HGG Advances

ARTICLE

Investigating the role of neighborhood socioeconomic status and germline genetics on prostate cancer risk

Jonathan Judd,[1] Jeffrey P. Spence,[1,2,3] Jonathan K. Pritchard,[1,4] Linda Kachuri,[5,6] and John S. Witte[1,5,6,7,*]

Summary

Genetic factors play an important role in prostate cancer (PCa) development with polygenic risk scores (PRS) predicting disease risk across genetic ancestries. However, there are few convincing modifiable factors for PCa and little is known about their potential interaction with genetic risk. Our study explores the role of neighborhood socioeconomic status (nSES)—and how it may interact with PRS—on PCa risk. We analyzed incident PCa cases and controls of European (cases = 5,960; controls = 93,990) and African (cases = 109; controls = 1,226) ancestry from the UK Biobank cohort. Using the English indices of deprivation, a set of validated metrics that quantify lack of resources within geographical areas, we performed logistic regression to investigate the main effects and interactions between nSES deprivation and genetic susceptibility to PCa, represented by a multi-ancestry PRS comprised of 269 genetic variants. The PRS was associated with PCa in the European (OR = 2.04; 95% confidence interval [CI], 2.00–2.09; $p = 5.34 \times 10^{-807}$) and African (OR = 1.35; 95% CI, 1.16–1.58; $p = 1.05 \times 10^{-4}$) ancestries. Additionally, nSES deprivation indices were inversely associated with PCa: employment, education, health, and income. From this, we suspect that PRS, through biological mechanisms, and nSES deprivation, likely through differences in screening, are associated with PCa, but act independently of each other. Our findings suggest that genetic factors and social determinants of health measured by neighborhood socioeconomic status do not synergistically increase risk of PCa.

Introduction

Prostate cancer (PCa) is the second most common non-skin cancer in men in the world and the most common non-skin cancer in men in the United Kingdom, with the highest incidence rates observed in men of African ancestry.[1] In addition to older age, there is evidence for a strong genetic component in PCa etiology, including family history and germline susceptibility loci.[2] Genome-wide association studies (GWAS) have identified hundreds of independent risk variants for PCa and these findings have been used to develop a polygenic risk score (PRS). A PRS combines multiple genetic variants to estimate an individual's risk of a trait or disease.[3,4] While the predictive ability of PRS has improved over time, it is often reduced among individuals of understudied genetic ancestries.[4] Although the most recent PRS for PCa has improved risk prediction across ancestry groups, performance in African and East Asian populations continues to lag behind European ancestry.[5]

Individual and neighborhood socioeconomic status (nSES) has been explored as a potential risk factor for PCa[6–8]; however, studies of nSES have produced mixed results.[9–11] Some find a positive relationship between nSES and PCa risk, theorizing that better off populations due to a lack of standardized PCa screening guidelines are more likely to undergo prostate-specific antigen (PSA) screening or engage with the healthcare system.[11] Other research has found the opposite effect with lower nSES groups being at higher risk, suggesting a target for public health interventions.[10,12] These conflicting results suggest that a more concrete relationship between nSES and PCa may be revealed by more in-depth analyses that investigate the different domains that make up nSES.

Gene-environment (GxE) interactions are also thought to play an important role in complex trait variation across populations.[13] In the case of PCa, GxE interactions may take the form of changes in environmental exposure modifying the variation in cancer development affected by genetics.[14] In addition to interactions between environmental factors and specific risk variants, there is accumulating evidence that PRS performance is context-dependent and may be modified by other factors, including age, sex, genetic ancestry, biobank, and socioeconomic status.[13] For example, the PRS effects found in major depressive disorder may vary across groups of people with different levels of stress.[14,15] In the case of PCa, context-specific PRS effects may arise from heterogeneous

[1]Department of Genetics, Stanford University, Stanford, CA, USA; [2]Institute for Human Genetics, University of California, San Francisco, San Francisco, CA, USA; [3]Department of Epidemiology & Biostatistics, University of California, San Francisco, San Francisco, CA, USA; [4]Department of Biology, Stanford University, Stanford, CA, USA; [5]Department of Epidemiology and Population Health, Stanford University, Stanford, CA, USA; [6]Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA
[7]Lead contact
*Correspondence: jswitte@stanford.edu
https://doi.org/10.1016/j.xhgg.2025.100492.

variability where nSES impacts the magnitude of PRS association on PCa. While the PRS is not a tool for disentangling etiologic pathways, it is useful to identify these potential context-specific results. An analysis of PCa GxE effects in turn may help explain the aforementioned discrepancy in findings for nSES and PCa. In this study, we investigated the main effects and interactions of PCa PRS and nSES using genetic information and the English indices of Deprivation in the UK Biobank (UKB), a verified and recently accessible metric of nSES deprivation.

Material and methods

Study population

The UKB is a prospective study of 503,317 participants aged 40–69 years across England, Wales and Scotland.[16] Between 2006 and 2010, the UKB collected demographic and questionnaire data at 22 assessment centers, genotyped the study participants, and linked them to cancer registries to assess cancer diagnoses and status post-assessment.

All quality control and phenotyping of data used in our analyses was described and performed in previous studies.[17] We included English men here since different countries utilize different measures of nSES. Since English indices of deprivation are assigned to individuals with a listed English postal code at assessment, all English men with a postal code possessed complete deprivation information. Furthermore, we restricted our analysis to men in England with concordant self-reported and genetically inferred sex, available genotyping data, known values for English deprivation indices, and known cancer status histories. Additionally, we excluded men with a cancer diagnosis before assessment or a post-assessment cancer diagnosis other than PCa or non-melanoma skin cancer. Controls included men without any cancer diagnosis (excluding non-melanoma skin cancer). Analyses were performed separately in populations groups defined based on self-reported ethnicity and genetic principal component (PCs) values within five standard deviations of the UK10K and 1000 Genomes phase 3 reference panel group means. Using this criteria, we analyzed two separate populations throughout this study that we will refer to as the European (5,960 cases and 93,990 controls) and African (109 cases and 1,226 controls) ancestries.[17,18] We only analyzed populations with a minimum of 100 cases.

Indices of deprivation and Townsend index

The English Indices of Deprivation are a series of metrics calculated by the English Government that assess relative deprivation of geographic areas each containing approximately 1,500 individuals across seven domains: Income Deprivation; Employment Deprivation; Health Deprivation and Disability; Education, Skills, and Training Deprivation; Barriers to Housing and Services; Living Environment Deprivation; and Crime.[19] Each provides a quantitative measurement of the broad range of issues and unmet needs. Domain-specific indices are combined into a single index of multiple deprivation (IMD) using predefined weights: Income = 22.5%; Employment = 22.5%; Health and Disability = 13.5%; Education, Skills, and Training = 13.5%; Housing and Services = 9.3%; Environment = 9.3%; Crime = 9.3%.[19] The Townsend index is another nSES deprivation metric composed of four area-based indicators: percentage of households without a car, overcrowded households, households not owner-occupied, and persons unemployed, which are standardized and summed.[20] For all UKB participants, values of deprivation indices were assigned based on their postcode at year of assessment. For detailed descriptions, see Technical Report and Section 3.2 of GOV.UK[19] and Townsend et al.,[20] respectively.

