21, 21–23, 23–25, 25–<27.5, 27.5–<30, ≥30)]. Baseline measures of all lifestyle covariates described above were used in our primary analysis. Vigorous physical activity was modeled as a five-level variable, with the lowest level corresponding to 0 METs of vigorous physical activity, and the remaining levels modeled as quartiles of nonzero vigorous METs. Model 2 corresponds to a confounding-adjusted model, and model 3 corresponds to the controlled direct effects model specified in our mediation analysis (eMethods S1; http://links.lww.com/EE/A82).

We chose to evaluate effect modification by population density because prior research had shown varying associations between neighborhood greenness and other health outcomes based on level of population density, including mortality among men with prostate cancer, obesity, and adolescent mental health. We chose to evaluate whether the association between neighborhood greenness and lethal prostate cancer might vary based on address type because prior research on location-based environmental exposures has revealed that the magnitude and direction of association can vary depending on where exposure is assessed, providing insights into possible mechanisms. We evaluated multiplicative interaction models with continuous exposure of interest (NDVI) and time up to 10 years from exposure locations. Age-adjusted characteristics of the study population are described in Table 1. Most participants were white (95%) with an average age of 64.4 years over follow-up. Participants in the highest quintile of NDVI reported higher nonvigorous physical activity (NDVI Q5: 17.6 vs. Q1: 15.6 MET-hours/week) and lower vigorous physical activity (NDVI Q5: 8.4 vs. Q1: 9.7 MET-hours/week) compared with participants in the lowest quintile. These patterns held in adjusted models (eTable S1; http://links.lww.com/EE/A82). Average census tract population density (NDVI Q5: 1,720 vs. Q1: 8,870 people/mi²) decreased with increasing quintiles of NDVI, while median income increased (NDVI Q5: $58,870 vs. Q1: $52,270). Maps of participant locations (eFigure S1; http://links.lww.com/EE/A82) and NDVI in July 1989 (eFigure S2; http://links.lww.com/EE/A82) show the geographic spread of exposure locations.  

In our analysis of the full cohort (Figure 1, eTable S2; http://links.lww.com/EE/A82), increasing quintiles of baseline NDVI were not significantly associated with lower rates of lethal prostate cancer compared with the lowest quintile (Q1) in age and calendar year- and confounding-adjusted models. Only the estimate for Q4 was statistically significant at the 0.05 level (adjusted hazard ratio [aHR] = 0.78, 95% confidence interval [CI] = 0.63, 0.96, \( P \) trend = 0.25). Inverse associations were stronger among the 42,492 (89%) participants who did not change addresses during follow-up (813 cases over 930,033 person-years) (Figure 1, eTable S2; http://links.lww.com/EE/A82). Among nonmovers, we observed an 8% lower rate of lethal prostate cancer associated with an IQR increase in NDVI (adjusted hazard ratio [aHR] = 0.92, 95% CI = 0.85, 1.01, \( P \) trend = 0.068). Results from models further adjusting for vigorous physical activity and BMI were similar to those from confounding models in the total and restricted populations (Figure 1, eTable S2; http://links.lww.com/EE/A82). Table 2 presents results from models evaluating the association between NDVI and incidence of lethal prostate cancer within levels of population density and address type. Stronger inverse associations were observed in high (>1,000 people/mi²) compared with low population density neighborhoods (<1,000 people/mi²).
people/mi²) though the P value for heterogeneity did not reach statistical significance (P_{het} = 0.086). In high population density areas, an IQR increase in NDVI was associated with a 10% lower rate of lethal prostate cancer (aHR = 0.90, 95% CI = 0.82, 0.99), while in low population density areas, the direction of this association was reversed (aHR = 1.11, 95% CI = 0.95, 1.29). When stratifying by address type, in general, characteristics of participants were similar across address types (eTable S3; http://links.lww.com/EE/A82), though those with work address were more likely to have been screened before diagnosis (42% vs. 35%) and were screened more frequently (40% vs. 31%). We observed stronger inverse associations among participants for whom NDVI was assessed at work (P_trend = 0.027) compared with home though evidence for effect modification was weak (P_{het} = 0.10). There was a 13% lower rate of lethal prostate cancer associated with an IQR increase in NDVI (aHR = 0.87, 95% CI = 0.75, 1.01) among men for whom NDVI was assessed at work, compared with a 4% increased rate among those with residential NDVI (aHR = 1.04, 95% CI = 0.91, 1.17). Linear associations for high population density and among those with work addresses were strengthened when restricting to nonmovers (Table 2). Further examination of effect modification by additional factors (PSA screening intensity, prior history of PSA screening, or geographic region) did not reveal any differences (Table 3).

