THE UNIVERSITY OF CHICAGO

INDIVIDUAL AND NEIGHBORHOOD CONTRIBUTIONS TO AFRICAN AMERICAN HEALTH DISPARITIES IN BIO-SPECIMEN RESEARCH PARTICIPATION, PROSTATE-SPECIFIC ANTIGEN LEVELS, AND PROSTATE CANCER AGGRESSIVENESS

A DISSERTATION SUBMITTED TO

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DEDICATION

I dedicate this dissertation to everyone who supported my childhood/ lifetime dream to go to the University of Chicago. In particular, I dedicate this work:

To my dad.

You inspired me to come here and persist.

Thank you for your love and support throughout the journey.

(Michael Press, MED MD 1977, BSD PhD 1975)

To my mom, my grandpa, and my grandma.

Thank you for your love, support, and encouragement from childhood until today.

(Sarah Elizabeth Pizzo Press, College AB 1975)

(Anthony Pizzo, College SB 1943, MED MD 1945)

(Patricia Pizzo, College X 1945)

To all my family, friends, and church community unaffiliated with the University of Chicago who also supported me. Thank you.

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ABSTRACT

African American (AA) persons are exposed to disproportionately high levels of social and environmental stressors, including low socioeconomic status (SES), social isolation, interpersonal and institutional discrimination, and residence in resource poor communities, which intersect at individual- and neighborhood- levels and are associated with poor lifestyle factors, healthcare utilization, and health outcomes. The glaring disparity in prostate cancer mortality between AA men and Non-Hispanic (NH) White men appears to be due to complex biological, socioeconomic, and socio-cultural determinants underlying disparities in presentation, diagnosis, treatment, and survival. The extent to which individual factors and neighborhood contextual factors separately and together contribute to health disparities is unclear. Our ability to elucidate the impact of neighborhood contextual factors on health outcomes is complicated by differential research participation by race/ethnicity, which persistently threatens the generalizability of epidemiological findings. Reasons for differential research participation, including bio-specimen research participation, appear to reflect a complex interplay between features of research study design and the underlying target communities. We were also interested in the association between neighborhood contextual factors and prostate cancer risk profile prostate-specific antigen (PSA) level in a non-screening population and prostate cancer aggressiveness at diagnosis in the general population. To examine the impact of neighborhood contextual factors on prostate cancer disparities, we conducted epidemiological studies at statewide and regional levels.

At a statewide level, we examined a population-based retrospective cohort of 17,787 AA men and 112,591 NHW men diagnosed with prostate cancer in California. We examined racial/ ethnic disparities in occurrence of prostate cancer aggressiveness as defined by binary outcomes

of high PSA, high Gleason score grade (GS), and high TNM stage (stage) using multivariable logistic regression analyses. We also used a previously established method to identify the relative contribution of covariables to racial/ ethnic disparities in prostate cancer aggressiveness outcomes. We observed evidence that racial/ ethnic disparities in prostate cancer aggressiveness at diagnosis for AA men relative to NHW men in California were driven by high PSA, not high GS and/ or stage. Specifically, AA men experienced an approximate 79% increase in odds of high PSA prostate cancer relative to NHW men, after full adjustment for year and age at diagnosis, marital status, and health insurance type, as well as stage and grade (odds ratio (OR)= 1.79; 95% confidence interval (CI)=1.69-1.90). On the other hand, when we added PSA as an independent variable to fully adjusted models, we observed that the OR for race (AA vs. NHW) was null for the high GS model (OR=0.97; 95% CI=0.92-1.03) and reduced for the high stage model (OR=0.86; 95% CI=0.80-0.91). The most influential variables in terms of racial/ ethnic disparities in high PSA prostate cancer were age at diagnosis and neighborhood SES, possibly as a surrogate for individual SES and/ or social stressors.

At a regional level, we examined the population-based ChicagO Multiethnic Prevention and Surveillance Study (COMPASS). Chicago has communities with high crime, racial and ethnic segregation, and resource deficits; alongside striking cancer disparities. COMPASS was used to examine the impact of neighborhood SES on bio-specimen research participation in one project and the impact of lifestyle factors and healthcare utilization on PSA levels (4+ ng/ mL vs. <4ng/ mL; as well as continuous) in another project. For our investigation of the impact of neighborhood SES on bio-specimen research participation, we used the COMPASS household database (consolidated from postal service, commercial vendor and interviewer recruitment

database information) enriched with a time-invariant census tract-level measure on neighborhood SES. In multivariable logistic regression models controlling for summarized data on households, interviewers, and design characteristics at addresses, we observed approximately three times the odds of bio-specimen research participation for predominantly AA addresses in the original target sample within low vs. average SES neighborhoods (OR=3.06; 95% CI=2.20-4.24) and no difference in odds of bio-specimen research participation for addresses in low vs. average SES neighborhoods that were not predominantly AA households in the original target sample (OR=0.94; 95% CI=0.71–1.25). Overall, we achieved a response rate of 80.3% among AA addresses in low SES neighborhoods. Taken together, our findings suggested that door-to-door recruitment and financial compensation ($50 in our study) may be effective strategies to recruit traditionally under-represented racial/ ethnic minority participants in COMPASS.

In our other COMPASS study, we examined the impact of self-reported lifestyle and healthcare factors on serum PSA levels based on clinical laboratory testing, among 928 AA men of predominantly low SES in COMPASS. Specifically, we examined the associations between self-reported cigarette smoking pack-years, other current regular tobacco use (including e-cigarettes and cigars), and current regular marijuana use on PSA in multivariable logistic regression models with outcome of elevated PSA 4.0+ ng/ mL and linear regression models with outcome of increasing PSA (continuous), after adjustment for age, marital status, individual and neighborhood SES, self-reported health, hypertension medication, body mass index (BMI), health insurance type, and quintiles of visits to doctor in last 12 months. Among fully adjusted stratified models of 430 AA men age 55+ years, we observed approximately 5 times the odds of elevated PSA among those with 1+ pack-years of cigarette smoking vs. never smokers (OR=5.03; 95% CI=1.56-16.2), a quarter the odds of elevated PSA among current marijuana

users vs. non-users (OR=0.28; 95% CI-0.08-0.99), and a mean PSA increase of 1.25 ng/ mL among other current tobacco users vs. non-users. We interpreted these findings to suggest that cigarette smoking history and current tobacco use were adversely related to PSA risk profile among AA men in predominantly low SES neighborhoods, and that PSA testing may be an inappropriate biomarker of PSA risk profile among current marijuana users.

The work presented in this dissertation demonstrates the importance of individual and neighborhood factors on PSA risk profile among AA men, a population that experiences adverse prostate cancer mortality. Our findings contribute to the literature by suggesting that high PSA prostate cancer drives racial/ ethnic disparities in prostate cancer aggressiveness among AA men; that AA participants traditionally under-represented in bio-specimen research may be effectively recruited through door-to-door approaches and financial compensation for participation; and that AA men of predominantly low SES with a smoking history, and current use of other tobacco products may experience an adverse PSA risk profile. Future work with individual and neighborhood-level exposure data with longitudinal data and prostate cancer survival outcomes with sufficient representation from AA men may elucidate the extent to which social stressors and lifestyle factors separately and together contribute to adverse prostate cancer outcomes currently experienced by AA men. Evidence-based, multi-level health policy reforms and multi-level health promotion/ disease prevention strategies are necessary to mitigate racial/ ethnic disparities in prostate cancer mortality.