PCa PRS

The multi-ancestry PCa PRS used in this analysis consists of 269 risk variants identified using multi-ancestry fine-mapping and summary statistics from a GWAS of 107,247 cases and 127,006 controls across three genetic ancestries.[21,22] UKB participants were not included in the GWAS meta-analysis used for training this PRS model. For individual i, $\mathrm{PRS}_i = \sum_{m=1}^{M} w_m g_{im}$, where g_{im} is the genotype dosage of variant m of M total variants and w_m is a variant-specific weight (logOR scale).

Associations with PCa were estimated separately in each population group using logistic regression with adjustment for age at assessment and the top 10 genetic PCs. We estimated odds ratios (ORs) per standard deviation (SD) increase in PRS_{269}, standardized within each ancestry group. We also modeled the PRS as a discrete variable with cut-points based on deciles with the 40%–60% group as the reference category.

Our primary analysis uses PRS_{269}, a validated PRS for PCa that was developed using the largest GWAS that excluded UKB. This was done to avoid overfitting the model to the data, which can occur when fitting PRS models to data in which they were developed. We also present sensitivity analyses using two of the most recent PCa PRS models for which UKB was part of the training data[3]: one model with 451 variants, and another developed using PRS-CSx.[23]

Modeling nSES

We used logistic regression to assess the potential association between nSES deprivation, as measured by the English indices of deprivation and the Townsend index, and PCa. Age at assessment was included as a covariate for all models. Additionally, to investigate if any associations between nSES deprivation and PCa are affected by PSA screening and healthcare utilization,[24] we used the "Ever had a PSA test" variable in UKB and calculated a proxy for healthcare utilization by summing the number of general practitioner visits and hospital inpatient episodes in the year prior to assessment.[25] Since our control group excluded individuals with any cancer diagnoses prior to enrollment, our measurement of healthcare utilization would not be affected by an increase in medical visits due to cancer treatment.

To evaluate the relationship between nSES deprivation, PSA screening, and PCa, we performed logistic regression between nSES deprivation and UKB's Ever had a PSA test variable before modeling the association between nSES deprivation and PCa while adjusting for PSA screening and age. We repeated this analysis for healthcare utilization by modeling the association between nSES deprivation and number of clinical visits, and by adjusting the potential association between nSES deprivation and PCa for the number of clinical visits and age. For this last model, we also perform Cox proportional hazards modeling to account for time. We also calculated the correlation between "Ever had a PSA test", number of clinical visits, PRS_{269}, and all nSES variables.

Finally, to further investigate the potential impact of high nSES on increasing PSA screening and prostate cancer, we performed a stratified analysis based on self-reported screening status. We

then performed a difference of means z-test for each nSES variable between the Ever had a PSA test and Never had a PSA test group. Due to small sample sizes in the other ancestry groups, we performed this analysis on only individuals of European ancestry. Additionally, using available general practitioner information about PSA testing, we analyzed the association between nSES deprivation and PCa while adjusting for number of clinical visits and age for only men with recorded PSA testing, which is a more accurate measure of PSA testing than the UKB survey question.

Evaluation of genetic effect modification

We investigated whether the PRS_{269} associations with PCa were modified by nSES deprivation in two ways. First, we fitted logistic regression models that included main effects and an interaction between PRS_{269} and nSES to estimate their effects on PCa risk. We assessed modification by looking at whether the interaction term was associated with PCa. Second, we evaluated the standardized PRS_{269} effect within quartiles of each nSES index. We computed Cochran's Q to assess heterogeneity in the effect size of the PRS across quartiles. This analysis was limited to men of European ancestry due to smaller sample sizes in the African ancestry (109 cases and 1,226 controls).

Results

Participant characteristics

From the 503,317 total participants in the UKB cohort, this study was restricted to 104,769 men from England, with genetic data and English postcodes (for calculating deprivation indices) without any previous history of cancer (Figure 1). This study included a total of 6,071 PCa cases and 95,320 cancer-free controls (Table 1). Most participants were of European ancestry (5,902 cases and 94,088 controls), compared with African (109 cases and 1,232 controls) ancestry. In these populations, 30% and 24% of participants reported having had at least one PSA test prior to recruitment. For both ancestries, the neighborhood deprivation scores, including the IMD and Townsend index, were lower in the cases compared with the controls. In contrast, the median number of clinical visits the year before assessment was higher for cases than controls in both European (7 vs. 6, $p = 3.97 \times 10^{-18}$) and African (9 vs. 7, $p = 0.238$) ancestries.

Relationship between PRS and prostate cancer

We reaffirmed the association between PRS_{269} and PCa using our specific sample.[21] We found PRS_{269} to be associated with PCa in both the European (OR = 2.04; 95% confidence interval [CI], 2.00–2.09; $p = 5.34 \times 10^{-807}$) and African (OR = 1.35; 95% CI, 1.16–1.58; $p = 1.05 \times 10^{-4}$) ancestries (ORs for a SD unit increase in the PRS). We also evaluated this association in two more recently developed PCa PRS models—one with 451 variants and the other from the genome-wide PRS-CSx—to investigate the change in the PRS and PCa association driven by models from a larger more-diverse GWAS.[3] We found associations of similar magnitude across all three models for both populations (Table S1). Even though the secondary PRS models were developed from a larger GWAS than PRS_{269}, they included UKB as part of their training data. Because this posed a risk of being overfit to our sample, PRS_{269} was used for all future analyses.

When we investigated if the relationship between PRS_{269} and PCa risk was linear, we found that the association increased across PRS deciles for men of European ancestry, but not men of African ancestry. Men in the top decile of the PRS distribution had a significantly increased risk of PCa compared with those with average PRS (40%–60%) in both the European (OR = 3.62; 95% CI, 3.38–3.89; $p = 1.04 \times 10^{-276}$) and African (OR = 1.9; 95% CI, 1.13–3.20; $p = 0.015$) ancestries. The association between PRS_{269} and PCa was statistically significant for all deciles in the European ancestry models, ranging from OR = 0.26 to OR = 3.62. However, in men of African ancestry, only the second highest decile of the PRS distribution had a significantly increased risk compared with the average (OR = 1.76; 95% CI, 1.04–3.00; $p = 0.04$) (Table 2). The associations in the African ancestry models were also less precise than those in the European models likely due to smaller samples, especially cases, in the lower decile groups.

