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Journal

American Journal of Epidemiology, 192(9)

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Publication Date

2023-09-01

DOI

10.1093/aje/kwad112

Peer reviewed

American Journal of Epidemiology

Vol. 192, No. 9
https://doi.org/10.1093/aje/kwad112
Advance Access publication:
May 3, 2023

Original Contribution

Influence of Neighborhood Social and Natural Environment on Prostate Tumor Histology in a Cohort of Male Health Professionals

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Initially submitted August 18, 2022; accepted for publication May 1, 2023.

Adverse neighborhood social and natural (green space) environments may contribute to the etiology of prostate cancer (CaP), but mechanisms are unclear. We examined associations between neighborhood environment and prostate intratumoral inflammation in 967 men diagnosed with CaP with available tissue samples from 1986–2009 in the Health Professionals Follow-up Study. Exposures were linked to work or residential addresses in 1988. We estimated indices of neighborhood socioeconomic status (nSES) and segregation (Index of Concentration at the Extremes (ICE)) using US Census tract–level data. Surrounding greenness was estimated using seasonal averaged Normalized Difference Vegetation Index (NDVI) data. Surgical tissue underwent pathological review for acute and chronic inflammation, corpora amylacea, and focal atrophic lesions. Adjusted odds ratios (aORs) for inflammation (ordinal) and focal atrophy (binary) were estimated using logistic regression. No associations were observed for acute or chronic inflammation. Each interquartile-range increase in NDVI within 1,230 m of the participant's work or home address (aOR = 0.74, 95% confidence interval (CI): 0.59, 0.93), in ICE-income (aOR = 0.79, 95% CI: 0.61, 1.04), and in ICE-race/income (aOR = 0.79, 95% CI: 0.63, 0.99) was associated with lower odds of postatrophic hyperplasia. Interquartile-range increases in nSES (aOR = 0.76, 95% CI: 0.57, 1.02) and ICE-race/income (aOR = 0.73, 95% CI: 0.54, 0.99) were associated with lower odds of tumor corpora amylacea. Histopathological inflammatory features of prostate tumors may be influenced by neighborhood.

atrophy; inflammation; neighborhood; prostate cancer; prostatic neoplasms; residence characteristics; socioeconomic factors

Abbreviations: aOR, adjusted odds ratio; CaP, prostate cancer; CI, confidence interval; HPFS, Health Professionals Follow-up Study; ICE, Index of Concentration at the Extremes; IQR, interquartile range; nSES, neighborhood socioeconomic status; NDVI, Normalized Difference Vegetation Index; PSA, prostate-specific antigen; SES, socioeconomic status.

Prostate cancer (CaP) is the most commonly diagnosed noncutaneous cancer in US men, with an estimated 268,490 diagnoses and 34,500 deaths in 2022 (1). CaP progression involves gradual changes to prostate cells driven by numerous physiological events (2). Chronic inflammation in prostate tissue is associated with focal atrophy, characterized by proliferative glandular epithelium in the peripheral zone of the prostate gland (3). Certain forms of focal atrophy are hypothesized to arise from the normal aging process. Postatrophic hyperplasia, a histopathological signature related to proliferative inflammatory atrophy, involves proliferation of the basal cells of the prostate gland. Postatrophic hyperplasia is associated with oxidative stress and inflammation, and may be a precursor lesion that leads to CaP (2, 4). The available animal and human evidence suggests that exposure to proinflammatory environments may lead to increased risk of aggressive CaP and poorer CaP outcomes after diagnosis (2, 3, 5). These data imply that environmental factors that influence inflammation pathways could affect risk of aggressive CaP and postdiagnostic CaP outcomes (2, 6).

Men living in more advantaged neighborhoods, defined by health-promoting environments and favorable socioeconomic status (SES), have better CaP outcomes (7–10). The multilevel pathways that link upstream neighborhood environmental factors to downstream CaP outcomes operate through mechanisms occurring at sociopolitical, individual, and biological scales (Figure 1). SES and segregation may influence societal and individual-level social stress pathways which drive inflammation and oxidative stress, among other mechanisms (11). Natural outdoor environments, which encompass natural systems and the flora and fauna that they contain, across varying spatial scales and with different levels of human management, have been linked to improved health (12, 13). For this study, we chose to focus on neighborhood green spaces ("greenness") (14) as a measure of natural outdoor environment, given the growing evidence of myriad health benefits of green space in humans (15, 16). Neighborhood greenness may influence CaP outcomes through the promotion of physical activity, promotion of social cohesion, and improved mental health (14, 17). Men living in neighborhoods with higher greenness experience lower risk of lethal CaP in urban settings and lower CaP mortality (18–20).

Those living in favorable neighborhood socioeconomic and built environments report lower levels of blood markers of inflammation, independently of lifestyle and behavioral risk factors (21–23). Together, these neighborhood factors may drive inflammation processes in the body and prostate tissue through psychosocial stress, behaviors, and chemical exposures. Social stressors encountered through discrimination and poverty can influence physiological wear and tear, a theory referred to as the "weathering" hypothesis and demonstrated empirically using allostatic load (24). Known behavioral drivers of inflammation in cancer include diet, obesity, and infections (2, 25, 26). These findings support the hypothesis that living in neighborhoods with low levels of greenness and lower SES may lead to increased inflammation via environmental and social stressors, which could then drive prostatic carcinogenesis and progression after diagnosis.

While much of the research on neighborhood exposures, inflammation-related pathways, and chronic disease has focused on residential surroundings, unfavorable occupational environments may also increase inflammation by exacerbating adverse effects of workplace stressors and exposures (27, 28). Numerous occupational exposures, including night-shift work, radiation (e.g., x-rays), and exposure to certain industrial chemicals (e.g., per- and polyfluoroalkyl substances), have been classified as potentially carcinogenic by the International Agency for Research on Cancer (29–31). Studies have found that night-shift work, radiation exposure, and job-related stress are associated with higher levels of inflammation (32–34). Improving occupational environments—for example, through physical and visual access to green spaces—has been linked to lower perceived workplace stress and higher workplace satisfaction (35). These reports suggest that workplace and residential neighborhood context could influence CaP progression through similar mechanisms.