In sensitivity analyses using cumulative updated average NDVI and baseline maximum NDVI, inverse associations were weaker (eTable S4; http://links.lww.com/EE/A82, eTable S5; http://links.lww.com/EE/A82) and failed to reveal evidence of effect modification by population density (eTable S4; http://links.lww.com/EE/A82). Strongest e-values for point estimates (2.12) and confidence intervals (1.29) were observed for NDVI Q5 compared with Q1 among men who did not move with addresses in high population density neighborhoods, suggesting that these estimates are less likely to be completely explained by unmeasured confounding (eTable S6; http://links.lww.com/EE/A82).

**Discussion**

We observed an inverse association between baseline neighborhood greenness and lethal prostate cancer, though this finding was restricted to those in high population density areas. Contrary to expectation, we found that neighborhood

| Characteristics | Total | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 |
|-----------------|-------|------------|------------|------------|------------|------------|
| Participants, no. | 47,958 | 9,504 | 9,562 | 9,688 | 9,718 | 9,486 |
| Agea-d, yrs | 64.4 (11.2) | 64.9 (11.4) | 64.6 (11.3) | 64.4 (11.2) | 64.2 (11.2) | 64.0 (11.3) |
| Baseline NDVId | 0.28 (0.09) | 0.14 (0.05) | 0.23 (0.02) | 0.28 (0.01) | 0.33 (0.02) | 0.41 (0.04) |
| NDVId (cumulative updated average) | 0.31 (0.09) | 0.19 (0.07) | 0.27 (0.05) | 0.31 (0.05) | 0.35 (0.04) | 0.41 (0.05) |
| Vigorous activityd, MET-hours/week | 8.9 (17.9) | 9.7 (18.7) | 9.1 (18.2) | 8.7 (17.0) | 8.5 (17.8) | 8.4 (17.6) |
| Nonvigorous activityd, MET-hours/week | 16.7 (22.1) | 15.6 (20.9) | 16.8 (22.1) | 16.4 (21.8) | 17.0 (22.3) | 17.6 (23.1) |
| Total activityd, MET-hours/week | 28.4 (30.6) | 28.2 (30.8) | 28.9 (30.9) | 27.9 (29.7) | 28.4 (30.5) | 28.9 (31.1) |
| Height, inches | 70.2 (2.8) | 70.1 (2.9) | 70.2 (2.8) | 70.2 (2.8) | 70.2 (2.7) | 70.2 (2.8) |
| BMI at age 21, kg/m² | 23.1 (3.0) | 23.1 (2.9) | 23.1 (2.9) | 23.1 (3.0) | 23.1 (3.0) | 23.0 (2.9) |
| Current BMId, kg/m² | 26.0 (3.8) | 25.9 (3.8) | 26.0 (3.8) | 26.1 (3.8) | 26.1 (3.7) | 26.0 (3.8) |
| Race | | | | | | |
| White, % | 95 | 94 | 96 | 97 | 96 | 97 |
| African American, % | 2 | 1 | 1 | 1 | 1 | 1 |
| Asian, % | 1 | 1 | 1 | 1 | 1 | 1 |
| Other, % | 2 | 2 | 2 | 1 | 2 | 1 |
| Smoking status | | | | | | |
| Nonsmoker, % | 57 | 59 | 58 | 56 | 57 | 56 |
| Past, quit >10 years ago, % | 29 | 27 | 28 | 29 | 29 | 30 |
| Current and past, quit ≤10 years ago, % | 14 | 14 | 14 | 15 | 14 | 14 |
| Diabetes, % | 6 | 6 | 6 | 6 | 6 | 5 |
| Family history of prostate cancer, % | 12 | 12 | 12 | 11 | 12 | 12 |
| PSA screening history | | | | | | |
| Had PSA test before diagnosis, % | 35 | 34 | 35 | 36 | 36 | 36 |
| PSA test on at least half of all questionnaires, 1994–2012, % | 33 | 31 | 32 | 33 | 33 | 34 |
| Census region | | | | | | |
| Northeast, % | 22 | 16 | 13 | 20 | 27 | 34 |
| Midwest, % | 26 | 20 | 22 | 28 | 27 | 8 |
| South, % | 29 | 20 | 21 | 25 | 33 | 45 |
| West, % | 23 | 44 | 28 | 17 | 13 | 12 |
| Population densityd, 1,000 people/mi² | 4.0 (9.5) | 8.9 (18.4) | 3.9 (6.4) | 3.0 (4.1) | 2.5 (3.5) | 1.7 (3.8) |
| Census tract median incomee, 1,000 USD | 54.3 (28.4) | 52.3 (30.4) | 52.3 (26.3) | 53.0 (26.1) | 54.9 (27.3) | 58.9 (31.8) |
| Census tract median home valued, 1,000 USD | 162.9 (145.3) | 183.6 (173.0) | 152.6 (135.7) | 146.6 (128.8) | 152.1 (128.1) | 179.8 (152.0) |
| Address type (1988) | | | | | | |
| Home, % | 33 | 24 | 30 | 33 | 37 | 42 |
| Work, % | 41 | 49 | 44 | 43 | 38 | 32 |
| Other, % | 1 | 2 | 1 | 1 | 1 | 2 |
| Not reported, % | 24 | 26 | 25 | 23 | 24 | 23 |
| Moved during follow-up, % | 12 | 13 | 12 | 12 | 12 | 11 |
| Cases of lethal prostate cancer | 898 | 206 | 178 | 180 | 156 | 178 |
| Person-years | 1,054,743 | 206,725 | 211,019 | 212,698 | 214,683 | 209,618 |
| Incidence rate per 100,000 person-years | 85 | 100 | 84 | 85 | 72 | 85 |