Relationship between nSES and PCa

For each ancestry, we assessed the relationship between nSES deprivation and PCa using a minimally adjusted model. In the European ancestry, six of the nine nSES deprivation indices had inverse associations with prostate cancer: Education (OR = 0.92; 95% CI, 0.90–0.95; $p = 7.89 \times 10^{-8}$), Employment (OR = 0.91; 95% CI, 0.88–0.93; $p = 1.03 \times 10^{-10}$), Health (OR = 0.91; 95% CI, 0.88–0.93; $p = 1.66 \times 10^{-12}$), Income (OR = 0.91; 95% CI, 0.89–0.94; $p = 1.44 \times 10^{-9}$), IMD (OR = 0.92; 95% CI, 0.89–0.95; $p = 1.03 \times 10^{-8}$), and Townsend index (OR = 0.93; 95% CI, 0.90–0.96; $p = 1.95 \times 10^{-7}$) (all ORs for an SD unit increase in the deprivation index) (Figure 2A; Table S2). These results signify that higher deprivation and lower neighborhood resources are associated with lower PCa risk. In the European ancestry, the Housing/Services index (OR = 1.04; 95% CI, 1.01–1.06; $p = 6.78 \times 10^{-3}$) was the only nSES domain with a positive association, and we found no associations between the Crime and Environment indices in this group. In men of African ancestry, none of the nSES deprivation indices were associated with PCa (Figure 2B; Table S2). While this may signify a difference in the underlying association between deprivation and PCa across ancestries, it is likely the result of a lack of power to identify associations due to a small African ancestry sample. These results were recapitulated when nSES deprivation was modeled as quartiles (Table S3).

PSA screening and healthcare utilization

We hypothesized that differences in PSA screening and healthcare utilization may mediate observed associations between nSES and PCa.[24] In men of European ancestry, eight deprivation indices were negatively associated with

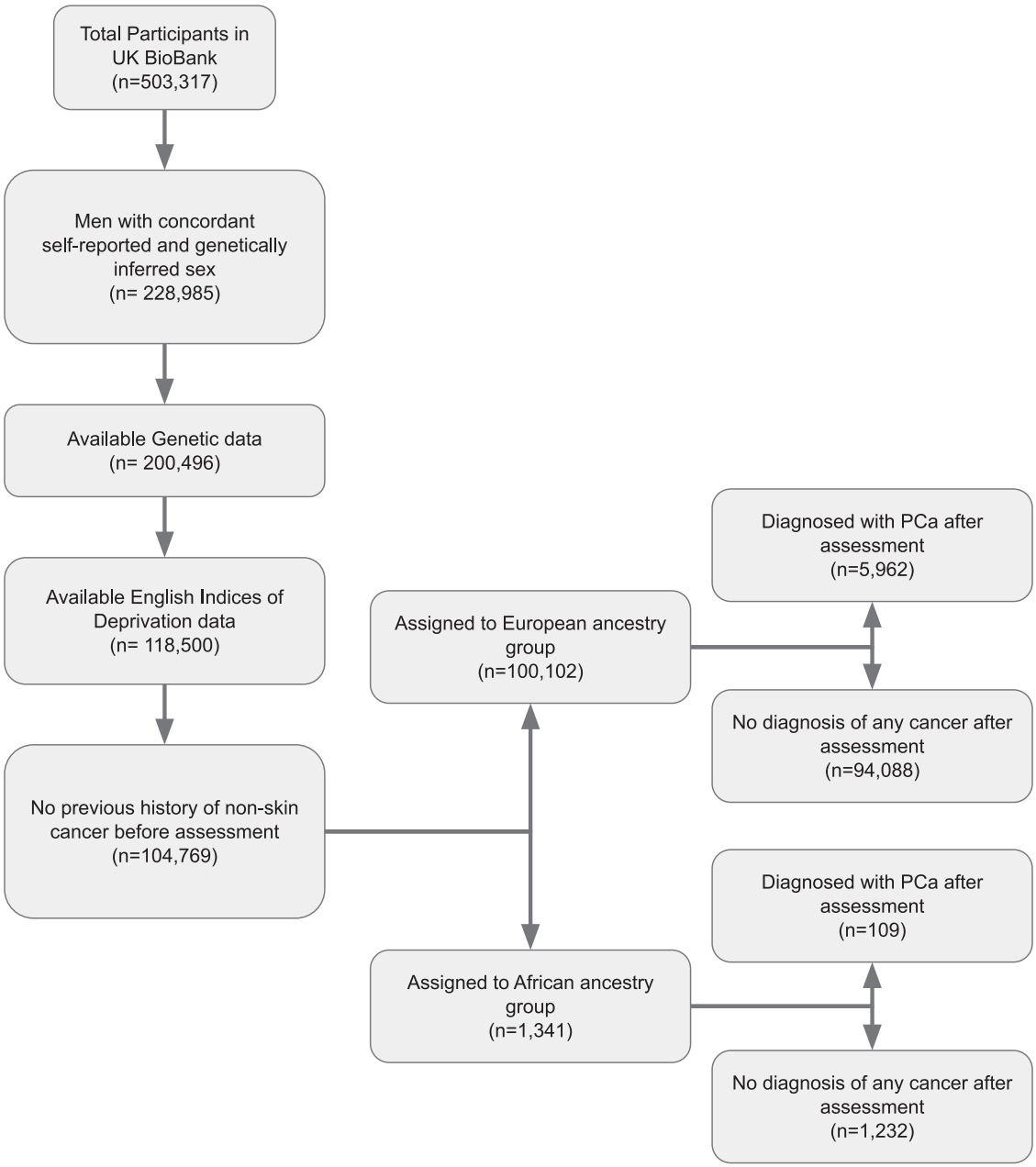

Figure 1. Inclusion criteria for study participants

Flowchart highlighting inclusion criteria for study participants from total membership of the UK Biobank. Number of individuals that meet inclusion criteria at each step are indicated in the parentheses. In the "Available English indices of deprivation data" box, all men with English postcodes possessed complete deprivation data and were included in the sample. Men of non-European and non-African ancestry were additionally excluded even though not noted in the chart.

the binary outcome of "Ever PSA Screened," with effects ranging from OR = 0.93 (Housing and Education) to OR = 0.97 (Environment) (for a SD unit increase in the deprivation index) (Table S4). The only positive association was for the Housing/Services index (OR = 1.13). In the African ancestry models, the IMD, Income, Employment, Health, Education, and Townsend indices, were also negatively associated with ever having had a PSA test (Table S4).

Inversely, all deprivation indices, except for Housing/Services ($\beta = -0.33$), were positively associated with the number of clinical visits in men of European ancestry. The IMD ($\beta = 1.07$), Health ($\beta = 1.06$), Education ($\beta = 0.81$), and Environment ($\beta = 1.00$) indices were also positively associated with the number of clinical visits in men of African ancestry (all Estimates for a one additional clinical visit in a year) (Table S5). When we calculated Pearson's correlation between PSA screening, clinical visits, and the nSES indices, PSA screening was inversely correlated with all nSES indices while clinical visits were positively correlated with them. The exception in both cases was the Housing/Services index that had a correlation in the opposite direction (Table S6).