CHAPTER 1

INTRODUCTION

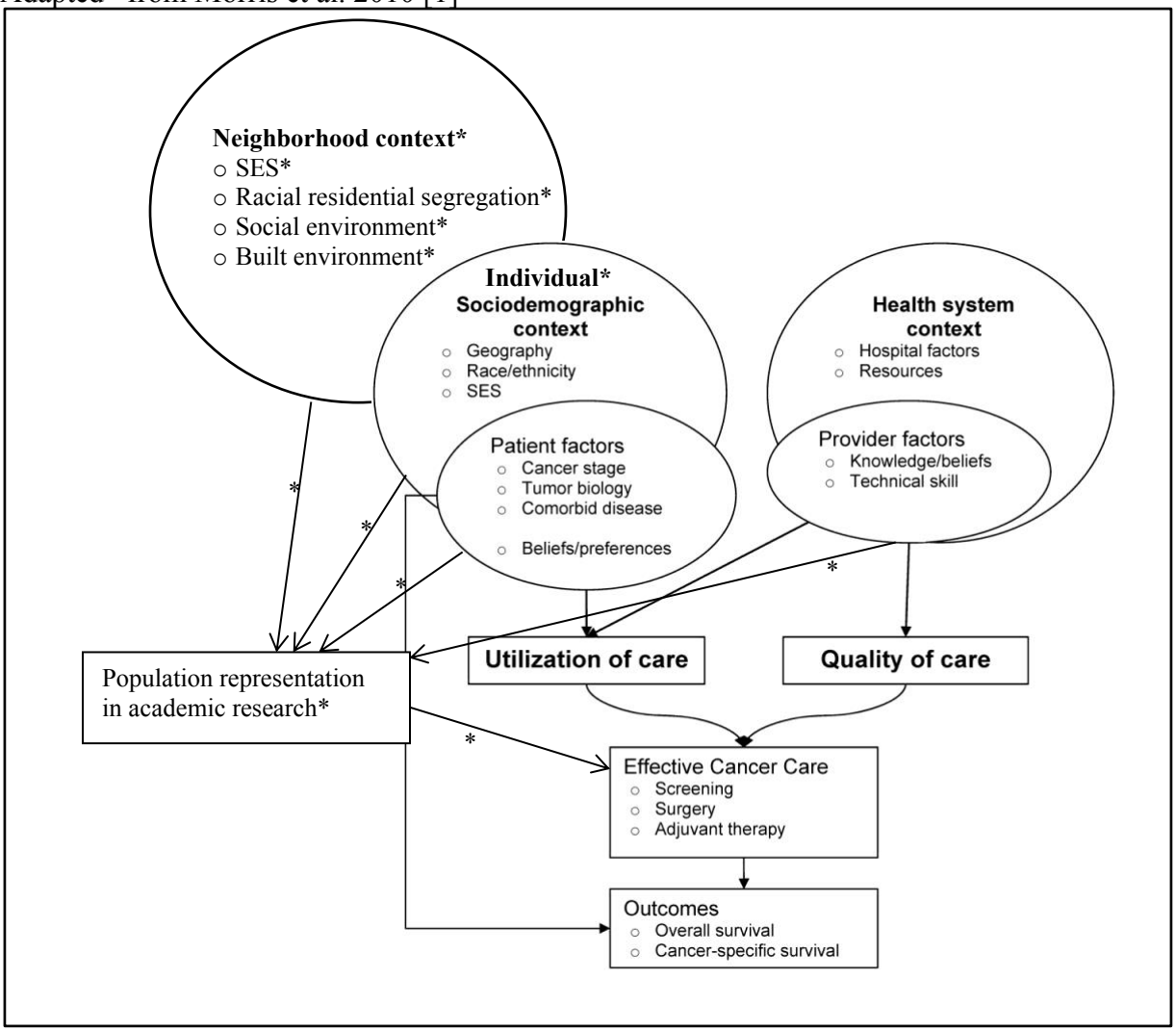
Conceptual framework

Sociodemographic and health systems contexts impact cancer outcomes

Our conceptual model for mechanisms underlying disparities in cancer care and outcomes is provided in **Figure 1**. This model is adapted from Morris et al. (2010) who describe disparities in effective cancer care and concomitant disparities in cancer outcomes [1]. As a part of the cancer care factors described by Morris et. al., we emphasize neighborhood-level factors as a part of the sociodemographic context (geography, race/ethnicity, SES) that may contribute to patient factors (cancer stage, tumor biology, comorbid disease and beliefs/preferences) and, in turn, utilization of care (screening, surgery, adjuvant therapy). In addition to the utilization of care and quality of care outlined as intermediary outcomes by Morris et al., we additionally conceptualize population representation, and particularly minority representation, in epidemiological and clinical research as essential to provide evidence-based cancer care [2]. According to this framework, we conceptualize individual-, neighborhood-, and provider-level determinants of bio-specimen research participation, (i.e., knowledge/ beliefs of minority representation in academic research at multiple levels). Presumably, disparities in research participation contribute to disparities in evidence-based cancer care. Disparities in evidence-based cancer care may impact quality of care through provider factors such as provider bias and cultural barriers to patient-provider communication. These disparities in evidence-based cancer care may in turn impact cancer outcomes (overall and cancer-specific survival). According to

this model, we conceptualize disparities in PSA levels and prostate cancer aggressiveness as due to disparities in multi-level exposures and healthcare utilization that impact effective cancer care. Moreover, disparities in prostate cancer outcomes may be due to the separate and joint contributions of individual-, neighborhood- and provider-level factors that impact effective cancer care, utilization of healthcare, and research participation.

Figure 1: Conceptual model of mechanisms underlying disparities in cancer care and outcomes. Adapted* from Morris et al. 2010 [1]

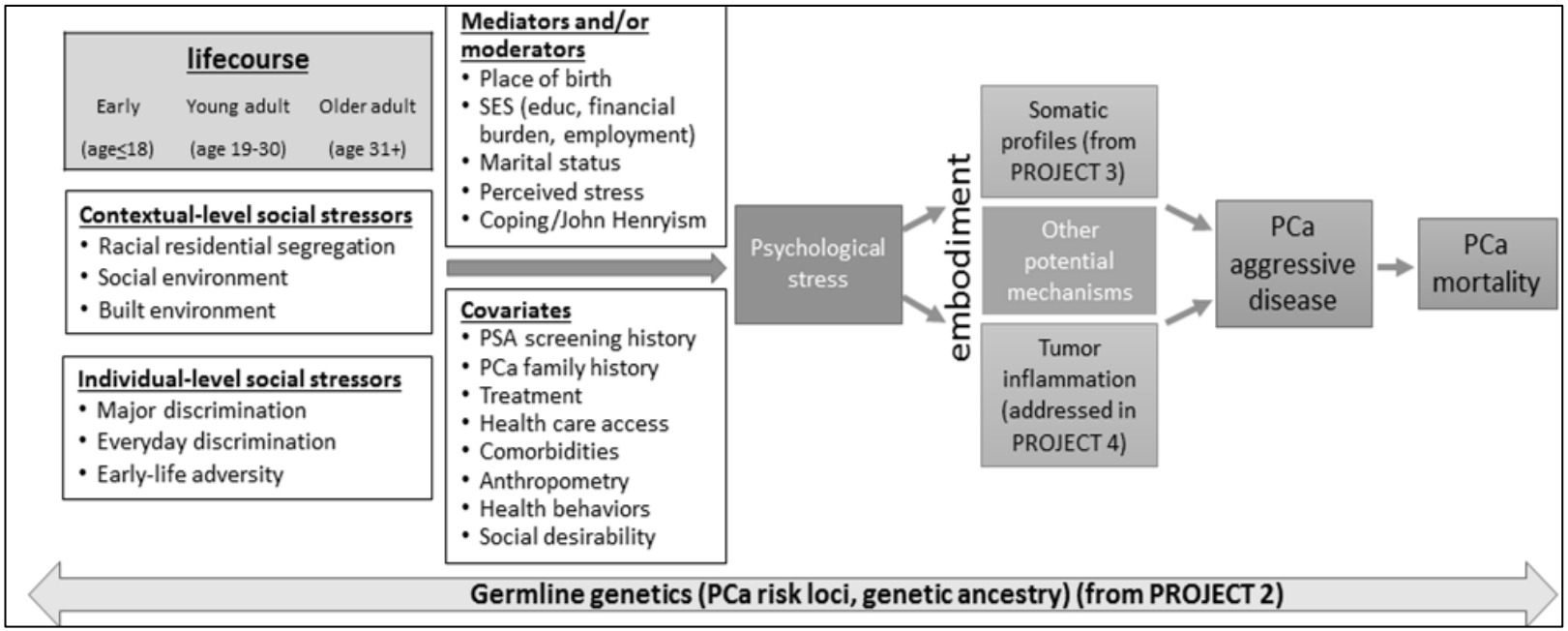


*Modifications to emphasize study purposes.

Neighborhood-level social stressors impact prostate cancer outcomes

We present a conceptual model for the impact of neighborhood-level social stressors on the development of prostate cancer with outcomes of aggressive prostate cancer and prostate cancer mortality in **Figure 2**. Individual-level social stressors include major discrimination, everyday discrimination, and early life adversity. Contextual-level social stressors include racial residential segregation, the social environment, and the built environment. These multi-level social stressors impact psychological stress across the life-course from early age through middle age to older adults. The relationship between multi-level social stressors on psychological stress across the life-course is mediated and moderated by factors including place of birth, SES, marital status, perceived stress, and coping including John Henryism. Covariates in these relationships include PSA screening history, prostate cancer family history, treatment, health care access, comorbidities, anthropometry, health behaviors, and social desirability. Embodiment of psychological stress may be reflected in somatic profiles, tumor inflammation, and other potential mechanisms that are related to aggressive prostate cancer and in turn prostate cancer mortality. Additionally, germline genetics, such as prostate cancer risk loci and genetic ancestry, underlie the relationships described here. Moreover, we conceptualize that social stressors in minority communities can be embodied biologically as psychological stress, which may influence risk of developing aggressive prostate cancer and prostate cancer mortality, through biological mechanisms such as inflammation and somatic mutations, with potential mediators including individual SES, coping mechanisms, and germline genetics.