*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).

**DISCUSSION**

We observed an inverse association between baseline neighborhood greenness and lethal prostate cancer, though this finding was restricted to those in high population density areas. Contrary to expectation, we found that neighborhood
greenness was associated with lower levels of vigorous physical activity in this population of health professionals. We did not observe evidence of a mediating role of vigorous physical activity. Restricting to men who remained at the same address

Figure 1. Hazard ratios and confidence intervals for the association between baseline NDVI and lethal prostate cancer incidence in the Health Professionals Follow-up Study, United States, 1986–2014. Sequentially adjusted for age in months and calendar time as strata (Age-adjusted Model), 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 (binary: high: ≥1,000, low:<1,000 people/mi²), history of prostate-specific antigen testing, intensity of prostate-specific antigen testing (Confounding Model), vigorous physical activity, non-vigorous physical activity, and current BMI (Mediation Model). A, Total population (N = 47,958); (B) participants who did not move over follow-up (N = 42,492). Cont indicates an IQR increase in continuous NDVI of 0.11 units. Q, quintile.

Table 2.
Hazard ratios for the association between baseline NDVI and lethal prostate cancer incidence in the Health Professionals Follow-up Study, United States, 1986–2014, stratified by population density (high: ≥1,000, low: <1,000 people/mi²) and address type (work, home)

| Baseline NDVI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI | aHR | 95% CI | P_<sub>total</sub> | P_<sub>het</sub> |
|---------------|-----|--------|-----|--------|-----|--------|-----|--------|-----|--------|-----|--------|-----|--------|-----|--------|-------|---------|
|               |     |        |     |        |     |        |     |        |     |        |     |        |     |        |     |        |       |         |
| Total Population |     |        |     |        |     |        |     |        |     |        |     |        |     |        |     |        |       |         |
| Population density<sup>a</sup> | 0.90 | 0.82, 0.99 | 1.00 | Referent | 0.96 | 0.75, 1.21 | 0.90 | 0.70, 1.15 | 0.84 | 0.65, 1.08 | 0.79 | 0.60, 1.02 | 0.87 | 0.68, 1.10 | 0.82 | 0.64, 1.04 | 0.042 | 0.086 |
| High (N = 34,229) |     |        |     |        |     |        |     |        |     |        |     |        |     |        |     |        |       |         |
| Low (N = 13,729) | 1.11 | 0.95, 1.29 | 1.00 | Referent | 1.07 | 0.70, 1.63 | 1.18 | 0.78, 1.80 | 1.21 | 0.81, 1.82 | 1.36 | 0.90, 2.03 | 0.12 |        |       |         |
| Address type<sup>b</sup> | 0.87 | 0.75, 1.01 | 1.00 | Referent | 0.80 | 0.57, 1.12 | 0.53 | 0.35, 0.79 | 0.73 | 0.50, 1.07 | 0.66 | 0.45, 0.98 | 0.027 | 0.10 |       |         |
| Work (N = 18,742) |     |        |     |        |     |        |     |        |     |        |     |        |     |        |     |        |       |         |
| Home (N = 16,732) | 1.04 | 0.91, 1.17 | 1.00 | Referent | 1.14 | 0.83, 1.57 | 1.07 | 0.77, 1.48 | 0.91 | 0.65, 1.29 | 1.19 | 0.85, 1.66 | 0.66 |        |       |         |
| Nonmovers |     |        |     |        |     |        |     |        |     |        |     |        |     |        |     |        |       |         |
| Population density<sup>a</sup> | 0.88 | 0.80, 0.97 | 1.00 | Referent | 0.96 | 0.75, 1.23 | 0.87 | 0.67, 1.13 | 0.81 | 0.62, 1.05 | 0.72 | 0.55, 0.95 | 0.0098 | 0.15 |       |         |
| High (N = 30,259) |     |        |     |        |     |        |     |        |     |        |     |        |     |        |     |        |       |         |
| Low (N = 12,233) | 1.07 | 0.91, 1.26 | 1.00 | Referent | 1.02 | 0.65, 1.62 | 1.34 | 0.85, 2.09 | 1.22 | 0.79, 1.92 | 1.21 | 0.78, 1.88 | 0.28 |        |       |         |
| Address type<sup>b</sup> | 0.85 | 0.73, 0.99 | 1.00 | Referent | 0.80 | 0.56, 1.14 | 0.51 | 0.34, 0.78 | 0.69 | 0.46, 1.02 | 0.63 | 0.42, 0.95 | 0.014 | 0.15 |       |         |
| Work (N = 16,967) |     |        |     |        |     |        |     |        |     |        |     |        |     |        |     |        |       |         |
| Home (N = 14,466) | 0.99 | 0.87, 1.14 | 1.00 | Referent | 1.11 | 0.79, 1.56 | 1.12 | 0.79, 1.59 | 0.86 | 0.60, 1.25 | 1.07 | 0.75, 1.53 | 0.89 |        |       |         |