Table 1. Baseline characteristics of men included in the analysis

	European		African	
Characteristic	Controls	Cases	Controls	Cases
No. of men	94,088	5,962	1,232	109
Anthropometrics	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age at assessment	56.9 (7.9)	62 (5.55)	51 (7.61)	57.1 (7.42)
nSES variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Index of multiple deprivation	0.02 (0.98)	−0.10 (0.90)	0.03 (1.04)	−0.09 (0.92)
Income index of deprivation	0.00 (0.96)	−0.13 (0.87)	−0.04 (1.03)	−0.13 (0.86)
Employment index of deprivation	0.02 (0.95)	−0.10 (0.84)	0.04 (1.03)	−0.10 (0.82)
Education index of deprivation	0.08 (1.07)	−0.03 (1.01)	0.20 (1.21)	0.14 (1.13)
Environment index of deprivation	0.01 (1.00)	−0.07 (0.96)	−0.03 (1.05)	−0.09 (1.04)
Health index of deprivation	0.10 (0.90)	−0.02 (0.87)	0.05 (0.92)	0.04 (0.98)
Housing/services index of deprivation	−0.06 (0.98)	−0.03 (0.97)	−0.17 (1.00)	−0.43 (0.86)
Crime index of deprivation	0.04 (1.00)	−0.04 (1.01)	0.06 (1.04)	0.10 (0.89)
Townsend index	−0.02 (0.96)	−0.14 (0.91)	−0.17 (0.97)	−0.27 (0.86)
Healthcare utilization	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
No. of clinical visits	6 (3–10)	7 (4–12)	7 (3–12)	9 (4–13)
PSA screening	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Never PSA tested	64,947 (70.7)	3,092 (53.0)	950 (77.5)	71 (62.8)
Ever PSA tested	269,44 (29.3)	2,741 (47.0)	276 (23.5)	42 (37.2)

Demographic and distribution characteristics for cases and controls for the European and African ancestries analyzed in the study. All values were obtained at time of assessment. Age is non-standardized. nSES deprivation variables include 2010 English indices of deprivation and Townsend index. Index means and SD are standardized for the total sample after stratifying on population, but before case/control status. Number of clinical visits is defined as the number of primary care and hospital inpatient visits per individual in the year prior to assessment. Median and interquartile range (IQR) for number of clinical visits is defined per population before stratifying on case/control status. PSA screening status per individual is determined by indicator for self-reported PSA screening at baseline (ever/never). Total number and percentages were calculated within both population and case/control status.

We further analyzed the potential association between nSES deprivation and PCa adjusting for the number of clinical visits, "Ever PSA Screened", and both of these potential confounders for both the European (Table S7) and African (Table S8) ancestry groups. When we include both potential confounders as covariates, the magnitude of association between the nSES deprivation variables and PCa remained consistent for all models, including the statistically significant European ancestry associations: Education (OR = 0.94), Employment (OR = 0.91), Health (OR = 0.91), Income (OR = 0.91), IMD (OR = 0.92), and Townsend index (OR = 0.94). These same indices were associated with PCa when Cox proportional hazards models were performed (Table S9). When nSES deprivation was modeled as quartiles with both of these covariates, results were mostly consistent when comparing against individuals in the top deprivation quartile. For these categorical models comparing the top and bottom quartile, the Townsend index was no longer statistically significant while the Environment index now was (Table S10).

Since PSA screening was associated with PCa when modeled with nSES, we also undertook an additional analysis stratified by PSA screening status to reduce residual confounding. In men of European ancestry, the association between nSES deprivation and prostate cancer remained consistent across screening status (Figure 3; Table S11). For the never screened individuals, the negative associations between nSES and PCa varied between OR = 0.91 (IMD) and OR = 0.94 (Townsend). In this group, we found no associations using the Crime, Environment, and Housing/Services indices. Within the screened group, IMD (OR = 0.95), Income (OR = 0.94), Employment (OR = 0.94), Education (OR = 0.95), and Townsend (OR = 0.93) indices were also inversely associated with PCa. The Crime index showed the largest difference between groups with PCa risk between never screened (OR = 0.97; 95% CI, 0.93–1.01; $p = 0.10$) and screened (OR = 1.01; 95% CI, 0.97–1.06; $p = 0.43$) participants. Reducing the sample to only men with known prediagnostic PSA testing attenuated the observed nSES associations for all nSES deprivations indices tested. However, we still observed a negative association between nSES deprivation and PCa for IMD, Income, and Employment for men of European ancestry with this subset of men (Table S12).

Table 2. ORs for PCa by PRS percentile stratified by genetic population

	European			African		
PRS category (%)	Case/control	OR (95% CI)	*p* value	Case/control	OR (95% CI)	*p* value
0–10	203/15,450	0.28 (0.25–0.33)	4.52E−68	9/295	0.55 (0.26–1.18)	1.24E−01
10–20	336/15,254	0.51 (0.45–0.57)	1.95E−31	13/280	0.91 (0.49–1.69)	7.58E−01
20–30	453/15,138	0.6 (0.54–0.67)	1.77E−20	19/281	1.35 (0.76–2.38)	3.07E−01
30–40	501/15,040	0.73 (0.66–0.8)	4.25E−10	22/263	1.05 (0.58–1.9)	8.78E−01
40–60	1471/29,540	reference	reference	34/549	reference	reference
60–70	953/14,506	1.29 (1.19–1.41)	3.58E−09	26/263	1.28 (0.72–2.26)	4.06E−01
70–80	1,148/14,286	1.59 (1.46–1.72)	6.27E−29	24/273	1.36 (0.79–2.36)	2.73E−01
80–90	1,425/13,899	2.11 (1.95–2.28)	2.76E−80	25/264	1.76 (1.04–3)	3.64E−02
90–100	2,299/12,804	3.62 (3.38–3.89)	1.04E−276	38/248	1.9 (1.13–3.2)	1.49E−02

OR and 95% CI for the association between a specified polygenic risk score 269 (PRS_{269}) decile and PCa compared with individuals in the 40%–60% percentile of scores (reference) for European and African ancestry samples. The number of cases and controls for each population and percentile group is given. PRS_{269} values were standardized per population before analysis.

PRS-by-nSES effect modification

Given the associations between deprivation and PCa, we aimed to identify potential PRS-by-nSES effect modification that results in population heterogeneity. When analyzing a potential GxE interaction between PRS_{269} and nSES deprivation, we found no effect modification across all indices for both the European ($p_{int} > 0.14$) and African ($p_{int} > 0.56$) ancestries (Table S13). When we repeated this analysis modeling deprivation as quartiles, we again found no effect modification (Table S14).

To more thoroughly analyze the lack of GxE interactions, we compared the PRS_{269} association across nSES quartiles in men of European ancestry. We did not observe any clear heterogeneity in the PRS_{269} associations. For the Townsend index, the second deprivation quartile had a slightly lower OR than the other three (OR = 1.93 vs. 2.1, giving a heterogeneity $p_{het} = 0.03$), this may have been spurious since there was no clear trend across the quartiles and effect for the other index measuring overall deprivation (i.e., the IMD) (Table 3). Lastly, we performed the opposite analysis where we compared deprivation association across PRS_{269} quartiles and found no heterogeneity (Table S15). These analyses were not performed in men of African ancestry due to the reduced power that would occur from stratifying an already small number of cases.