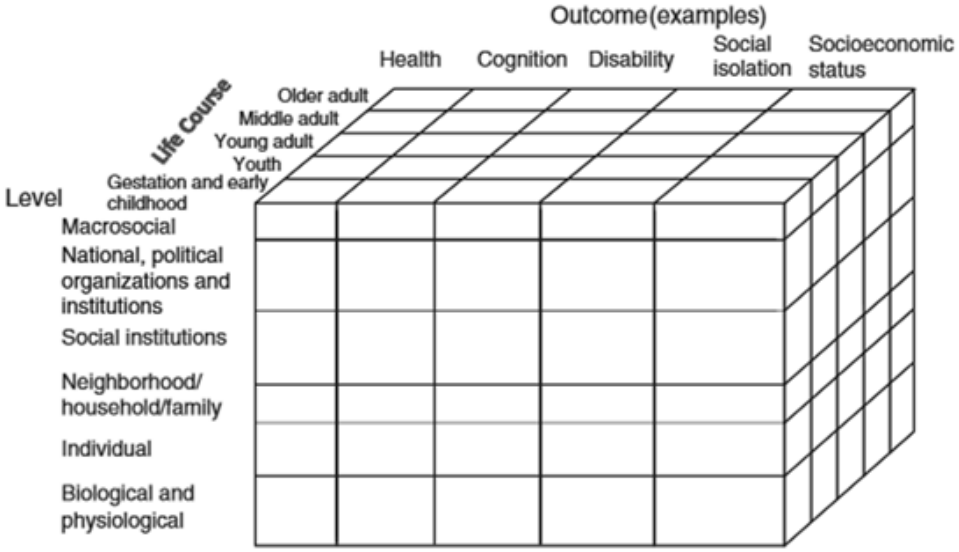
Figure 2: Conceptual model for embodiment of neighborhood-level social stressors on prostate cancer (PCa). Figure used with permission from Scarlett Gomez (personal correspondence).



There is a complex interplay of sociodemographic factors at multiple levels

Contextual factors, from the macro, national, institutional, neighborhood, individual, and intra-individual levels, impact health, cognition, psychologic health, disability, social isolation, and SES [3]. **Figure 3** provides a conceptual model for studying social processes in aging that provides a useful framework for our projects. Specifically, Waite and Plewes' model conceptualizes neighborhood-level factors as one level within a complex interplay of sociodemographic factors at other levels (including macro, institutional, individual, and within individual). This complex interplay of sociodemographic factors at different levels is associated with outcomes including health, cognition, disability, social isolation and SES.

Figure 3: Conceptual model for studying social processes. From Waite and Plewes 2013 [3].



There is a burgeoning literature on the multi-level interplay of features from these various levels on the factors within other levels [3-8]. Interest in neighborhood-level effects began during the mid-1990s to 2001 and was followed by a large increase in academic research [9]. For example, the Moving to Opportunity (MTO) experiment recently reported substantial treatment effects among persons whose families moved when randomly selected to receive vouchers to move to lower-poverty neighborhoods: improved college attendance rates, higher earnings, and reduced likelihood of becoming single parents [10]. Specifically, evidence from the MTO suggests that growing up in the western suburbs of Chicago would increase a given child's income by approximately 30% relative to Cook County; in part due to less concentrated poverty, less income inequality, better schools, a larger share of two-parent families, and lower crime rates. Treatment effects observed in the MTO were more pronounced for males than females [11].

Persons residing in lower SES neighborhoods tend to experience poorer physical functioning, less social integration, less perceived control, greater financial strain, and poorer quality of care [12, 13]. Healthcare access, including proximity to hospitals and community pharmacies, appear to be limited in segregated AA communities [14, 15]. Further, individuals residing in low SES communities tend to have higher smoking rates and are exposed to fewer smoking prevention education programs in schools [16]. Neighborhood poverty appears to impact crime rates in part through mediating neighborhood-level effects of social cohesion, residential mobility, ethnic heterogeneity, and social organization [17, 18]. In turn, persons residing in low SES neighborhoods with high violent crime tend to experience adverse lifestyle factors including decreased park use, physical activity, and healthy diets [19-21]. Nevertheless,

health-promoting features of poorer communities have also been observed [22]. Moreover, evidence indicates that neighborhood-level determinants of individual health include SES, social and lifestyle factors including immigration and acculturation, crime, park use, and community assets. Based on our review of the literature, we conceptualize SES to interact within communities to convert community assets and parks from settings that may otherwise be health-promoting to become health-disrupting. We suggest that additional research is necessary to inform the complex interplay between individual- and neighborhood-level features of lifestyle factors, access to and utilization of primary and secondary prevention resources, and health outcomes among AA persons.

Previous work using data from the California Cancer Registry (CCR) with rich data on small area-level geo-spatial data have demonstrated differences in tumor, sociodemographic, institutional, and neighborhood characteristics that help to explain racial and ethnic disparities in the occurrence of and mortality from prostate cancer among California men [5, 22-26]. In a recent study with NHW men, AA men, and Asian American men, racial and ethnic disparities in prostate cancer risk profiles (a combination of TNM stage [stage], Gleason score grade [GS], and PSA, appeared to be driven by higher GS and PSA rather than by advanced clinical stage at diagnosis [26]. Our current work aims to elucidate multi-level exposures that impact racial and ethnic disparities in prostate cancer aggressiveness at diagnosis among AA men relative to NHW men.

Data Sources

RESPOND

Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers and Social Stress (RESPOND) is a collaboration of investigators at population-based cancer registries covering 6 states and 1 metropolitan region – California, Detroit, New Jersey, Georgia, Louisiana, Texas, and Florida. RESPOND is the largest coordinated research effort to date to study aggressive prostate cancer in AA men relative to NHW men. RESPOND researchers anticipate that projects within the RESPOND studies will elucidate how multi-level factors contribute to enduring racial/ ethnic disparities in prostate cancer aggressiveness among AA men, using a nationwide sample of approximately 667,590 NHW men and 149,358 AA men. The frequency of prostate cancer diagnoses by state and race/ethnicity are provided in **Table 1**. All prostate cancers diagnosed among AA men and NHW men in the catchment areas during the time period 2000 to 2013 will be included in a study, which is designed to examine associations between exposures to neighborhood social stressors and risk of aggressive prostate cancer and prostate cancer mortality, with geospatial data linkages currently being conducted by individual cancer registries. The present work will lay the groundwork for that larger study, by examining cases diagnosed during a time period for which PSA and GS were available in CCR (2004 to 2013).

Table 1: Prostate cancer cases diagnosed in RESPOND cancer registries, 2000-2013

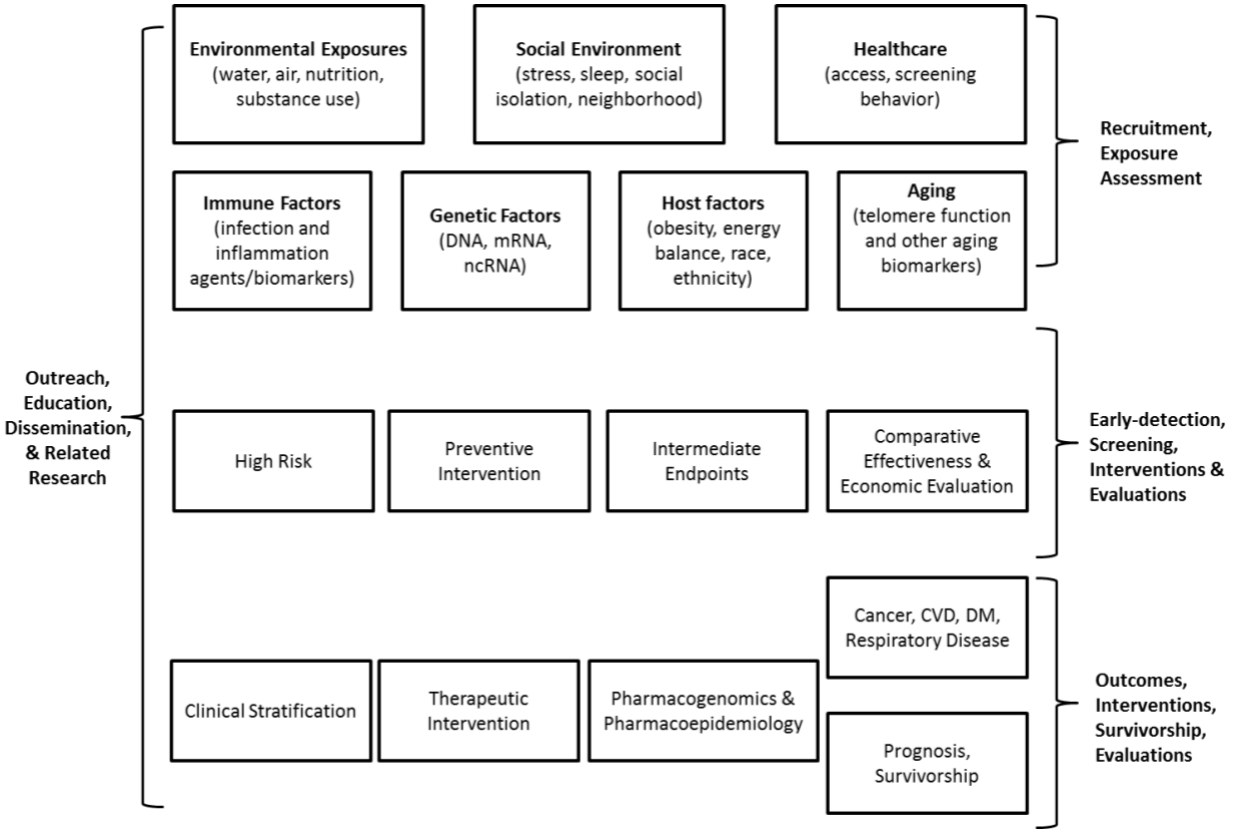
State	NHW men	AA men	Total
California	194,288	27,952	222,240
Florida	158,413	25,499	183,912
Texas	121,956	24,248	146,204
New Jersey	74,636	15,130	89,766
Georgia	53,945	27,591	81,536
Detroit	33,799	13,857	47,656
Louisiana	30,553	15,081	45,634
Total	**667,590**	**149,358**	**816,948**