We examined associations between neighborhood socioeconomic status (nSES) and greenness and inflammatory signatures of prostatic intratumoral histology within a cohort of male health professionals. A better understanding of these relationships could help reveal neighborhood natural and social environments in which prostatic inflammation occurs more frequently. Because inflammation is modifiable through lifestyle or medications, neighborhoods characterized by features that are associated with prostatic inflammation could be targeted for multilevel interventions.

METHODS

Study population and design

Data were obtained from participants in the Health Professionals Follow-up Study (HPFS), an ongoing prospective cohort study in which 51,529 male health professionals aged 40–75 years were recruited across the United States in 1986. Participants completed biennial questionnaires that captured detailed demographic, clinical, and lifestyle information. In addition, each participant's home or work address was recorded in 1988, and addresses were updated biennially thereafter.

In 2000, a CaP survivor subcohort was established for collection of detailed clinical information among men with CaP. Participants reported diagnoses of CaP in biennial questionnaires, which were then confirmed by study physicians through medical record and pathology review. Clinical information on stage and grade, prostate-specific antigen (PSA) level at diagnosis, pathology, and progression was obtained from medical records and CaP survivor-specific questionnaires. A sample of archival tissue specimens with hematoxylin and eosin–stained slides were collected and available for pathological review with at least 1 histological marker. The current study, sampling from 6,176 men diagnosed with CaP from 1988 to 2009, included 967 cases (16%) available for histology review. Specimens were mostly obtained from radical prostatectomy ($n = 886$; 92%), with the remaining samples ($n = 81$; 8%) being obtained from transurethral resection of the prostate or biopsy. Further details on the CaP survivor cohort are available elsewhere (36, 37).

The study protocol was approved by the institutional review boards of Brigham and Women's Hospital (Boston, Massachusetts) and the human subjects committee of Harvard T.H. Chan School of Public Health (Boston, Massachusetts), and those of participating cancer registries as required. Completion of questionnaires was considered to imply informed consent to obtain medical records and tissue samples.

Neighborhood social and natural environmental exposures

We assessed nSES using a cohort-specific score. Briefly, the measure included 9 Census tract–level variables from the decennial US Census and the American Community Survey capturing area-level educational attainment, income,

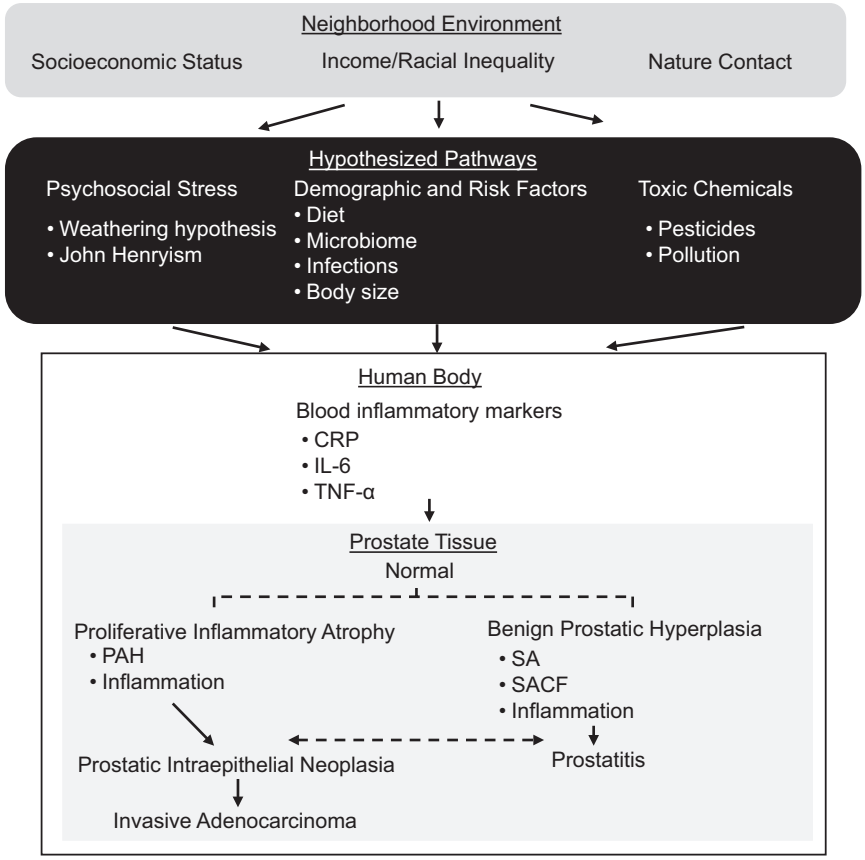

Figure 1. Multilevel conceptual framework for the impact of neighborhood environment, behavior, and inflammation on prostatic carcinogenesis. Neighborhood environments, characterized by socioeconomic status, income/racial inequality, and nature contact, are upstream environmental factors that may influence development of prostate cancer (CaP). Pathways linking neighborhood environment to CaP risk include physiological and psychosocial stress, manifested as allostatic load. Neighborhood environment may also drive individual-level risk factors, including diet, comorbidity, and infections, that may be associated with elevated risk of CaP. Finally, neighborhood environment may be associated with exposure to chemicals, including pollution and pesticides, which have been linked with elevated risk of CaP in agricultural workers and in urban areas. At the level of the human body, favorable neighborhood environments are associated with lower levels of blood inflammatory markers. Systemic inflammation may influence the development of distinct prostatic tissue histologies, including proliferative inflammatory atrophy, a potential precursor lesion for CaP. Inflammation is also linked with benign prostatic inflammation and prostatitis. CRP, C-reactive protein; IL-6, interleukin 6; PAH, postatrophic hyperplasia; SA, simple atrophy; SACF, simple atrophy with cyst formation; TNF-α, tumor necrosis factor α.

wealth, occupation, and racial composition. We calculated a summary score by z-scaling each component measure such that increasing values indicated increasing affluence. The summary score was computed by summing the components. Further details about the development of the nSES score were published previously (23). In earlier work, we found that the distribution of nSES measures, including Census tract–level median income, median home value, percent poverty, and percent White, were comparable between the HPFS study population and the US total, suggesting that there is sufficient variability in these measures to both investigate these contextual nSES influences on CaP and other health outcomes and to obtain inferences regarding impacts of adverse nSES that can inform studies in smaller geographic areas (23).