<sup>a</sup>Adjusted for age in months and calendar time as strata (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.

<sup>b</sup>Estimate corresponds to an IQR increase in continuous NDVI of 0.11 units.

<sup>c</sup>Likelihood ratio test with one degree of freedom for interaction between continuous NDVI and stratification variable.

<sup>d</sup>Quintiles reflect within group distributions for population density (high: ≥1,000, low: <1,000 people/mi²). Models additionally adjusted for address type (categorical: home, work, missing category).

<sup>e</sup>Restricted to only participants who reported home or work address. Quintiles reflect within group distributions for home and work. Models additionally adjusted for population density (binary: ≥1,000, <1,000 people/mi²).
over follow-up strengthened the inverse association between neighborhood greenness and lethal prostate cancer incidence, suggesting that mechanisms are related to environmental context or reduced home or work mobility.

Few studies have assessed the association between neighborhood greenness and prostate cancer.27,44 Our findings corroborate results from a population-based case–control study conducted by Demouur and colleagues27 in Montreal, the second-largest city in Canada. In an urban population, they reported effect estimates of similar magnitude to ours, though they used maximal annual residential NDVI at diagnosis and 10 years before diagnosis. They also found no evidence of physical activity as a mediating pathway. Because we used different exposure and outcome measures, our studies are not directly comparable, but both are consistent with a hypothesis that green spaces and contextual environment could play a role in prostate cancer risk.

There is limited evidence for direct effects of exposure to neighborhood greenness and carcinogenesis. However, physiologic changes that arise from spending time in green environments could serve as a mechanism. Interventional studies conducted in Japan comparing visits to urban areas with forests observed higher parasympathetic activation, lower cardiometabolic response, and lower natural killer cell activity following forest visits.43,44 Cross-sectional studies in the United States reported inverse associations between neighborhood greenness and allostatic load, a composite index derived from biomarkers to capture physiologic adaptation to stress.45 One of these inflammatory biomarkers, interleukin-8, could drive cancer progression by decoupling tumor growth from androgen hormone regulation.46,47 Further studies are needed to clarify biological mechanisms.

The magnitude and direction of the association between neighborhood greenness and incidence rate of lethal prostate cancer varied by levels of high and low population density, though we lacked power to detect statistically significant effect modification. Because neighborhood greenness varies spatially, these different relationships could be related to different geographic patterns of care seeking and treatment for lethal prostate cancer. Geographic patterns of prostate cancer care have been observed in the United States; for example, rural prostate cancer patients are less likely to receive radiotherapy and surgery compared with urban patients.46,51 In rural areas, benefits of greenness could be offset by increased lethal prostate cancer mortality resulting from the absence of these treatment modalities.