In separate RESPOND projects, investigators will examine associations between exposure to multi-level social stressors across the life course and genetic factors, as well as their combined effects on aggressive prostate cancer, among ~10,000 AA men in the RESPOND collaboration. **Figure 2** provides a conceptual model for the multi-level factors that are currently under examination in RESPOND projects.

COMPASS

Investigators at the University of Chicago aim to recruit 100,000+ participants into a multiethnic cohort study with multiple decades of follow up to identify etiologic questions and opportunities for disease prevention. Components of this study are provided in **Figure 4**. Specifically, COMPASS components include recruitment and exposure assessment, early detection, screening, interventions, evaluations, and outcomes research [27].

Figure 4: Components of the Chicago Multiethnic Cohort study. From Ahsan et. al (2012) [27]



COMPASS Pilot Phase recruited approximately 4,521 participants to assess study feasibility of the larger cohort study. Currently, the study is comprised of Chicago urban persons who are predominantly of AA race (76.8%). In the COMPASS study, a variety of design features – including interviewers concordant on race, financial compensation, and differential recruitment strategies for high crime regions – enabled the achievement of a high cooperation to date among AA participants. COMPASS investigators previously conducted a qualitative examination of interviewer-reported factors of research participation among AA persons in the COMPASS study, including facilitators (interviewer race and interviewer skills) and barriers (fear of the

blood draw and mistrust of medical researchers including privacy concerns) (**Table 2)** [27, 28]. Additionally, COMPASS investigators have observed a wide variation in screening rates by community for breast, cervical, and colorectal cancers, with statistically significant linear trends in screening rates by average community income, and by race/ethnicity [29].

Table 2: Interviewer-reported* facilitators and barriers to study participation among AA participants in the COMPASS study†

Facilitators to AA participation		**Barriers to AA participation**	
Ability to gain trust	33%	No real barriers	30%
Interviewer skills (ie. approachability, knowledge)	23%	Incorrect recruitment approach	25%
Respect	13%	Race of recruiter	20%
Feeling of inclusion	10%	Mistrust of researchers	10%
Location	7%	Location of residence	5%
Neighborhood communication	7%	Socioeconomics	5%
Power behind name of organization	7%	Privacy concerns	5%
Total	100%	Total	100%

*N=11 members of the COMPASS field interviewer team. Demographic characteristics of interviewers were: 8 males, 3 females; ages 25 to 76; 7 AA, 2 Hispanic, and 1 NH White
†Derived from: Owolabi T and Aschebrook-Kilfoy B 2017 [28]

CHAPTER 2

Independent disparities in high prostate-specific antigen (PSA), but not Gleason grade or TNM stage, observed among African American men and White men diagnosed with invasive prostate cancer in California

ABSTRACT

BACKGROUND: African American (AA) men are more likely than non-Hispanic White (NHW) men to be diagnosed with advanced prostate cancer and are more likely to die from their disease. Racial/ ethnic differences in prostate specific antigen (PSA), Gleason score grade (GS), and TNM stage (stage) at diagnosis remain unclear. As the AA population presents with more advanced prostate cancer, these characteristics of prostate cancer aggressiveness may contribute to their poorer prostate cancer outcomes.

METHODS: We assembled a retrospective cohort of all California AA men and NHW men diagnosed with prostate cancer from 2004 to 2013 using the California Cancer Registry enriched with census block group-level data on neighborhood socioeconomic status (SES). Using multivariable logistic regression models adjusted for year and age at diagnosis, marital status, and health insurance type, prostate cancer aggressiveness outcomes were modeled separately as binary variables that combined low and intermediate classifications versus high (outcomes of high PSA, high GS, high stage, and combined high risk). We examined the contribution of these

covariables to racial/ ethnic disparities in prostate cancer aggressiveness outcomes. Additionally, for PSA, we compared age-specific incidence rate ratios (IRRs) for AA men and NHW men, and age-adjusted IRRs for neighborhood SES, both stratified by PSA aggressiveness.

RESULTS: Among 17,787 AA men and 112,591 NHW men diagnosed with prostate cancer, adverse PSA, GS, stage, and risk profiles were observed for AA men relative to NHW men. Co-occurrence of high GS and high PSA tumors and high stage and high PSA tumors was more frequent for AA men than NHW men. Relative to NHW men, we observed no difference in fully adjusted odds of high GS prostate cancer among AA men after adjusting for PSA (odds ratio [OR]=1.0; 95% confidence interval [CI]=0.9-1.0), a 14% reduction in high stage prostate cancer among AA men after accounting for high PSA (OR=0.86; 95% CI=0.80-0.91), and a persistent 79% racial/ ethnic disparity for high PSA prostate cancer among AA men after adjustment for high stage and high GS (OR=1.8; 95% CI=1.7-1.9). The most influential variables in terms of racial/ ethnic disparities in high PSA prostate cancer were age at diagnosis and neighborhood SES. Relative to NHW men, approximately 4 times the incidence of high PSA prostate cancer was observed in AA men at ages 45-49 years (IRR=3.8; 95% CI=3.6-4.1), which decreased to approximately 2 times the incidence at ages 85+ years (IRR=2.0; 95% CI=1.8-2.2). Relative to all men residing in the highest neighborhood SES quintile (IRR=1.9; 95% CI=1.8-2.1), those in the lowest neighborhood SES quintile experienced a higher incidence of high PSA prostate cancer and a lower incidence of low PSA prostate cancer (IRR=0.9; 95% CI=0.8-0.9).

CONCLUSIONS: Racial/ ethnic disparities in prostate cancer aggressiveness at diagnosis for AA men and NHW men in California appear to be due to high PSA, not high GS nor stage. Primary contributors to racial/ ethnic disparities in high PSA prostate cancer appear to be due to

differences in age at diagnosis and neighborhood SES, possibly as a surrogate for individual SES and/ or social stressors. Additional research may elucidate whether high PSA prostate cancer is primarily responsible for mortality disparities among AA men and NHW men.

BACKGROUND

Prostate cancer is the most common and second most lethal cancer among men in the United States (US) [30]. Glaring and persistent racial/ ethnic disparities in prostate cancer have been observed for African American (AA) men, who currently experience about 1.8 times the incidence and 2.2 times the mortality as non-Hispanic White (NHW) men [31]. In California, we recently observed in a diverse sample of NHW, Asian, and AA men, that racial/ ethnic disparities in advanced prostate cancer, or prostate cancer aggressiveness, appeared to be driven by higher prostate specific antigen (PSA) and Gleason score grade (GS) rather than clinical TNM stage of disease (stage) [26]. Others have previously observed that AA men with prostate cancer present with higher PSA levels and larger tumor volumes per ng/mL of serum PSA than NHW men [32-35]. However, it remains unclear whether the racial/ ethnic disparity in advanced or aggressive prostate cancer among AA men specifically is driven by PSA, GS, and/ or stage.