Impacts of neighborhood segregation were assessed using the Index of Concentration at the Extremes (ICE) (38), a measure of the homogeneity of a population within a given area with respect to socioeconomic privilege or disadvantage. Although this population is predominantly White, we chose to include measures of Black-White segregation to capture neighborhood-level inequities that flow from discrimination in housing and economic opportunities (39), and because we previously observed that participants with reported addresses in neighborhoods with racialized income segregation had higher levels of inflammation (23). We calculated ICE-income and joint ICE-race/income metrics to capture information on segregation by income and segregation occurring jointly across race/ethnicity (Black vs. White) and income (lowest quintile of income vs. highest) following previously described methods (38). ICE metrics range from -1 to 1, where a value of -1 represents a concentration of socioeconomically disadvantaged populations and a value of 1 represents a concentration of

socioeconomically privileged populations. The distributions of Census tract–level median ICE-income, ICE-race, and joint ICE-race/income were similar in the HPFS and the total US population (see Web Figure 1, available at https://doi.org/10.1093/aje/kwad112). The median value for ICE-income was higher for the HPFS (median, 0.36; interquartile range (IQR), −0.18 to 0.73) than for the US total (median, 0.22; IQR, −0.29 to 0.66). Similar findings were observed for joint ICE-race/income (HPFS: median, 0.59 (IQR, 0.32–0.79); US total: median, 0.50 (IQR, 0.22–0.74)).

Greenness exposure was estimated using a satellite-derived index, the Normalized Difference Vegetation Index (NDVI). The NDVI captures the photosynthetic activity of leafy vegetation (40). We acquired 4 seasonal images (January, April, July, and September) for each year within the study period. We then calculated focal statistics, or spatial averages, of NDVI within 1,230 m of the participant's address to capture data on the health-promoting impacts of green space, such as improved mental health or increased engagement in physical activity, that may operate within the neighborhood surrounding the address. Annual NDVI exposure was estimated by averaging the data over the 4 seasonal measures in each year.

Our primary exposures were assigned to the addresses reported in 1988. We assigned exposures using the 1990 decennial Census measures for nSES and ICE and the annual average of 4 seasonal NDVI measures. To evaluate potential long-term associations between neighborhood exposures and inflammation outcomes, we also assessed cumulative updated average exposures using nSES, ICE, and NDVI measures to addresses collected from baseline through diagnosis. Further details regarding neighborhood measures are available in Web Appendix 1.

Assessment of intraprostatic histology and inflammatory markers

Tumor specimens with hematoxylin and eosin–stained slides were reviewed by an experienced genitourinary pathologist blinded to exposure, disease outcome, and other clinical information. Inflammation scoring was done on tumor and adjacent normal areas. Acute inflammation was assessed on the basis of presence of neutrophils and was defined as absent vs. present. Chronic inflammation was characterized on the basis of the presence of lymphocytes and macrophages and was graded as absent, mild (≤10% of the microscopically benign area), moderate (11%–19%), or severe (≥20%) (41). Focal atrophy was assessed on the basis of classifications from the 2006 working group for histological classification of prostate atrophy lesions (4). The following subtypes were identified: simple atrophy, simple atrophy with cyst formation, and postatrophic hyperplasia. These subtypes capture different morphological features of atrophy in the peripheral zone of the prostate gland. Further details regarding these classifications have been provided elsewhere (4, 41).

In addition to tumor histology, trained investigators reviewed slides for corpora amylacea, which are amyloid bodies found within the lumen of cellular acini in proximity to damaged prostate epithelium. Corpora amylacea in the prostate are hypothesized to result from acute inflammation caused by infections (42, 43). Available hematoxylin and eosin–stained slides were reviewed using 10× objective microscopy (Labomed CxL microscope; Labo America, Inc., Fremont, California). The numbers of corpora amylacea were manually counted for up to 50 randomly selected 10× fields, separately in the benign and tumor tissue areas. The density of corpora amylacea for a participant was calculated by summing the numbers of corpora amylacea across slides and dividing by the total area viewed. These numerical density measures were dichotomized into high- versus low-density corpora amylacea, separately for benign and tumor tissue. Further details regarding the assessment of corpora amylacea are available elsewhere (42).

Statistical analysis

Logistic regression models were fitted for binary outcomes, and ordinal logistic regression models were fitted for categorical outcomes to estimate odds ratios and 95% confidence intervals (CIs). Neighborhood measures were scaled to a 1-IQR increase and modeled as linear terms. We also parameterized neighborhood exposures using tertiles, with an ordinal test for linear trend across median values for each tertile to assess potential nonlinearity. Models adjusted for age at diagnosis (years; continuous), PSA test value at diagnosis (categorical: <10 ng/mL, 10–20 ng/mL, ≥20 ng/mL, or unknown), body mass index (weight (kg)/height $(m)^2$) at baseline, height (inches), nonvigorous and vigorous physical activity (metabolic equivalent of task–hours/week), population density (binary: <1,000 people/$mile^2$ or ≥1,000 people/$mile^2$), and year of diagnosis (binary (<1993 or ≥1993), representing diagnosis before or after widespread adoption of PSA-based screening by health-care providers). Covariates were selected on the basis of prior research (41) and examination of correlations between covariates, neighborhood exposures, and prostate tumor biomarkers (Web Figure 2).