Discussion

We investigated potential main effects and interactions between a well-established risk factor, germline genetics, and a less well-studied exposure, nSES as measured through deprivation, and PCa. We found that the PRS and nSES were associated with PCa, but do not interact to impact risk of this common but complex disease.

Previous studies analyzing nSES and PCa reported conflicting results with some finding a positive association[9,11,26] and others finding a negative association.[10,12,27] These discrepancies may reflect differences in study population, methodology, country of study, healthcare systems, and utilization of different measures of nSES deprivation and covariates. And while the association between nSES and PCa incidence is unclear, studies consistently found nSES deprivation positively associated with both PCa stage and mortality.[6,8,11] Our findings agree with studies undertaken in the United States, Taiwan, and Scotland, which find that increasing neighborhood resources (or decreasing deprivation) increase PCa risk. We specifically identify novel associations in the domains of education, employment, health, and income.[11,26,27] These studies suggest that higher nSES groups are more likely to be PSA screened or utilize the healthcare system.[28] While PSA screening was positively associated with PCa, healthcare utilization was not. Moreover, nSES was associated with PCa after adjusting for self-reported screening at baseline. One possible explanation is that, while we account for variables associated with PCa screening bias, this effect may persist in the nSES associations due to limitations in the UKB cohort.[6] Another explanation for the nSES association is that while PSA screening may lead to overdiagnosis, there may be environmental exposures more common in resourced neighborhoods that increase PCa incidence.[2] Examples of exposures potentially associated with PCa incidence include per- and polyfluroalkyl substances (PFAS), endocrine-disrupting chemicals,[29,30] and nighttime light exposure.[31,32] However, like many environmental exposures associated with PCa, results have been inconclusive and necessitate further study.

The only nSES deprivation domain positively associated with PCa was the Housing/Services index, implying that men in neighborhoods with less access to housing and services were more likely to be diagnosed with PCa. The mechanism underlying this association, and its opposite effect from other domains, is unknown. It is likely

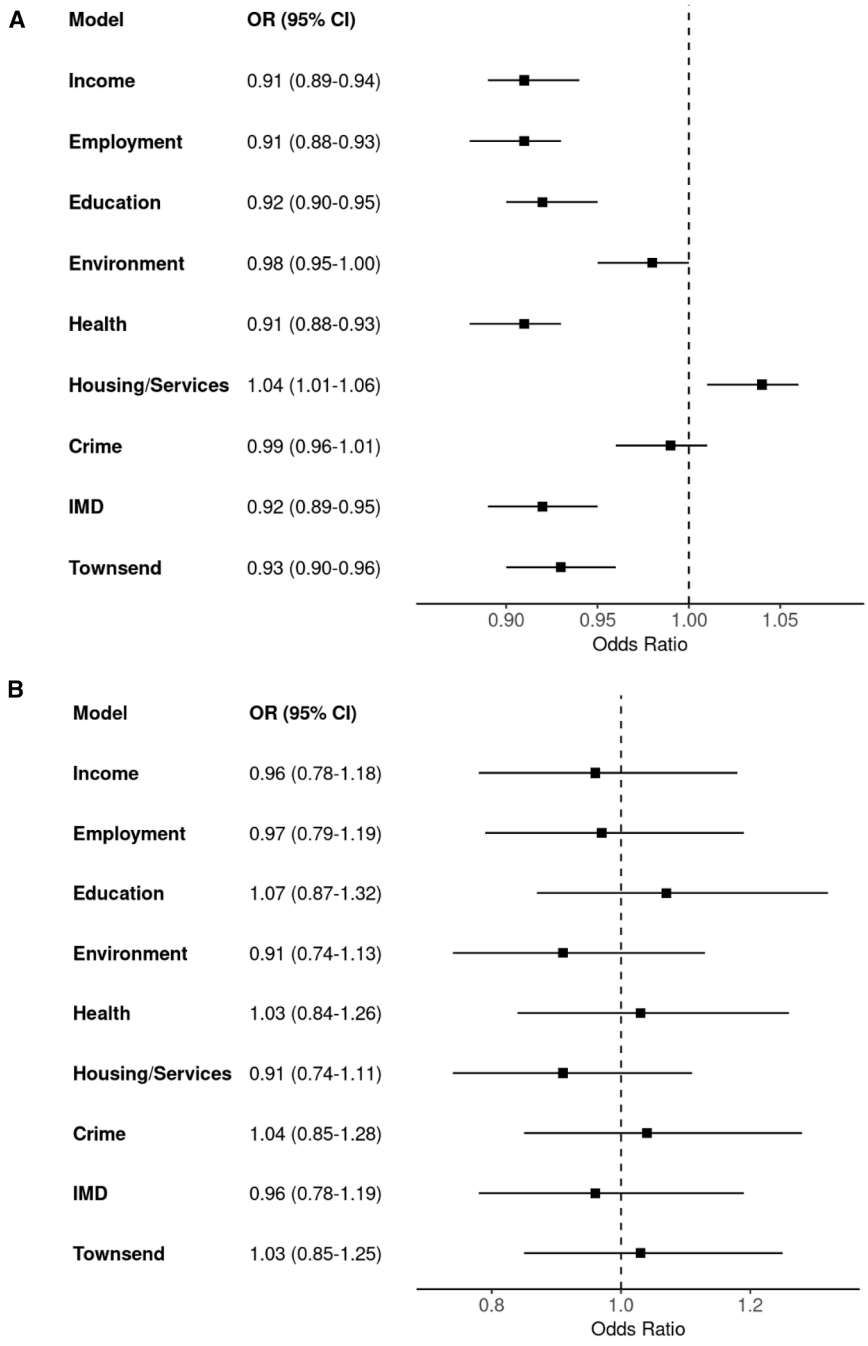

Figure 2. Association between nSES indices of deprivation and PCa

(A and B) (A) In European ancestry individuals and (B) in African ancestry individuals. ORs and 95% CIs reflect a one SD change in nSES indices (standardization within each group). ORs < 1 indicate that higher deprivation is inversely associated with PCa. IMD is constructed from other indices of deprivation based on weights given in methods.

connected to our finding that the Housing/Services index is uncorrelated with the other indices, except for the Environment and Townsend indices that include housing deprivation in their calculation. When we remove housing-relevant indicators, the Housing/Services index is calculated using the average distance to key services, such as intensive medical care, supermarkets, schooling, and post offices. The association between Housing/Services and PCa is likely driven by services deprivation, particularly factors associated with distance to medical care and schooling. The associations between nSES deprivation and PCa were also only seen in the European ancestry group. Due to the smaller number of African ancestry men, it is difficult to ascertain if there is no effect in this group or if we were underpowered to detect these associations. Nevertheless, reporting findings in this population was important in light of their increased risk of PCa and the need to include understudied populations in biomedical research.[33] Future research should analyze these relationships in a larger population of African ancestry men.