Others have previously provided evidence that the AA-NHW disparity in prostate cancer aggressiveness and mortality is due to complex biological, socioeconomic, and socio-cultural determinants underlying racial/ ethnic disparities in presentation, diagnosis, treatment, and survival [36]. AA men are exposed to considerably more social stressors than NHW men, including residence in resource-poor settings such as low socioeconomic status (SES), alongside higher exposure to racial discrimination (individual and institutional), more social isolation and

unmarried status, and under-utilization of medical and social services [37-45]. In California, we previously reported a 60% higher age-adjusted prostate cancer mortality among AA men relative to NHW men with prostate cancer, which was reduced to the null after full adjustment for tumor, sociodemographic, institutional, and neighborhood characteristics. We observed that stage, marital status, and neighborhood socioeconomic status (SES) were the most influential variables contributing to prostate cancer mortality disparities among all races/ethnicities [23]. However, it remains unclear what factors contribute to the higher risk of advanced prostate cancer at diagnosis among AA men specifically as defined by PSA, GS, and stage. In order to examine racial/ ethnic disparities in prostate cancer aggressiveness, and factors mediating such disparities, we conducted a population-based study of 17,787 AA men and 112,591 NHW men in California diagnosed with invasive prostate cancer from 2004 to 2013 whose records included sufficiently detailed information on PSA, GS, and stage.

METHODS

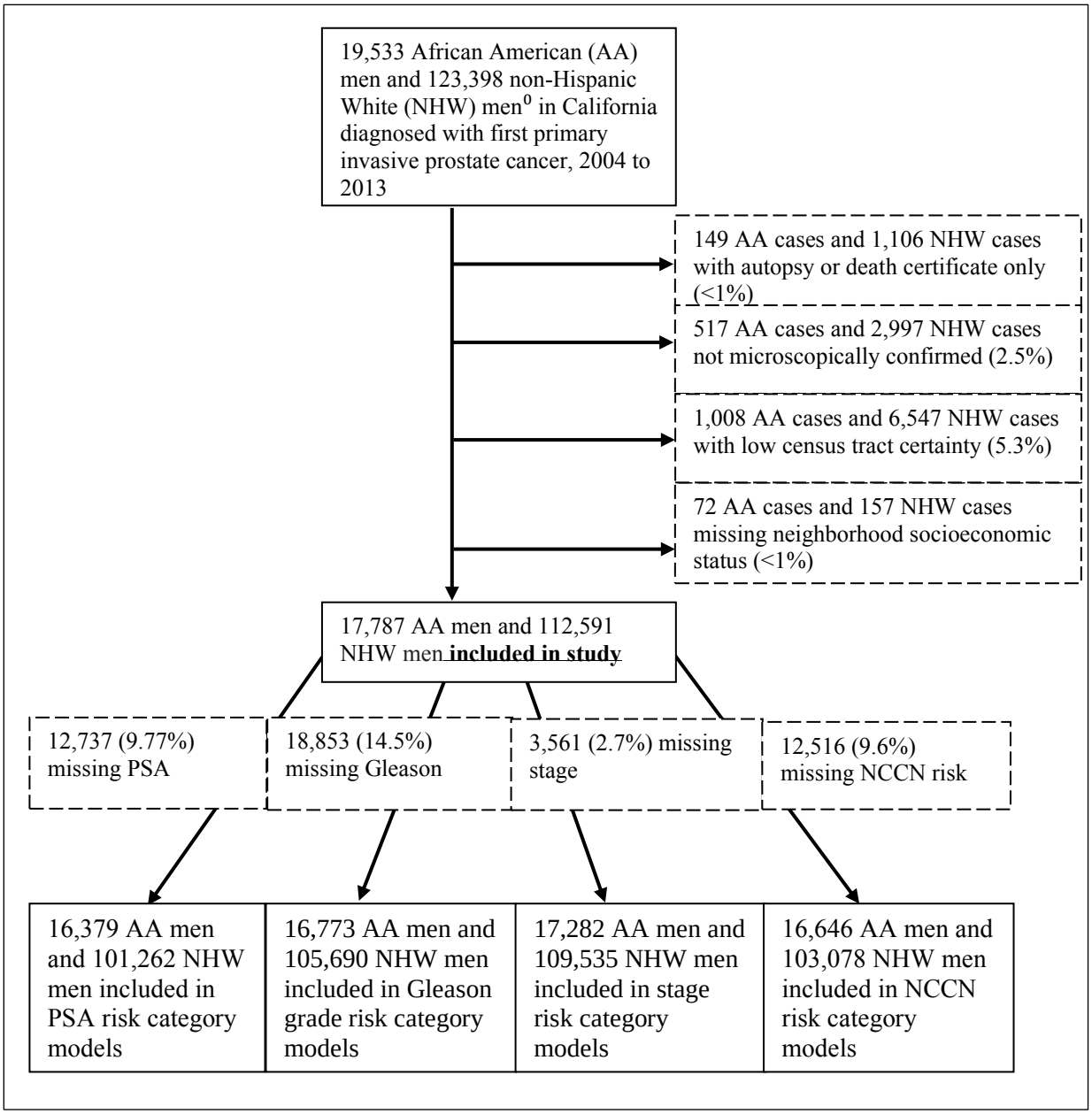
Study Population

California law mandates that all cancer cases diagnosed among California residents be registered with the population-based California Cancer Registry (CCR) [46]. The CCR comprises four registries from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, which maintains the highest level of registry data quality and accuracy. We obtained registry information routinely abstracted from the medical record on individual characteristics (age at and year of diagnosis, marital status, insurance type based on

primary payer, and residence) and tumor characteristics associated with prostate cancer aggressiveness (PSA, GS, stage, and combined risk).

We identified 19,533 AA and 123,398 NHW men residing in California diagnosed with first primary invasive prostate cancer (International Classification of Disease for Oncology, 3rd edition [ICD-O-3] site code C619 [47]) during the period from January 1, 2004 to December 31, 2013. These years were selected because PSA and GS were unavailable before 2004 [48]. This study was conducted in preparation for the RESPOND study (Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers and Social Stress), which includes cases diagnosed through 2013 in order to have a minimum of 5 years of follow up for all cases. We limited the study to those individuals with adenocarcinoma or other prostate cancer histology (ICD-O-3 morphology codes 8000-8110, 8140-8576, 8940-8950, and 8980-8981) [47]. We excluded patients whose cancer was diagnosed by autopsy or death certificate only (n=1,255), those with tumors that were not microscopically confirmed (n=3,514), those residing in neighborhoods with low census tract certainty (n=7,555), and those missing neighborhood SES (n=229). The final population study size for analysis included 17,787 AA men and 112,591 NHW men. Of those, we separately examined prostate cancer aggressiveness outcomes for subjects with complete data on the respective risk category – 16,379 AA men and 101,262 NHW men with data on PSA; 16,773 AA men and 105,690 NHW men with data on GS; 17,282 AA men and 109,535 NHW men with data on stage; and 16,646 AA men and 103,078 NHW men with data on combined NCCN risk. A flow diagram for the study overall and for prostate cancer aggressiveness outcomes, is presented in **Figure 5**.

Figure 5: Flow diagram for study overall and for prostate cancer aggressiveness outcome models (prostate-specific antigen (PSA) risk category, Gleason grade risk category, stage risk category, and National Comprehensive Cancer Network (NCCN) risk category)



[o] Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

Variables

In the primary analyses, race was classified as White and non-Hispanic ethnicity for NHW men and AA for Black men regardless of Hispanic ethnicity. In the incidence rate ratio (IRR) analyses, race/ethnicity was classified as NHW for NHW men and AA for NH Black men, as different definitions for race/ethnicity were due to availability of population denominator data in SEER*Stat [49]. This reflected a difference in classification for 104 AA men who were of Hispanic ethnicity (<0.01%). Insurance type was defined as primary payer at diagnosis. Neighborhood SES was measured using a previously defined composite index developed with principal components analysis of 2000 Census (for cases diagnosed 2004-2005) or 2007 to 2011 American Community Survey (for cases diagnosed 2006-2013) data on education, occupation, employment, household income, poverty, and rent and house values [50, 51]. Address of residence at time of diagnosis was collected and geocoded by the CCR and used to assign each individual to a census block group. Each cancer case was then assigned to a neighborhood SES quintile based on the distribution of SES across all census block groups in California.

We used SEER data items on PSA, GS, and American Joint Committee on Cancer (AJCC) stage [48] to categorize men into binary "low" risk (including both low and intermediate) and "high" risk groups based on a modification of the original D'Amico risk groups [52] and National Comprehensive Cancer Network (NCCN) risk categories [53]. Our categorizations were as follows: low PSA as <20 ng/ mL (n=104,740), high PSA as 20+ ng/ mL (n=12,901); low GS as <8 (n=103,610), high GS as 8+ (n=18,853); low Stage as N0, M0 and cT1-cT2a (n=112,765), high stage as N1, M1, and/ or T2b+ (n=14,052); and low risk as low PSA, low GS, and low stage (n=87,603), high risk as high PSA, high GS, and/ or high stage

(n=32,121). In robustness tests, we included a third set of intermediate categories and removed the intermediate group from the low group (intermediate PSA as 10 to <20 ng/ mL, intermediate GS as 7, and intermediate stage as T2b/T2c). Higher proportions of missing outcome data for prostate cancer aggressiveness were observed for AA men relative to NHW men and older men relative to younger men (<3.5% for combinations of age- and race examined; **Table 3**).