We performed additional sensitivity analyses to examine the robustness of our findings to various analytical decisions. First, we examined impacts of long-term exposure that leveraged addresses over the course of follow-up. Second, we examined whether associations with nSES and tissue inflammation varied when we used a principal components analysis–based approach rather than the z score approach, using previously described methods (44). Third, we compared findings using log-binomial models rather than logistic regression models, because odds ratios exaggerate risk ratio effect estimates when outcomes are common. Fourth, we examined whether associations between neighborhood measures and intraprostatic inflammation varied by address type (home or work). Finally, we evaluated sensitivity to potential selection bias. These analyses were done using postatrophic hyperplasia and tumor corporal amylacea measures and are described in detail in Web Appendix 1.

All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina), and all statis-

Table 1. Characteristics of Men Diagnosed With Prostate Cancer (n = 967) in the Health Professionals Follow-up Study, Overall and by Tertile of Neighborhood Socioeconomic Status, 1988–2009

Characteristic[a,b]	Tertile of nSES in 1988						Total (n = 967)	
	Tertile 1 (Lowest) (n = 337)		Tertile 2 (n = 320)		Tertile 3 (Highest) (n = 310)			
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Sociodemographic characteristics								
Age at diagnosis, years		66.8 (6.2)		65.9 (6.1)		66.1 (6.0)		66.3 (6.1)
Race/ethnicity								
White	98		96		96		97	
Other	2		4		4		3	
Height, inches[c]		70.4 (2.9)		70.2 (2.6)		70.3 (2.6)		70.3 (2.7)
Physical activity, MET-hours/week								
Vigorous activity		7.98 (14.37)		11.57 (22.55)		11.90 (22.34)		10.42 (20.07)
Nonvigorous activity		9.07 (13.91)		8.36 (13.84)		7.35 (13.44)		8.28 (13.74)
Body mass index[d]		25.54 (3.51)		25.33 (2.64)		25.09 (2.81)		25.33 (3.03)
Smoking status								
Nonsmoker	27		34		31		31	
Current smoker	31		24		30		28	
Former smoker	20		17		19		19	
Family history of prostate cancer	22		25		20		22	
AHEI diet score		51.4 (10.9)		52.5 (11.3)		54.3 (11.1)		52.7 (11.2)
Geographic and neighborhood measures								
Population density, thousands of people/mile^2		2.14 (3.08)		3.45 (3.47)		4.08 (4.62)		3.20 (3.84)
NDVI within 1,230 m of address		0.30 (0.094)		0.30 (0.078)		0.31 (0.089)		0.30 (0.088)
nSES		−3.51 (1.46)		−0.61 (0.86)		3.83 (2.47)		−0.20 (3.47)
ICE score[e]								
ICE-income		−0.21 (0.42)		0.32 (0.41)		0.67 (0.36)		0.25 (0.54)
ICE-race/income		0.28 (0.31)		0.57 (0.28)		0.75 (0.20)		0.53 (0.33)
US Census region								
Northeast	13		18		21		17	
Midwest	34		34		20		30	
South	34		19		22		25	
West	19		29		37		28	

Table 1. Continued

Characteristic[a,b]	Tertile of nSES in 1988						Total (n = 967)	
	Tertile 1 (Lowest) (n = 337)		Tertile 2 (n = 320)		Tertile 3 (Highest) (n = 310)			
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Address type								
Home	34		35		47		38	
Work	47		51		38		46	
Missing data	19		14		15		16	
Moved during follow-up	12		13		16		14	
Clinical characteristics[f]								
Ever being screened for PSA over follow-up[g]	44		47		47		46	
Intensity of PSA screening over follow-up[h]	38		43		38		40	
Gleason score								
<7	18		17		17		17	
7 (3 + 4)	35		38		38		37	
7 (4 + 3)	21		18		17		19	
8	9		9		10		9	
9–10	16		18		17		17	
Tumor stage[i]								
Localized: T1b–T3a/N0/M0	85		87		84		85	
Regional/distant: T3b/T4/N1/M1	14		13		16		14	
PSA test result at diagnosis, ng/mL								
<10	65		71		63		66	
10–20	13		12		19		15	
>20	9		8		8		8	
Unknown	13		8		11		11	
Primary treatment								
Radical prostatectomy	90		93		91		91	
TURP, biopsy	9		7		8		8	

Abbreviations: AHEI, Alternative Healthy Eating Index; ICE, Index of Concentration at the Extremes; MET, metabolic equivalent of task; NDVI, Normalized Difference Vegetation Index; nSES, neighborhood socioeconomic status; PSA, prostate-specific antigen; SD, standard deviation; TURP, transurethral resection of the prostate.

[a] Percentages may not add up to 100 because of rounding.

[b] Sociodemographic characteristics and geographic and neighborhood measures were assessed at baseline (start of follow-up) unless otherwise stated.

[c] 1 inch = 2.54 cm.

[d] Weight (kg)/height $(m)^2$.

[e] ICE-race/income measures capture Black vs. White segregation.

[f] Clinical characteristics were assessed at diagnosis.

[g] Ever having a PSA test before diagnosis (lagged to reflect screened rather than diagnostic PSA).

[h] Defined as reporting having had PSA screening in over half of prior visits since 1994.

[i] Two participants had a tumor stage of NX or MX (stage unknown).

Table 2. Prevalence of Focal Atrophic and Inflammatory Lesions Among Men Diagnosed With Prostate Cancer Who Had Available Inflammatory Histological Data (n = 967), Health Professionals Follow-up Study, 1988–2009

Tumor Characteristic	Sample Size (n)	No. of Cases	%
Acute inflammation	900	268	29.8
Chronic inflammation	910		
Absent		142	15.6
Mild		462	50.8
Moderate		239	26.3
Severe		67	7.4
SACF	903	159	17.6
Simple atrophy	903	657	72.8
Postatrophic hyperplasia	903	206	22.8
CAM-T	358	195	54.5
CAM-B	370	312	84.3

Abbreviations: CAM-B, corpora amylacea—benign; CAM-T, corpora amylacea—tumor; SACF, simple atrophy with cyst formation.

tical tests were 2-sided, with P values below 0.05 considered statistically significant.