Environmental factors could also explain this effect heterogeneity. Ultraviolet light exposure, which has been linked with reduced rates of prostate cancer in prospective studies, could be influenced by neighborhood greenness and vary by population density.52,53 Several reports have documented increased risk of prostate cancer among farmers, hypothesized to arise from long-term use of endocrine disrupting chemicals found in pesticides.54,55 Given that agricultural land accounts for much of the natural green vegetation in rural environments, refining neighborhood greenness exposure to account for source of green vegetation could shed light on possible mechanisms. A recent study reported effect modification of the association between neighborhood greenness and risk of breast cancer, another hormone-dependent cancer, with inverse associations in urban areas, but elevated risk in rural areas with surrounding agricultural land.56 Joint consideration of multiple environmental exposures could improve mechanistic understanding of how neighborhood greenness could influence risk of lethal prostate cancer,57 but these studies would require longitudinal designs with changing trends in these exposures to distinguish confounding from mediation pathways.57 In future studies, refining measurement of exposure to natural green vegetation at different locations, using higher resolution data and detailed information on the type of natural green environment, could reveal underlying mechanisms.58

We observed stronger associations among participants for whom greenness was assessed at work compared with home address. A possible explanation could be enhancement of mental and related health benefits from greenness in stressful work environments. A recent prospective study reported lower levels of job-related stress among people living in neighborhoods with higher levels of residential greenness.59 Indirect support for this hypothesis comes from observations that health benefits of greenness appear greater in urban compared with rural settings.11,28 and in more deprived neighborhoods.60–64 Many health care professionals engage in shift work or long hours, leading to disruption of circadian rhythm, altered social patterns, and adverse cardiovascular and mental health.65,66 Though the evidence is mixed, there are several reports of increased risk of prostate cancer among shift workers compared with nonshift workers, hypothesized to arise from circadian disruption that could lead to hormonal shifts which promote tumor growth.67,68 In this context, it is possible that for health professionals, greenness exposure at their work place could provide greater benefits than at their residential address.

Interpretation of our results warrants consideration of our study limitations. Unmeasured confounding is a major threat to validity. Though we did not adjust for individual-level socioeconomic status, assuming that area-level socioeconomic status serves as a reliable measure of individual-level socioeconomic status49 and that premove lifestyle factors are not associated with neighborhood selection,70 adjustment for individual lifestyle factors and
area-level socioeconomic status would be expected to mitigate confounding bias. Furthermore, this occupational cohort of male health professionals exhibits limited variability in terms of income and education, and therefore, restriction would mitigate confounding from individual-level socioeconomic status. Using e-values, we quantified the magnitude of bias needed to change our inference and found that moderate bias conditional on covariates would be required. Our prospective design allowed us to control for major individual clinical, lifestyle, and socioeconomic contextual factors, making it unlikely for an unmeasured covariate to exhibit associations with neighborhood greenness and lethal prostate cancer as extreme as those presented in our sensitivity analysis.

Nearly a quarter (24%) of participants were missing address type. For the remainder, only home or work address was available. We consider this to be an issue of measurement error, in which we have randomly sampled greenness exposure for some participants at home and others at work within strata of confounding variables. This nondifferential measurement error means that our reported associations are weaker than what one would expect to see with perfect exposure assessment. Our satellite-derived measure captures vegetation exhibiting high levels of photosynthesis and so may not capture green vegetation with low photosynthetic activity. When using NDVI as an exposure, we are limited in the spatial and temporal measures we can use to estimate the full extent of neighborhood greenness exposure that may be etiologically meaningful. Our choice of using seasonal average NDVI as the primary exposure assumes that the etiologically meaningful measure of neighborhood greenness is a weighted average of NDVI exposure measured during each season. Under a classical measurement error structure, this decision could lead to bias if the etiologically relevant measure is better reflected by greenness experienced in a single season. We found stronger associations between seasonal average NDVI and lethal prostate cancer incidence than maximal NDVI from a single season, suggesting that the seasonal measure may better reflect etiologically meaningful exposure. Finally, results obtained from this select population of predominantly white health professionals may not extend to other populations. A different study of residential greenness and mortality among men with prostate cancer reported an inverse association between neighborhood greenness and rate of lethal prostate cancer in high population density areas. These findings suggest that health benefits of neighborhood greenness could include reduced incidence of lethal prostate cancer. Future studies should apply more precise measurements of exposure to greenness, clarify mechanisms, and assess transportability of these findings.

Conflicts of interest statement
M.D.H. declares relationships with Bayer AG (provides aspirin/ placebo for trial NCG02927249, consulting for Arla Foods), Cambridge Savings Bank (advisory board member), and United States Social Securing Administration, VISIONS Inc. The other authors have no conflicts to report.

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