Table 3: Missing outcome data on prostate cancer aggressiveness among African American (AA) and non-Hispanic White (NHW) men diagnosed with first primary invasive prostate cancer between 2004 and 2013 in California, using 4 risk categorizations as separate outcomes (prostate specific antigen [PSA], Gleason score grade [GS], TNM stage and risk

Risk categories and age at diagnosis	NHW men		AA men		AA men and NHW men	
	Outcome missing (%)*	Total	Outcome missing (%)*	Total	Outcome missing (%)*	Total
PSA						
Age at diagnosis (y)						
15-54	6.6	10,166	6.0	2,967	6.5	13,133
55-64	7.2	37,091	6.5	6,868	7.1	43,959
65-74	9.2	42,229	8.0	5,792	9.1	48,021
75+	17.6	23,105	14.7	2,160	17.4	25,265
Total	10.1	112,591	7.9	17,787	9.8	130,378
Gleason grade						
Age at diagnosis (y)						
15-54	4.7	10,166	4.7	2,967	4.7	13,133
55-64	4.7	37,091	5.1	6,868	4.8	43,959
65-74	5.5	42,229	5.4	5,792	5.5	48,021
75+	10.1	23,105	9.9	2,160	10.0	25,265
Total	6.1	112,591	5.7	17,787	6.1	130,378

Table 3 continued.

Risk categories and age at diagnosis	NHW men		AA men		AA men and NHW men	
	Outcome missing (%)*	Total	Outcome missing (%)*	Total	Outcome missing (%)*	Total
TNM stage						
Age at diagnosis (y)						
15-54	1.2	10,166	1.2	2,967	1.2	13,133
55-64	1.5	37,091	2.2	6,868	1.6	43,959
65-74	2.3	42,229	2.9	5,792	2.4	48,021
75+	6.1	23,105	7.1	2,160	6.2	25,265
Total	2.7	112,591	2.8	17,787	2.7	130,378
Risk						
Age at diagnosis (y)						
15-54	6.5	10,166	5.9	2,967	6.4	13,133
55-64	6.8	37,091	5.7	6,868	6.6	43,959
65-74	8.0	42,229	6.4	5,792	7.8	48,021
75+	12.8	23,105	9.5	2,160	12.5	25,265
Total	8.4	112,591	6.4	17,787	8.2	130,378

* All Chi-square P-values <0.001

Statistical analyses

We used multivariable logistic regression analyses to examine the odds ratio (OR) and 95% confidence interval (CI) of advanced prostate cancer, adjusted for age at and year of diagnosis, marital status, insurance type, and neighborhood SES, with outcomes separately modeled as high PSA, high GS, high stage, and high risk. In order to examine whether observed differences in AA-NHW ORs were independent of other categorizations of prostate cancer aggressiveness, we developed a series of models jointly stratified by the risk categorizations not evaluated in the given model. For example, fully adjusted logistic regression models with outcome of high PSA were assessed in models that were: unstratified; stratified by GS (low and high); stratified by stage (low and high); stratified jointly by GS and stage (both low and both high); and unstratified with adjustment for GS and stage; for a total of 8 models with outcome of

high PSA. A similar approach was taken for models with outcomes of high GS and high stage, for a total of 24 logistic regression models. We further conducted robustness tests for fully adjusted unstratified models using multinomial logistic regression with the same high risk categories as the outcome and intermediate categories as the reference group.

We examined the relative influence of each covariable on AA-NHW disparities in prostate cancer aggressiveness using a previously developed method [54]. The baseline model includes race/ethnicity plus age. The AA-NHW prostate cancer aggressiveness disparity for a particular model was $D = \sqrt{\left(\sum n_i \{\beta_i - \bar{\beta}_\bullet\}^2\right) / \sum n_i}$, the sample-size weighted standard deviation of the OR estimate for AA men relative to NHW men. Here, β_i is the $log_e OR$ estimate of AA men relative to NHW men (i.e., the logistic regression coefficient), n_i is the sample size of AA men, and $\bar{\beta}_\bullet$ is the sample size-weighted mean for β_i. The relative influence was then defined as $(\{D_- - D_+\}/D_0) * 100$ in which D_0 was the OR from the baseline model, D_- was the OR from the model without the covariable of interest, and D_+ was the OR from the model with the covariable of interest. In the multivariable context, D_- was the OR from the model with the covariable of interest, and D_+ was the OR from the model without the covariable of interest.

The influence of each covariable on AA-NHW prostate cancer aggressiveness disparities was first tested in a base model to identify univariable influence: race/ethnicity plus age plus covariable. Covariables were then ranked in order of their univariable influence on AA-NHW prostate cancer aggressiveness disparities (i.e., by how much the logistic regression OR predicting advanced prostate cancer decreased when included in the base model) and sequentially added to the baseline model by the univariable influence rank order. With each

addition to the multivariable model, the change in OR was assessed as a measure of the relative change in racial/ ethnic disparity (i.e., the proportion of the total disparity contributed by that covariable, after accounting for previously added covariables). We also obtained a measure of multivariable influence comparing the baseline model and the multivariable models including all covariables except for the covariable of interest. The process was performed separately for each prostate cancer aggressiveness outcome (PSA, GS, stage, and combined risk). In addition to the application of the relative influence method with the baseline model including age-adjustment, we also conducted analyses to examine disparities by age, in which the baseline model was not age-adjusted.

Separately, we also developed fully adjusted logistic regression models stratified by age at diagnosis <60 and 60+ years. In order to visually compare age-specific differences for our AA and NHW cohorts for each of our prostate cancer aggressiveness categorizations, we calculated age-specific incidence rates among AA men and NHW men by age group at diagnosis (20-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and ≥85 years) using US census population estimates, with the 2000 decennial count applied to cases diagnosed 2004-2006 and the 2010 US census population count applied to cases diagnosed 2007-2013.

IRRs for age-specific incidence rates were computed for the entire study period for AA men relative to NHW men within each age group at diagnosis (20-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and ≥85 years). Additionally, IRRs for age-adjusted incidence rates were computed for neighborhood SES quintiles for years of diagnosis 2008 to 2012. Restricting the neighborhood SES analysis to the 5-year interval around the 2010 decennial census was due to the availability of pericensal (2008-2012) tract-level population

estimates. Neighborhood SES incidence rate analyses were conducted at the census tract level. SEER*Stat software version 8.3.5 [49] was used to compute age-specific incidence rates by race/ethnicity. Age-adjusted incidence rates by neighborhood SES, IRRs, and corresponding 95% CIs were based on the Poisson distribution [55]. Population estimates were developed by SEER and CCR based on US Census projections. To aid visual estimation of proportional rates of change, incidence rate plots were scaled semi-logarithmically [56].

All analyses were conducted in accordance with Institutional Review Board approval of the University of California, San Francisco. All statistical comparisons were two-sided. We used SAS 9.4 (Cary, NC) for multivariable logistic regression analyses.

RESULTS

Descriptive characteristics for the 17,787 AA men and 112,591 NHW men diagnosed with prostate cancer are presented in **Table 4**. AA men were diagnosed with proportionally more advanced prostate cancer than NHW men, with larger differences occurring for high PSA than for high GS or stage. Specifically, 16.7% of AA men and 10.0% of NHW men were diagnosed with high PSA prostate cancer; 16.4% of AA men and 15.2% of NHW men were diagnosed with high GS prostate cancer; 12.6% of AA men and 10.8% of NHW men were diagnosed with high stage prostate cancer; and 30.9% of AA men and 26.2% of NHW men were diagnosed with high NCCN risk prostate cancer. AA men had a younger age profile than NHW men, a lower proportion were residents of high neighborhood SES neighborhoods, a lower proportion had Medicare insurance, and a higher proportion had public insurance. A decreased frequency of

prostate cancers was observed in both races for years of diagnosis 2012 and 2013. For all descriptive patient characteristics examined, the χ^2 P-values were <0.001.