RESULTS

Population characteristics

We identified 967 men diagnosed with CaP with at least 1 atrophic or inflammatory les ion. Men were followed for a median of 12.2 (IQR, 7.0–16.6) person-years from baseline neighborhood exposure to diagnosis. Characteristics of the study population by nSES tertile are reported in Table 1. The men had a mean age of 66.3 years at diagnosis, and most were White (97%). Most men were diagnosed with localized CaP (85%), with 17% presenting with Gleason grade <7, 37% with Gleason grade 7 (3 + 4), 19% with Gleason grade 7 (4 + 3), and 26% with Gleason grade 8–10. Characteristics of the study population according to address type are provided in Web Table 1. Neither CaP risk factors (age, family history, and race/ethnicity) nor clinical characteristics of patients varied substantially by address type. However, participants with home addresses were more likely to be from the South and West US Census regions, participants with work addresses were more likely to be from the Midwest, and those who did not provide address information were most likely to be from the West.

Neighborhood social and natural environments and tumor inflammatory and atrophic lesions

Overall summaries of the proportions of men with different tumor inflammatory and atrophic lesions are provided in Table 2. Bivariate associations between neighborhood measures and inflammatory and atrophic lesions are displayed in Figure 2 (numerical results are provided in Web Table 2). No associations were observed between acute or chronic inflammation and nSES, NDVI, or ICE measures. For atrophic lesions, tumors from men living or working in the highest tertiles of NDVI (tertile 3 (19.7%) vs. tertile 1 (28.3%), P = 0.040) and ICE-race/income (tertile 3 (18.7%) vs. tertile 1 (26.2%), P = 0.084) exhibited lower prevalence of postatrophic hyperplasia than tumors from men in the lowest tertiles. The prevalence of simple atrophy varied by tertile of ICE-race/income (tertile 1, 71.1%; tertile 2, 77.7%; tertile 3, 69.3% (P = 0.051)).

Odds ratios for associations between neighborhood measures and atrophic lesions from adjusted logistic regression models are presented in Table 3. There were no associations between any of the neighborhood measures and simple atrophy. A 1-IQR increase in nSES was associated with lower odds of simple atrophy with cyst formation (adjusted odds ratio (aOR) = 0.77, 95% CI: 0.60, 0.99). There were no other associations between neighborhood measures and simple atrophy with cyst formation.

Tumors from participants living in neighborhoods with higher NDVI and ICE-race/income exhibited lower levels of postatrophic hyperplasia. An IQR increase in NDVI was associated with significantly lower odds of postatrophic hyperplasia (for a 1-IQR increase, aOR = 0.74, 95% CI: 0.59, 0.93). A linear dose-response relationship was observed for NDVI (tertile 3 vs. tertile 1: aOR = 0.57, 95% CI: 0.38, 0.87; P for trend = 0.0076). IQR increases in ICE-income (aOR = 0.79, 95% CI: 0.61, 1.04) and ICE-race/income (aOR = 0.79, 95% CI: 0.63, 0.99) were associated with lower odds of postatrophic hyperplasia. Analyses using tertiles confirmed the linear dose response for ICE-income (tertile 3 vs. tertile 1: aOR = 0.68, 95% CI: 0.46, 1.00; P for trend = 0.038) and ICE-race/income (tertile 3 vs. tertile 1: aOR = 0.63, 95% CI: 0.43, 0.94; P for trend = 0.028). Neighborhood measures were generally not associated with corpora amylacea in tumor or benign tissue (Table 3). IQR increases in nSES (aOR = 0.76, 95% CI: 0.57, 1.02) and ICE-race/income (aOR = 0.73, 95% CI: 0.54, 0.99) were associated with lower odds of tumor corpora amylacea, though trends were not statistically significant. No statistically significant associations were observed between neighborhood measures and acute or chronic inflammation (Table 4).

Associations between time-varying neighborhood measures and tissue inflammatory markers were generally weaker than those for enrollment measures (Web Table 3, Web Table 4, Web Appendix 2). We developed a PCA-based nSES index with 3 components—"racial composition," "wealth and education," and "poverty and unemployment"—based on variables with the strongest loadings on these 3 factors (Web Appendix 1, Web Table 5). Associations with postatrophic hyperplasia and tumor corpora amylacea remained null when nSES was evaluated using a PCA-based approach (Web Table 6). As expected, ratio measures produced from log-binomial models were closer to the null than those produced from logistic regression models, but inferences remained generally the same, particularly for postatrophic hyperplasia (Web Table 7). There was no effect modification by address type for associations with neighborhood measures and postatrophic hyperplasia or with