As in previous studies, we observed attenuated PRS associations with PCa for non-European ancestries, including African ancestries, have been consistently replicated across PCa PRS models.[3,4,21,34,35] This reflects population differences in linkage disequilibrium patterns, allelic effect size, and causal allele frequency, as well as smaller GWAS sample size for PRS training in African ancestry populations.[21] The combination of a less predictive PRS and small sample size for African ancestry in UKB, further reduced our power for detecting interactions with nSES in this population.

GxE interactions may reflect biological processes, statistical interaction, or spurious associations, and are of increasing interest for improving genetic discovery and explaining missing heritability and population heterogeneity.[14] As neither the biological pathways nor environmental exposures of PCa are known, analyzing the interaction between the PRS, a quantification of overall germline risk, and nSES provides an initial investigation into effect modification in PCa. When we investigated the potential role of gene-nSES interactions to explain PCa heritability and heterogeneity in previous studies, we identified an interaction between PRS_{269} and the Townsend index. The lack of an interaction for the other index measuring overall deprivation, the IMD, may signify that the interaction with Townsend index is a

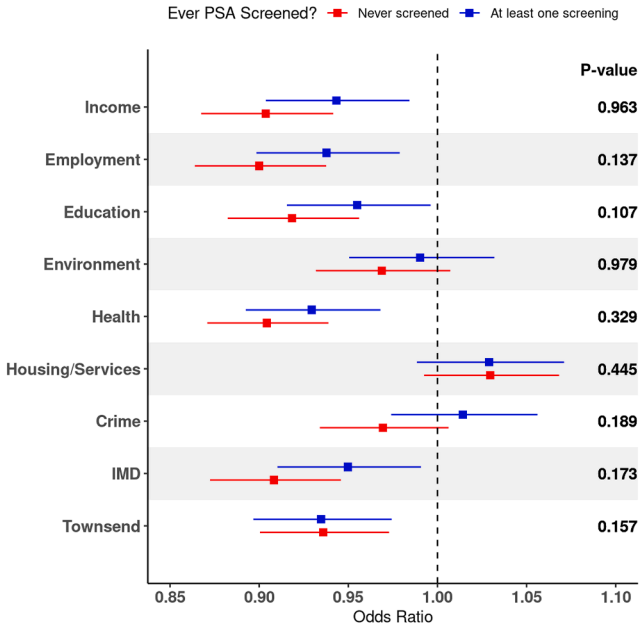

Figure 3. Association between nSES indices of deprivation and PCa in European group individuals stratified by PSA screening status

ORs and 95% CI estimates between a SD change in nSES deprivation indices and PCa for the European ancestry stratified by indicator for self-reported PSA screening at baseline (ever/never). All indices of deprivation, including IMD and Townsend, were standardized prior to stratifying on screening status. *p* values calculated as a difference of means z-test for each nSES variable stratified on the PSA screening group. ORs < 1 signify increased nSES deprivation and less neighborhood resources lower odds of PCa.

spurious association. While GxE interactions are challenging to detect due to limited statistical power, the absence of interactions for the other indices may reflect that nSES and PRS act independently. It could also reflect differences in factors affecting PCa development vs. those affecting PCa detection. There may be environmental factors that modify genetic susceptibility to PCa, but more work must be done to identify additional risk factors that are risk factors themselves for PCa. Future work should also incorporate novel frameworks and techniques to facilitate the discovery of these interactions and explain the remaining variation in PCa risk.[14,36]

Several key limitations prevent us from interpreting our results more broadly. First, the UKB is a largely European ancestry sample; moreover, due to differences in nSES indices we restricted the study sample to English men. Both of these limit the generalizability of our findings. Additionally, the small number of African ancestry individuals in UKB reduces our ability to detect associations.[4,37] Future studies require larger cohorts that are more diverse in ancestry, personal identity, and socioeconomic background.[38] Second, we lacked in-depth cancer stage and screening information to obtain an unbiased estimate of the PCa associations and PSA screening effect. For example, our PSA screening was only ascertained once, by self-report at cohort enrollment, without any information regarding the timing and frequency of screening. With a more accurate measure of PSA screening (e.g., based on medical records) and screening data over time, the potential associations between nSES indices and PCa among the non-PSA screened may become weaker indicating a remaining screening bias effect. Additional information on PSA screening would also illuminate potential differences in screening behavior between cases and controls due to age, which may have resulted in an association between nSES and PCa. The discrepancies in findings across studies of nSES and prostate cancer may reflect the limited information on PSA screening over time. Another limitation is the potential for undiagnosed PCa among the controls, which would tend to bias results to the null.

Lastly, nSES indices are broad measures of deprivation assigned at assessment without considering how long individuals live in a particular neighborhood. This could lead to exposure misclassification for nSES in the etiologically relevant time frame prior to PCa diagnosis.

Table 3. ODs (95% CI) for PCa in relation to PRS stratified by nSES deprivation quartiles

nSES variables	Deprivation quartile 1 PRS OR (95% CI)	Deprivation quartile 2 PRS OR (95% CI)	Deprivation quartile 3 PRS OR (95% CI)	Deprivation quartile 4 PRS OR (95% CI)	Heterogeneity *p* value
Index of multiple deprivation	1.99 (1.89–2.1)	2.12 (2–2.24)	2.14 (2.02–2.26)	2.03 (1.91–2.15)	0.226
Income index of deprivation	2.03 (1.93–2.14)	2.03 (1.92–2.15)	2.15 (2.04–2.28)	2.06 (1.94–2.19)	0.418
Employment index of deprivation	2.04 (1.94–2.15)	2.05 (1.94–2.16)	2.17 (2.06–2.3)	2.01 (1.89–2.13)	0.231
Health index of deprivation	2.03 (1.92–2.14)	2.14 (2.03–2.26)	2.12 (2–2.24)	1.97 (1.86–2.1)	0.159
Education index of deprivation	2.1 (1.99–2.21)	2.03 (1.92–2.15)	2.06 (1.95–2.18)	2.08 (1.95–2.2)	0.857
Housing/services index of deprivation	2.03 (1.92–2.15)	2.06 (1.94–2.17)	2.02 (1.91–2.14)	2.16 (2.04–2.29)	0.324
Crime index of deprivation	2.01 (1.91–2.13)	2.02 (1.91–2.13)	2.19 (2.07–2.32)	2.06 (1.94–2.18)	0.115
Environment index of deprivation	1.98 (1.88–2.09)	2.11 (2–2.23)	2.09 (1.98–2.22)	2.1 (1.98–2.22)	0.37
Townsend index of deprivation	2.13 (2.02–2.25)	1.93 (1.83–2.03)	2.1 (1.99–2.23)	2.12 (2–2.25)	0.029

OR and 95% CI for the association between continuous PRS_{269} values and PCa stratified by individuals in each nSES deprivation quartile for men of European ancestry. PRS_{269} values were standardized in the European ancestry sample prior to separating on deprivation quartile. Heterogeneity *p* value calculated from a Cochran's Q test comparing PRS_{269} associations within each stratified nSES deprivation index.