Table 4: Patient characteristics among 17,787 African American (AA) men and 112,591 White men diagnosed with first primary invasive prostate cancer between 2004 and 2013 in California, by race[0]

Patient characteristics	Race[0]				Total
	White		African American		
	n	Col (%)	n	Col (%)	
Prostate cancer aggressiveness					
Prostate-specific antigen category					
Low (<20 ng/ mL)	91,103	80.9	13,637	76.7	104,740
High (20+ ng/ mL)	10,159	9.0	2,742	15.4	12,901
Missing	11,329	10.1	1,408	7.9	12,737
Gleason grade risk category					
Low (<8)	89,584	79.6	14,026	78.9	103,610
High (8+)	16,106	14.3	2,747	15.4	18,853
Missing	6,901	6.1	1,014	5.7	7,915
Stage risk category					
Low (N0, M0, and <T2b)	97,658	86.7	15,107	84.9	112,765
High (N1, M1, and/ or T2b+)	11,877	10.6	2,175	12.2	14,052
Missing	3,056	2.7	505	2.8	3,561
National Comprehensive Cancer Network (NCCN) prostate cancer risk category•					
Low	76,094	67.6	11,509	64.7	87,603
High	26,984	24.0	5,137	28.9	32,121
Missing	9,513	8.5	1,141	6.4	10,654
Individual characteristics					
Age at diagnosis (y)					
15-54	10,166	9.0	2,967	16.7	13,133
55-64	37,091	32.9	6,868	38.6	43,959
65-74	42,229	37.5	5,792	32.6	48,021
75+	23,105	20.5	2,160	12.1	25,265
Year of diagnosis					
2004	12,008	10.7	1,664	9.4	13,672
2005	10,632	9.4	1,607	9.0	12,239
2006	12,056	10.7	1,809	10.2	13,865
2007	12,903	11.5	1,930	10.9	14,833
2008	11,964	10.6	1,811	10.2	13,775
2009	11,556	10.3	1,870	10.5	13,426
2010	11,350	10.1	1,893	10.6	13,243
2011	11,485	10.2	1,837	10.3	13,322
2012	9,499	8.4	1,729	9.7	11,228
2013	9,138	8.1	1,637	9.2	10,775

Table 4 continued

Patient characteristics	Race[0]				Total
	White		African American		
	n	Col (%)	n	Col (%)	
Marital status					
Single, never married†	11,229	10.0	3,557	20.0	14,786
Married	77,456	68.8	9,303	52.3	86,759
Separated	820	0.7	370	2.1	1,190
Divorced	7,462	6.6	1,779	10.0	9,241
Widowed	4,634	4.1	760	4.3	5,394
Unknown	10,990	9.8	2,018	11.4	13,008
Insurance type‡					
No insurance	949	0.8	288	1.6	1,237
Private	59,964	53.3	9,378	52.7	69,342
Medicare only	25,104	22.3	2,215	12.5	27,319
Any Public/Medicaid/Military	21,418	19.0	5,241	29.5	26,659
Unknown or missing	5,156	4.6	665	3.7	5,821
Neighborhood characteristics					
Neighborhood socioeconomic staus (SES)					
Quintile 1 (Low)	7,355	6.5	4,413	24.8	11,768
Q2	15,275	13.6	4,167	23.4	19,442
Q3	22,239	19.8	3,751	21.1	25,990
Q4	28,768	25.6	3,355	18.9	32,123
Quintile 5 (High)	38,954	34.6	2,101	11.8	41,055
Total	112,591	100.0	17,787	100.0	130,378

[0]Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

•Prostate cancer risk stratification criteria based on the NCCN classification using TNM stage, Gleason grade, and prostate-specific antigen (PSA) level. Low included low-risk (T1/T2a and Gleason ≤ 6 and PSA<10 ng/ml) and intermediate-risk (T2b/T2c or biopsy Gleason 7 or PSA 10-20 ng/ml); and high included high-risk (T3/T4 or Gleason 8+ or PSA>20 ng/ml or N1) and metastatic (M1).

† Single, never married included unmarried or domestic partner (same sex or opposite sex, registered or unregistered other than common law marriage)

‡Primary payer at diagnosis

Fully adjusted logistic regression models are provided in **Table 5**. AA men experienced higher odds of advanced prostate cancer than NHW men for all risk outcomes, after full adjustment. Higher odds of advanced prostate cancer were also observed for men who were diagnosed at older ages, later calendar years, non-married men, men with no insurance or public insurance, and men who resided in low neighborhood SES quintiles.

Table 5: Individual- and neighborhood-level characteristics associated with advanced prostate cancer among African American (AA) men and White men[0] diagnosed with first primary invasive prostate cancer between 2004 and 2013 in California, using 4 risk categorizations (prostate specific antigen [PSA[1]], Gleason score grade[GS[2]], TNM stage[3], and National Comprehensive Cancer Network [NCCN] prostate cancer risk category[4]). All variables are included in each of the models.

Characteristics	PSA[1]		Grade[2]	
	OR	(95% CI)	OR	(95% CI)
Race[0]				
White	1.00	(Reference)	1.00	(Reference)
African American	1.69	(1.61-1.78)	1.15	(1.10-1.21)
Age at diagnosis in years (continuous)	1.06	(1.06-1.06)	1.05	(1.05-1.06)
Year of diagnosis (continuous)	1.01	(1.00-1.01)	1.04	(1.03-1.05)
Marital status				
Married	1.00	(Reference)	1.00	(Reference)
Single, never married†	1.74	(1.65-1.84)	1.24	(1.18-1.30)
Separated	1.58	(1.33-1.87)	1.42	(1.22-1.65)
Divorced	1.47	(1.37-1.57)	1.19	(1.12-1.27)
Widowed	1.60	(1.48-1.73)	1.28	(1.19-1.37)
Unknown	1.32	(1.24-1.41)	0.87	(0.82-0.92)
Insurance type				
Private	1.00	(Reference)	1.00	(Reference)
No insurance	2.23	(1.90-2.61)	1.82	(1.56-2.12)
Medicare only	0.89	(0.84-0.93)	1.14	(1.09-1.19)
Any Public/Medicaid/Military	1.31	(1.24-1.37)	1.33	(1.27-1.38)
Unknown or missing	1.10	(0.99-1.22)	1.19	(1.09-1.29)
Neighborhood socioeconomic status (SES)				
Quintile 5 (High)	1.00	(Reference)	1.00	(Reference)
Q4	1.25	(1.19-1.32)	1.10	(1.05-1.15)
Q3	1.45	(1.37-1.54)	1.16	(1.11-1.21)
Q2	1.59	(1.50-1.69)	1.17	(1.11-1.23)
Quintile 1 (Low)	1.76	(1.65-1.89)	1.25	(1.18-1.33)
Total men included in analysis	N = 117,641		N = 122,463	

Table 5 continued

Characteristics	Stage[3]		Risk[4]	
	OR	(95% CI)	OR	(95% CI)
Race[0]				
White	1.00	(Reference)	1.00	(Reference)
African American	1.13	(1.07-1.19)	1.31	(1.26-1.37)
Age at diagnosis in years (continuous)	1.04	(1.03-1.04)	1.06	(1.06-1.06)
Year of diagnosis (continuous)	1.08	(1.07-1.09)	1.03	(1.02-1.03)
Marital status				
Married	1.00	(Reference)	1.00	(Reference)
Single, never married†	1.53	(1.45-1.61)	1.42	(1.36-1.49)
Separated	1.48	(1.25-1.75)	1.39	(1.22-1.59)
Divorced	1.30	(1.21-1.39)	1.24	(1.17-1.30)
Widowed	1.60	(1.48-1.73)	1.48	(1.39-1.58)
Unknown	1.28	(1.21-1.36)	1.04	(0.99-1.10)
Insurance type				
Private	1.00	(Reference)	1.00	(Reference)
No insurance	2.38	(2.05-2.78)	2.01	(1.76-2.29)
Medicare only	1.17	(1.11-1.23)	1.07	(1.03-1.11)
Any Public/Medicaid/Military	1.50	(1.43-1.57)	1.37	(1.32-1.42)
Unknown or missing	3.53	(3.29-3.80)	1.69	(1.57-1.82)
Neighborhood socioeconomic status (SES)				
Quintile 5 (High)	1.00	(Reference)	1.00	(Reference)
Q4	1.09	(1.04-1.15)	1.14	(1.10-1.19)
Q3	1.19	(1.13-1.25)	1.25	(1.20-1.30)
Q2	1.21	(1.14-1.28)	1.32	(1.26-1.38)
Quintile 1 (Low)	1.28	(1.20-1.37)	1.45	(1.38-1.53)
Total men included in analysis	N = 126,817		N = 117,862	

[0] Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

[1] Prostate-specific antigen risk category low (<20 ng/ mL) vs. high (20+ ng/ mL)

[2] Gleason grade risk category low (<8) vs. high (8+)

[3] Stage risk category low (N0, M0, and <T2b) and high (N1, M1, and/ or T2b+)

[4] Prostate cancer risk stratification criteria based on the NCCN classification using TNM stage, Gleason grade, and prostate-specific antigen (PSA) level. Low included low-risk (T1/T2a and Gleason ≤ 6 and PSA<10 ng/ml) and intermediate-risk (T2b/T2c or biopsy Gleason 7 or PSA 10-20 ng/ml); and high included high-risk (T3/T4 or Gleason 8+ or PSA>20 ng/ml or N1) and metastatic (M1).