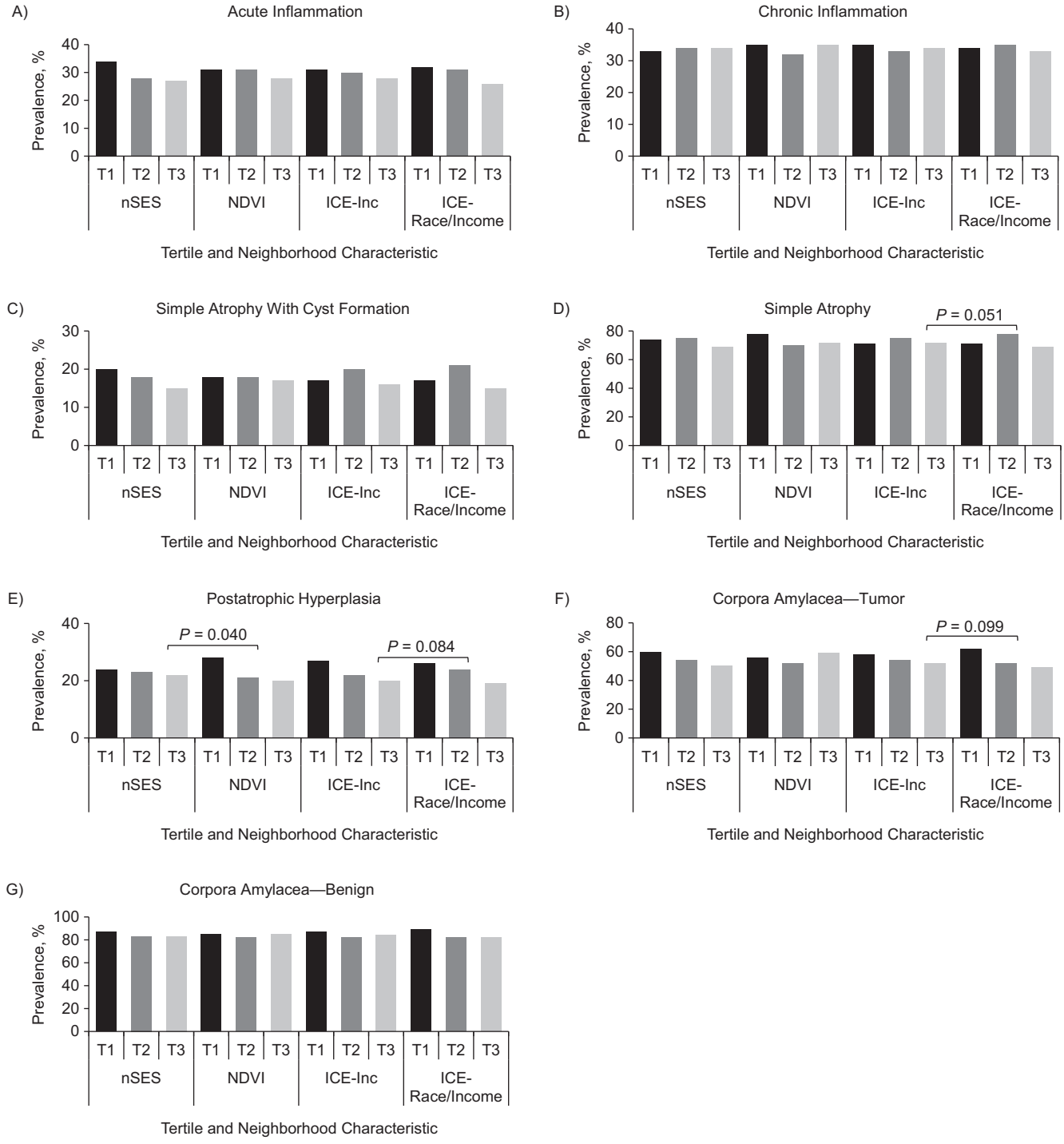

Figure 2. Prevalence of focal atrophic and inflammatory lesions in men diagnosed with prostate cancer (n = 967) in the Health Professionals Follow-up Study, by tertile (T) of neighborhood socioeconomic status (nSES), Normalized Difference Vegetation Index (NDVI), and segregation (Index of Concentration at the Extremes (ICE)), 1988–2009. A) Acute inflammation; B) chronic inflammation (moderate/severe vs. none/mild); C) simple atrophy with cyst formation; D) simple atrophy; E) postatrophic hyperplasia; F) corpora amylacea—tumor; G) corpora amylacea—benign. ICE-Inc, ICE segregation index for income; ICE-race/income, ICE segregation index for race/ethnicity (Black vs. White) and income.

Table 3. Odds Ratios (Simple and Ordinal Logistic Regression Models[a]) for Associations Between Neighborhood Contextual Factors Assessed at Enrollment (1988) and Atrophic Lesions in Men Diagnosed With Prostate Cancer (n = 967), Health Professionals Follow-up Study, 1988–2009

Tumor Characteristic	Model						*P* for Trend
	Continuous Variable[b]		Tertiles[c]				
			Tertile 2 (Middle)		Tertile 3 (Highest)		
	aOR	95% CI	aOR	95% CI	aOR	95% CI	
Simple atrophy							
NDVI within 1,230 m of address	0.86	0.69, 1.07	0.64	0.43, 0.95	0.73	0.48, 1.10	0.13
nSES	0.89	0.73, 1.09	1.02	0.70, 1.49	0.74	0.51, 1.09	0.10
ICE-income[d]	0.97	0.76, 1.25	1.17	0.81, 1.70	1.01	0.70, 1.45	0.87
ICE-race/income[d]	0.91	0.73, 1.13	1.39	0.95, 2.02	0.89	0.62, 1.28	0.72
Simple atrophy with cyst formation							
NDVI within 1,230 m of address	1.02	0.79, 1.32	0.94	0.60, 1.47	0.88	0.55, 1.41	0.60
nSES	0.77	0.60, 0.99	0.84	0.55, 1.28	0.65	0.41, 1.03	0.07
ICE-income	0.94	0.70, 1.26	1.15	0.75, 1.75	0.92	0.59, 1.44	0.82
ICE-race/income	0.97	0.75, 1.25	1.23	0.81, 1.88	0.89	0.57, 1.39	0.73
Postatrophic hyperplasia							
NDVI within 1,230 m of address	0.74	0.59, 0.93	0.61	0.41, 0.91	0.57	0.38, 0.87	0.01
nSES	0.97	0.77, 1.21	0.85	0.57, 1.25	0.79	0.52, 1.19	0.27
ICE-income	0.79	0.61, 1.04	0.71	0.48, 1.04	0.68	0.46, 1.00	0.04
ICE-race/income	0.79	0.63, 0.99	0.84	0.57, 1.23	0.63	0.43, 0.94	0.03
Corpora amylacea—tumor							
NDVI within 1,230 m of address	0.99	0.72, 1.36	0.81	0.47, 1.40	0.95	0.54, 1.67	0.82
nSES	0.76	0.57, 1.02	0.77	0.45, 1.31	0.67	0.38, 1.17	0.17
ICE-income	0.74	0.52, 1.05	0.87	0.50, 1.51	0.80	0.47, 1.33	0.38
ICE-race/income	0.73	0.54, 0.99	0.69	0.40, 1.20	0.62	0.37, 1.04	0.07
Corpora amylacea—benign							
NDVI within 1,230 m of address	1.04	0.69, 1.56	0.68	0.33, 1.42	0.88	0.40, 1.91	0.69
nSES	0.84	0.57, 1.23	0.65	0.30, 1.40	0.62	0.28, 1.37	0.26
ICE-income	0.81	0.50, 1.34	0.78	0.37, 1.66	0.82	0.39, 1.73	0.57
ICE-race/income	0.81	0.52, 1.25	0.60	0.28, 1.31	0.59	0.28, 1.26	0.16