Similarly, PSA testing is assessed at one point in time, limiting our ability to evaluate changes over time. Both of these sources of misclassification are anticipated to be non-differential. In addition, individual SES, which varies within geographic regions, can add unmeasured confounding to the nSES relationship studied in this research.[26,39] Given available data, it was not possible to adjust for this confounding across indices measuring domain-specific deprivation and overall deprivation in a principled manner. While previous research has adjusted for individual SES and identified associations with nSES,[10,11] future work should account for an individual's SES in specific socioeconomic domains and length of exposure in a specific neighborhood.

In conclusion, we reproduced the positive association between PRS and PCa and identified an inverse relationship between several domains of neighborhood deprivation and PCa while accounting for potential mediators, such as PSA screening and healthcare utilization. We did not, however, detect any interactions between the PRS and nSES, suggesting that these factors act independently on PCa risk. Nevertheless, these findings merit further investigation in studies considering other axes of social determinants of health.

Data and code availability

- Analyses were conducted using R/4.2.2.
- Scripts for the analyses, including data preprocessing and model fitting, are available on GitHub (https://github.com/jonjudd/PCa-nSES-PRS) to facilitate reproducibility and verification of our findings.
- The research was conducted with approved access to UK Biobank data under application number 14105 (PI: witte).
- UK Biobank data are publicly available by request from https://www.ukbiobank.ac.uk.
- Informed consent was obtained from all study participants.
- UK Biobank received ethics approval from the Research Ethics Committee (REC ref. 11/NW/0382).
- PRS269 (PRS ID: PGS000662) and PRS451 (PRS ID: PGS003765) are publicly available on the PGS catalog from https://www.pgscatalog.org/.

Acknowledgments

This work was supported by the National Institutes of Health grants T32HG000044 (to J.J.), R01CA241410 (to J.S.W.), and U01CA 261339 (to J.S.W.). The funder had no role in the design of the study, the collection, analysis, or interpretation of the data, or the writing of the manuscript and decision to submit it for publication.

Declaration of interests

The authors declare no competing interests.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.xhgg.2025.100492.

Received: March 18, 2025
Accepted: August 5, 2025

References

1. Cancer Research UK (2015). Prostate cancer statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer.
2. Bergengren, O., Pekala, K.R., Matsoukas, K., Fainberg, J., Mungovan, S.F., Bratt, O., Bray, F., Brawley, O., Luckenbaugh, A.N., Mucci, L., et al. (2023). 2022 Update on Prostate Cancer Epidemiology and Risk Factors—A Systematic Review. Eur. Urol. *84*, 191–206. https://doi.org/10.1016/j.eururo.2023.04.021.
3. Wang, A., Shen, J., Rodriguez, A.A., Saunders, E.J., Chen, F., Janivara, R., Darst, B.F., Sheng, X., Xu, Y., Chou, A.J., et al. (2023). Characterizing prostate cancer risk through multi-ancestry genome-wide discovery of 187 novel risk variants. Nat. Genet. *55*, 2065–2074.
4. Kachuri, L., Chatterjee, N., Hirbo, J., Schaid, D.J., Martin, I., Kullo, I.J., Kenny, E.E., Pasaniuc, B., Polygenic Risk Methods in Diverse Populations PRIMED Consortium Methods Working Group, Witte, J.S., and Ge, T. (2024). Principles and methods for transferring polygenic risk scores across global populations. Nat. Rev. Genet. *25*, 8–25.
5. Lambert, S.A., Gil, L., Jupp, S., Ritchie, S.C., Xu, Y., Buniello, A., McMahon, A., Abraham, G., Chapman, M., Parkinson, H., et al. (2021). The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. Nat. Genet. *53*, 420–425.
6. Coughlin, S.S. (2020). A review of social determinants of prostate cancer risk, stage, and survival. Prostate Int. *8*, 49–54.
7. Riveros, C., Al-Toubat, M., Chalfant, V., Elshafei, A., Feibus, A., Forero, A., and Balaji, K.C. (2023). The impact of socioeconomic status on the survival of men with early-onset prostate cancer. Am. J. Clin. Exp. Urol. *11*, 146–154.
8. DeRouen, M.C., Schupp, C.W., Koo, J., Yang, J., Hertz, A., Shariff-Marco, S., Cockburn, M., Nelson, D.O., Ingles, S.A., John, E.M., and Gomez, S.L. (2018). Impact of individual and neighborhood factors on disparities in prostate cancer survival. Cancer Epidemiol. *53*, 1–11.
9. Perez-Cornago, A., Key, T.J., Allen, N.E., Fensom, G.K., Bradbury, K.E., Martin, R.M., and Travis, R.C. (2017). Prospective investigation of risk factors for prostate cancer in the UK Biobank cohort study. Br. J. Cancer *117*, 1562–1571.
10. Salmon, C., Quesnel-Vallée, A., Barnett, T.A., Benedetti, A., Cloutier, M.S., Datta, G.D., Kestens, Y., Nicolau, B., and Parent, M.É. (2023). Neighbourhood social deprivation and risk of prostate cancer. Br. J. Cancer *129*, 335–345.
11. Wu, C.C., Lin, C.H., Chiang, H.S., and Tang, M.J. (2018). A population-based study of the influence of socioeconomic status on prostate cancer diagnosis in Taiwan. Int. J. Equity Health *17*, 79.
12. Pichardo, M.S., Minas, T.Z., Pichardo, C.M., Bailey-Whyte, M., Tang, W., Dorsey, T.H., Wooten, W., Ryan, B.M., Loffredo, C.A., and Ambs, S. (2023). Association of Neighborhood Deprivation With Prostate Cancer and Immune Markers in African American and European American Men. JAMA Netw. Open *6*, e2251745.
13. Herrera-Luis, E., Benke, K., Volk, H., Ladd-Acosta, C., and Wojcik, G.L. (2024). Gene–environment interactions in human health. Nat. Rev. Genet. *25*, 768–784.