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICE, Index of Concentration at the Extremes; MET, metabolic equivalent of task; NDVI, Normalized Difference Vegetation Index; nSES, neighborhood socioeconomic status; PSA, prostate-specific antigen.

[a] The logistic regression models adjusted for age, body mass index, height, vigorous and nonvigorous physical activity (MET-hours/week), PSA testing at diagnosis, year of diagnosis, and population density. All variables were assessed at the start of follow-up unless otherwise specified.

[b] Estimated risk per interquartile-range increase.

[c] Tertile 1 (lowest tertile) was the referent group for tertile-based comparisons.

[d] ICE-race/income measures capture Black vs. White segregation.

Table 4. Odds Ratios (Simple and Ordinal Logistic Regression Models[a]) for Associations Between Neighborhood Contextual Factors Assessed at Enrollment (1988) and Prostatic Chronic Inflammation in Men Diagnosed With Prostate Cancer (n = 967), Health Professionals Follow-up Study, 1988–2009

Tumor Characteristic	Model						*P* for Trend
	Continuous Variable[b]		Tertiles[c]				
			Tertile 2 (Middle)		Tertile 3 (Highest)		
	aOR	95% CI	aOR	95% CI	aOR	95% CI	
Acute inflammation							
NDVI within 1,230 m of address	0.91	0.74, 1.12	0.91	0.63, 1.32	0.76	0.52, 1.12	0.17
nSES	0.83	0.68, 1.03	0.73	0.51, 1.04	0.73	0.50, 1.05	0.11
ICE-income[d]	0.83	0.65, 1.06	0.92	0.65, 1.31	0.86	0.60, 1.23	0.41
ICE-race/income[d]	0.89	0.72, 1.10	0.96	0.68, 1.37	0.74	0.51, 1.06	0.12
Chronic inflammation[e]							
NDVI within 1,230 m of address	0.98	0.81, 1.19	0.77	0.54, 1.09	0.94	0.66, 1.34	0.69
nSES	0.99	0.82, 1.20	0.97	0.70, 1.35	0.92	0.65, 1.30	0.62
ICE-income	0.90	0.72, 1.13	0.90	0.65, 1.25	0.89	0.64, 1.24	0.46
ICE-race/income	0.94	0.78, 1.15	1.05	0.76, 1.45	0.92	0.67, 1.28	0.69

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICE, Index of Concentration at the Extremes; MET, metabolic equivalent of task; NDVI, Normalized Difference Vegetation Index; nSES, neighborhood socioeconomic status; PSA, prostate-specific antigen.

[a] The logistic regression models adjusted for age, body mass index, height, vigorous and nonvigorous physical activity (MET-hours/week), PSA testing at diagnosis, year of diagnosis, and population density. All variables were assessed at the start of follow-up unless otherwise specified.

[b] Estimated risk per interquartile-range increase.

[c] Tertile 1 (lowest tertile) was the referent group for tertile-based comparisons.

[d] ICE-race/income measures capture Black vs. White segregation.

[e] Chronic inflammation was assessed using multinomial regression models.

tumor corpora amylacea (Web Table 8). Results from analyses using inverse probability weights to account for potential selection bias due to tissue availability only among men diagnosed with CaP were similar to our primary results (Web Table 9). Results from these sensitivity analyses are described in greater detail in Web Appendix 2.

DISCUSSION

In a cohort of health professionals diagnosed with CaP, neighborhood social environment and greenness assessed at enrollment were not associated with most tissue markers of inflammation. Specifically, there were no associations with acute or chronic inflammation or with simple atrophy with or without cyst formation. However, we observed lower postatrophic hyperplasia among men living and working in neighborhoods with higher ICE-income, ICE-race/income, and NDVI. nSES and ICE measures were associated with lower tumor corpora amylacea, but not all associations reached statistical significance. Inverse associations persisted following adjustment for diagnostic PSA testing, age, and behavioral risk factors and potential selection bias.

We did not observe associations between NDVI, nSES, or ICE measures and acute or chronic inflammation. The prevalence of chronic inflammation in prostate tissue was elevated in our study because most men who provided samples had indications for biopsy or treatment, which limited variability in these outcomes. Prior studies examining inflammation and risk of aggressive CaP in men without indications for biopsy suggested that intraprostatic inflammation may be a cause of more aggressive CaP (5, 45), suggesting that evaluating associations with tissue markers obtained earlier in the natural progression of CaP may yield different inferences. Current understanding of prostate tumor development suggests that certain atrophic lesions (simple atrophy with or without cyst formation) arise from the biological aging process, while others (postatrophic hyperplasia) arise from proliferative inflammation in basal cells and therefore may increase CaP risk (2). We observed lower postatrophic hyperplasia among men living or working in neighborhoods with higher nSES and greenness, which may be related to lower systemic inflammation in the blood (21–23). Corpora amylacea is hypothesized to arise from infection or other environmental stressors that may contribute to inflammation in surrounding prostate tissue (2, 42). Our findings support the hypothesis that favorable nSES may be associated with lower levels of infection and inflammation in the prostate microenvironment, leading to lower tumor corpora amylacea. Neighborhood measures were not associated with simple atrophy with and without cyst formation, suggesting that these age-related processes may not be affected by neighborhood exposures.

These results complement earlier research suggesting that neighborhood social environment and greenness may influence CaP outcomes independently of behavioral risk factors (7, 46, 47). Adverse SES and income segregation may influence systemic inflammation through adverse social environments, mediated through limited social capital, civic engagement, and employment (48, 49). Psychosocial stressors linked with social hierarchies operate through physiological changes to the hypothalamus-pituitary-adrenal axis and downstream impacts on sympathetic nervous system activation and adrenal hormone release (50). Neighborhood greenness is associated with lower physiological stress, including allostatic load and inflammation, independent of behavioral risk factors (23, 51–55). Access to physical and visual green spaces at work has been linked to improved job satisfaction and lower stress (35). In prior work conducted in the HPFS cohort, we found no evidence of effect modification by address type in studies examining associations between neighborhood greenness and lethal CaP incidence (19) and studies examining associations between neighborhood context (nSES, ICE measures, and greenness) and circulating inflammatory biomarkers (23). These findings suggest that mechanisms through which residential and occupational neighborhoods influence inflammation may be similar. Inflammation pathways may also mediate associations between green space exposure and CaP risk and mortality (18–20), though evidence is more mixed.

Our findings support the hypothesis that adverse neighborhood social environments have an impact on systemic inflammation, which could then affect prostatic inflammation, resulting in different histological signatures (Figure 1). While our data did not allow for investigation of impacts on CaP, it is possible that these inflammatory histological markers may serve as relics of prior exposure that drove aggressive CaP development in certain men. Testing this hypothesis would require investigation of longitudinal effects of systemic inflammation on tissue-level proliferative inflammation pathways via genetic, molecular, or histological signatures. Studies in animals have revealed impacts of social environmental factors, including social isolation, on cancer development (56). A recent review indicated that animal studies support a role of stress in cancer initiation and progression, though evidence from human studies is weaker (57). Given well-documented social stressors that lead to poorer health in adverse neighborhood environments (11, 24, 58), men living in adverse neighborhood environments diagnosed with CaP may benefit more from targeted behavioral counseling aimed at reducing inflammation.

This study had some limitations. Because all study participants had CaP and histological samples were taken at the time of diagnosis or primary treatment, we could not assess whether inflammation was a cause or consequence of CaP. Confounding by unmeasured lifestyle, psychological, or access-related factors could have led to bias. Study participants were all male health professionals and predominantly White, so confounding by health-care access is unlikely. Individual SES was not examined as a potential buffer of the effect of neighborhood stressors on tissue markers, partly due to restricted variability in racial/ethnic, sex, occupational, and educational factors. However, this limited variability in individual SES means that any observed associations with neighborhood factors likely occurred independently of individual SES. The overlapping distributions of nSES and ICE measures between HPFS participants and the US population as a whole suggest that our study captured sufficient variability in neighborhood context to detect associations with tissue inflammation markers. Our findings can inform future research on how neighborhood environments influence inflammation in tumor tissue in more diverse populations, a necessary step in evaluating the external validity of these findings, which may be limited due to the demographic characteristics and SES of our population.

Selection bias arising from spurious associations between neighborhood factors, CaP diagnosis, and availability of tissue samples (a condition of selection into the study) may be a threat to validity. Findings were similar after application of inverse probability weights, implying that they were robust to this potential bias, assuming correct specification of our weighting models. Given that the prevalence of tissue inflammation markers was common in the study population and that odds ratios exaggerate risk ratios when the outcome is common, effect estimates with CI limits close to 1.00 should be interpreted with caution. Misclassification of histological assessments and neighborhood measures taken at a single address are possible. Because the participants' preference for the address (home or work) where they wished to receive their study questionnaire was not a cause of inflammation in the prostatic tumor, we consider the primary bias introduced by pooling of neighborhood exposure assessments across address types to have been nondifferential measurement error after adjustment for covariates. Moreover, because nSES, ICE, and NDVI measures were obtained from administrative databases and because the pathologist assigning inflammation and atrophic lesions was blinded to neighborhood environmental factors, misclassification was probably nondifferential and therefore would, on average, be expected to attenuate estimates towards the null.

We found lower odds of postatrophic hyperplasia and corpora amylacea among men living and working in more favorable neighborhood socioeconomic and natural environments, suggesting that neighborhood environment may influence inflammatory signatures in prostate tissue. These findings can support future research to determine whether neighborhood-level interventions to address these adverse social and natural features can improve CaP outcomes by preventing inflammation-related cancer progression.

ACKNOWLEDGMENTS

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This work was supported by National Institutes of Health (NIH) grant U01 CA167552 from the National Cancer Institute (NCI) and partially supported by funding from NCI Cancer Center Support Grants P30 CA006516 and P30 CA006973. Individual authors were supported by the following NIH grants: H.S.I., grant T32 CA 009001; N.V.D., grant T32 ES007069; T.R.R., grant P20 CA233255; J.E.H. and F.L., grant P30 ES000002; F.L., grant R01 ES028033; J.E.H., grant R01 ES028712; and P.J., grant R01 HL150119.

The data set analyzed in the current study is not publicly available, but limited data can be accessed upon request.

We thank the participants and staff of the Health Professionals Follow-up Study for their valuable contributions. We acknowledge the contributions made to this study by central cancer registries supported through the Centers for Disease Control and Prevention's National Program of Cancer Registries and the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. Central cancer registries may be supported by state agencies, universities, and cancer centers. Participating central cancer registries in this study included the Seattle SEER Registry (Seattle, Washington) and the registries of the following states and territories: Alabama, Alaska, Arizona, Arkansas, California, Delaware, Colorado, Connecticut, Florida, Georgia, Hawaii, Idaho, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Mississippi, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Tennessee, Texas, Utah, Virginia, West Virginia, and Wyoming.

This work was presented at the 34th Annual Conference of the International Society for Environmental Epidemiology, Athens, Greece, September 18–21, 2022.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflict of interest: none declared.

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