14. Westerman, K.E., and Sofer, T. (2024). Many roads to a gene-environment interaction. Am. J. Hum. Genet. *111*, 626–635.
15. Fabbri, C., Lewis, C.M., and Serretti, A. (2024). Polygenic risk scores for mood and related disorders and environmental factors: Interaction effects on wellbeing in the UK biobank. Prog. Neuropsychopharmacol. Biol. Psychiatry *132*, 110972.
16. Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., et al. (2015). UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS Med. *12*, e1001779.
17. Kachuri, L., Graff, R.E., Smith-Byrne, K., Meyers, T.J., Rashkin, S.R., Ziv, E., Witte, J.S., and Johansson, M. (2020). Pan-cancer analysis demonstrates that integrating polygenic risk scores with modifiable risk factors improves risk prediction. Nat. Commun. *11*, 6084.
18. Rashkin, S.R., Graff, R.E., Kachuri, L., Thai, K.K., Alexeeff, S.E., Blatchins, M.A., Cavazos, T.B., Corley, D.A., Emami, N.C., Hoffman, J.D., et al. (2020). Pan-cancer study detects genetic risk variants and shared genetic basis in two large cohorts. Nat. Commun. *11*, 4423.
19. GOV.UK. English indices of deprivation 2010. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010.
20. Townsend, P., Phillimore, P., and Beattie, A. (1988). Health and Deprivation: Inequality and the North (Routledge).
21. Conti, D.V., Darst, B.F., Moss, L.C., Saunders, E.J., Sheng, X., Chou, A., Schumacher, F.R., Olama, A.A.A., Benlloch, S., Dadaev, T., et al. (2021). Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. Nat. Genet. *53*, 65–75.
22. Newcombe, P.J., Conti, D.V., and Richardson, S. (2016). JAM: A Scalable Bayesian Framework for Joint Analysis of Marginal SNP Effects. Genet. Epidemiol. *40*, 188–201.
23. Ruan, Y., Lin, Y.F., Feng, Y.C.A., Chen, C.Y., Lam, M., Guo, Z., Stanley Global Asia Initiatives, He, L., Sawa, A., Martin, A.R., et al. (2022). Improving polygenic prediction in ancestrally diverse populations. Nat. Genet. *54*, 573–580.
24. Moses, K.A., Zhao, Z., Bi, Y., Acquaye, J., Holmes, A., Blot, W. J., and Fowke, J.H. (2017). The impact of sociodemographic factors and PSA screening among low-income Black and White men: data from the Southern Community Cohort Study. Prostate Cancer Prostatic Dis. *20*, 424–429.
25. Wang, J., Buto, P., Ackley, S.F., Kobayashi, L.C., Graff, R.E., Zimmerman, S.C., Hayes-Larson, E., Mayeda, E.R., Asiimwe, S.B., Calmasini, C., and Glymour, M.M. (2023). Association between cancer and dementia risk in the UK Biobank: evidence of diagnostic bias. Eur. J. Epidemiol. *38*, 1069–1079.
26. Shafique, K., Oliphant, R., and Morrison, D.S. (2012). The impact of socio-economic circumstances on overall and grade-specific prostate cancer incidence: a population-based study. Br. J. Cancer *107*, 575–582.
27. Major, J.M., Norman Oliver, M., Doubeni, C.A., Hollenbeck, A.R., Graubard, B.I., and Sinha, R. (2012). Socioeconomic status, healthcare density, and risk of prostate cancer among African American and Caucasian men in a large prospective study. Cancer Causes Control. *23*, 1185–1191.
28. Fu, J., Fu, C., Wang, R.S., Geynisman, D.M., Ghatalia, P., Lynch, S.M., Harrison, S.R., Tagai, E.K., and Ragin, C. (2023). Current Status and Future Direction to Address Disparities in Diversity, Equity, and Inclusion in Prostate Cancer Care. Curr. Oncol. Rep. *25*, 699–708.
29. Lacouture, A., Lafront, C., Peillex, C., Pelletier, M., and Audet-Walsh, É. (2022). Impacts of endocrine-disrupting chemicals on prostate function and cancer. Environ. Res. *204*, 112085.
30. Rhee, J., Barry, K.H., Huang, W.Y., Sampson, J.N., Hofmann, J.N., Silverman, D.T., Calafat, A.M., Botelho, J.C., Kato, K., Purdue, M.P., and Berndt, S.I. (2023). A prospective nested case-control study of serum concentrations of per- and polyfluoroalkyl substances and aggressive prostate cancer risk. Environ. Res. *228*, 115718.
31. Chowdhury-Paulino, I.M., Hart, J.E., James, P., Iyer, H.S., Wilt, G.E., Booker, B.D., Nethery, R.C., Laden, F., Mucci, L.A., and Markt, S.C. (2023). Association between Outdoor Light at Night and Prostate Cancer in the Health Professionals Follow-up Study. Cancer Epidemiol. Biomarkers Prev. *32*, 1444–1450.
32. Garcia-Saenz, A., Sánchez de Miguel, A., Espinosa, A., Valentin, A., Aragonés, N., Llorca, J., Amiano, P., Martín Sánchez, V., Guevara, M., Capelo, R., et al. (2018). Evaluating the Association between Artificial Light-at-Night Exposure and Breast and Prostate Cancer Risk in Spain (MCC-Spain Study). Environ. Health Perspect. *126*, 047011.
33. Martin, A.R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B.M., and Daly, M.J. (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. Nat. Genet. *51*, 584–591.
34. Mars, N., Kerminen, S., Feng, Y.C.A., Kanai, M., Läll, K., Thomas, L.F., Skogholt, A.H., Della Briotta Parolo, P., Biobank Japan Project, FinnGen, et al. (2022). Genome-wide risk prediction of common diseases across ancestries in one million people. Cell Genom. *2*, 100118.
35. Hou, K., Xu, Z., Ding, Y., Mandla, R., Shi, Z., Boulier, K., Harpak, A., and Pasaniuc, B. (2024). Calibrated prediction intervals for polygenic scores across diverse contexts. Nat. Genet. *56*, 1386–1396.
36. Zhu, X., Yang, Y., Lorincz-Comi, N., Li, G., Bentley, A.R., de Vries, P.S., Brown, M., Morrison, A.C., Rotimi, C.N., Gauderman, W.J., et al. (2024). An approach to identify gene-environment interactions and reveal new biological insight in complex traits. Nat. Commun. *15*, 3385.
37. Martin, A.R., Gignoux, C.R., Walters, R.K., Wojcik, G.L., Neale, B.M., Gravel, S., Daly, M.J., Bustamante, C.D., and Kenny, E.E. (2017). Human Demographic History Impacts Genetic Risk Prediction across Diverse Populations. Am. J. Hum. Genet. *100*, 635–649.
38. Oh, S.S., Galanter, J., Thakur, N., Pino-Yanes, M., Barcelo, N.E., White, M.J., de Bruin, D.M., Greenblatt, R.M., Bibbins-Domingo, K., Wu, A.H.B., et al. (2015). Diversity in Clinical and Biomedical Research: A Promise Yet to Be Fulfilled. PLoS Med. *12*, e1001918.
39. Sangaramoorthy, M., Shariff-Marco, S., Conroy, S.M., Yang, J., Inamdar, P.P., Wu, A.H., Haiman, C.A., Wilkens, L.R., Gomez, S.L., Le Marchand, L., and Cheng, I. (2022). Joint Associations of Race, Ethnicity, and Socioeconomic Status With Mortality in the Multiethnic Cohort Study. JAMA Netw. Open *5*, e226370.