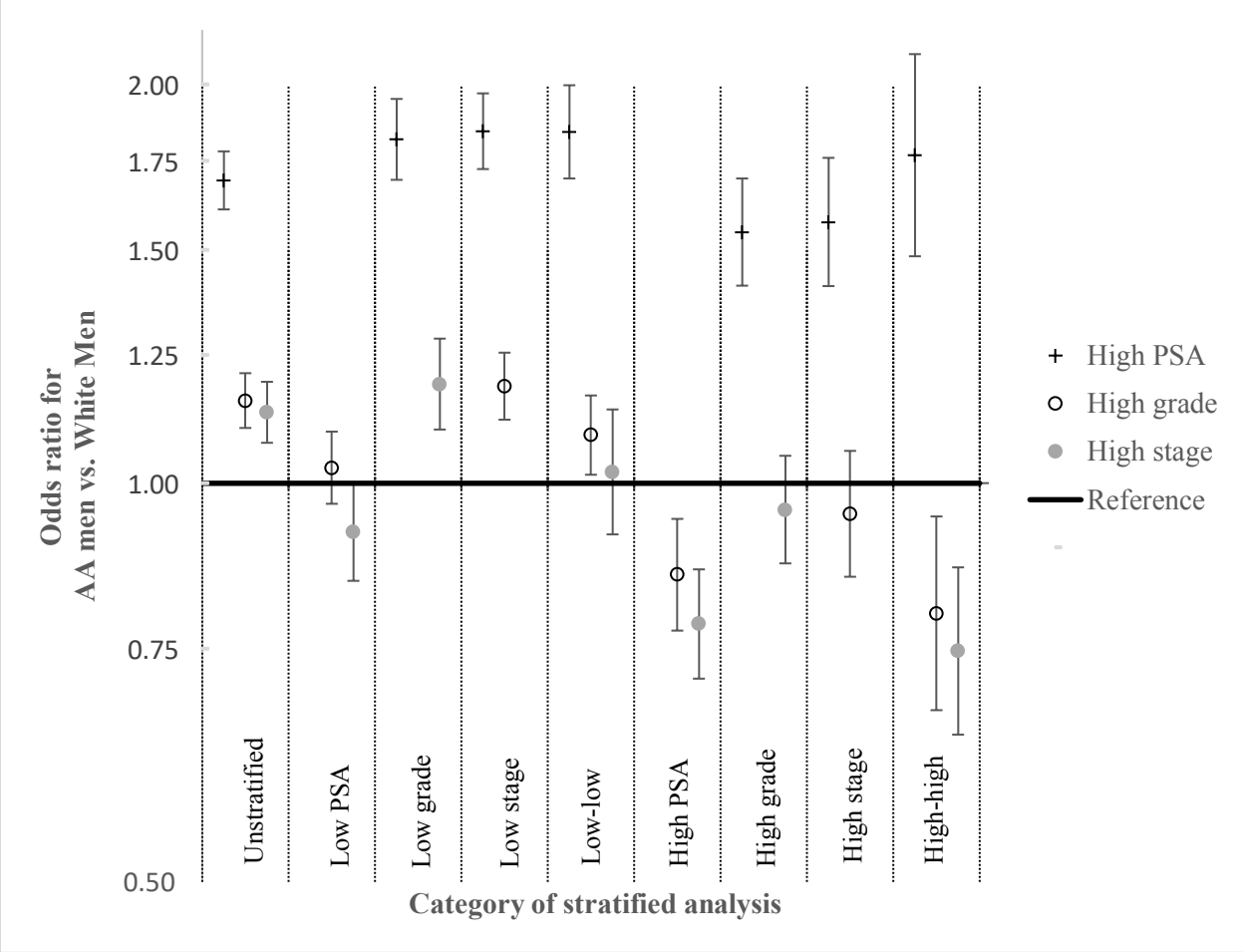
† Single, never married included Unmarried or Domestic Partner (same sex or opposite sex, registered or unregistered other than common law marriage)

Lack of racial/ ethnic disparities in high GS or high stage disease observed among AA men

In multivariable logistic regression models of advanced prostate cancer for the individual risk categorizations jointly stratified by the other risk categorizations, we observed attenuations to the null for racial/ ethnic disparities for high GS and high stage prostate cancer when stratified

by PSA (**Figure 6**). Specifically, there was no difference in high GS or high stage disease among AA men and NHW men with low PSA disease (OR=1.03; 95% CI=0.97-1.09 and OR=0.92; 95% CI=0.84-1.00; **Table 6**). Furthermore, among AA men and NHW men with high PSA disease, a reversal in risk was observed, with AA men experiencing 15% lower odds of high GS disease and 22% lower odds of high stage disease, than NHW men (OR=0.85; 95% CI=0.77-0.93; and OR=0.78; 95% CI=0.71-0.86, respectively).

Figure 6: multivariable adjusted odds ratio● of advanced prostate cancer for African American (AA) men relative to White men[0] among AA and white men diagnosed with first primary invasive prostate cancer between 2004 and 2013 in California using 3 risk categorizations (prostate specific antigen (PSA)[1], Gleason grade[2], and stage[3]), fully adjusted models● stratified by PSA[1], Gleason grade[2], and stage[3]



●All models adjusted for age at diagnosis, year of diagnosis, marital status, insurance type, and neighborhood socioeconomic status (SES)

[0] Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

[1] Prostate-specific antigen risk category low (<20 ng/ mL) vs. high (20+ ng/ mL)

[2] Gleason grade risk category low (<8) vs. high (8+)

[3] Stage risk category low (N0, M0, and <T2b) and high (N1, M1, and/ or T2b+)

Table 6: Advanced prostate cancer among African American men and White men[0] diagnosed with first primary invasive prostate cancer between 2004 and 2013 in California, using 3 risk categorizations (prostate specific antigen (PSA)[1], Gleason grade[2], and stage[3]), fully adjusted models● stratified by PSA[1], Gleason grade[2], and stage[3]

	Outcome = high PSA[1]							
	Low grade[2]				High grade[2]			
	Low (n)	High (n)	OR	(95% CI)	Low (n)	High (n)	OR	(95% CI)
Race[0]								
White	77,431	4,495	1.00	(Reference)	10,121	4,554	1	(Reference)
African American	11,791	1,319	1.82	(1.70-1.95)	1,395	1,150	1.55	(1.41-1.70)
	Low stage[3]				High stage[3]			
	Low (n)	High (n)	OR	(95% CI)	Low (n)	High (n)	OR	(95% CI)
Race[0]								
White	84,713	5,356	1.00	(Reference)	5,190	4,464	1.00	(Reference)
African American	12,768	1,503	1.85	(1.73-1.97)	697	1,107	1.58	(1.41-1.76)
	Low grade[2] and low stage[3]				High grade[2] and high stage[3]			
	Low (n)	High (n)	OR	(95% CI)	Low (n)	High (n)	OR	(95% CI)
Race[0]								
White	73,687	3,308	1.00	(Reference)	1,986	2,584	1.00	(Reference)
African American	11,220	962	1.84	(1.70-2.00)	218	607	1.77	(1.48-2.11)
	Outcome = high grade[2]							
	Low PSA[1]				High PSA[1]			
	Low (n)	High (n)	OR	(95% CI)	Low (n)	High (n)	OR	(95% CI)
Race[0]								
White	77,431	10,121	1.00	(Reference)	4,495	4,554	1.00	(Reference)
African American	11,791	1,395	1.03	(0.97-1.09)	1,319	1,150	0.85	(0.77-0.94)
	Low stage[3]				High stage[3]			
	Low (n)	High (n)	OR	(95% CI)	Low (n)	High (n)	OR	(95% CI)
Race[0]								
White	83,012	10,672	1.00	(Reference)	4,880	5,029	1.00	(Reference)
African American	12,845	1,747	1.18	(1.12-1.26)	917	910	0.95	(0.85-1.06)
	Low PSA[1] and low stage[3]				High PSA[1] and high stage[3]			
	Low (n)	High (n)	OR	(95% CI)	Low (n)	High (n)	OR	(95% CI)
Race[0]								
White	73,687	8,037	1.00	(Reference)	1,051	2,584	1.00	(Reference)
African American	11,220	1,161	1.09	(1.02-1.17)	300	607	0.8	(0.67-0.94)

Table 6 continued.

	Outcome = high stage[3]							
	Low PSA[1]				High PSA[1]			
	Low (n)	High (n)	OR	(95% CI)	Low (n)	High (n)	OR	(95% CI)
Race[0]								
White	84,713	5,190	1.00	(Reference)	5,356	4,464	1.00	(Reference)
African American	12,768	697	0.92	(0.84-1.00)	1,503	1,107	0.78	(0.71-0.86)
	Low grade[2]				High grade[2]			
	Low (n)	High (n)	OR	(95% CI)	Low (n)	High (n)	OR	(95% CI)
Race[0]								
White	83,012	4,880	1.00	(Reference)	10,672	5,029	1.00	(Reference)
African American	12,845	917	1.19	(1.10-1.29)	1,747	910	0.96	(0.87-1.05)
	Low PSA[1] and low grade[2]				High PSA[1] and high grade[2]			
	Low (n)	High (n)	OR	(95% CI)	Low (n)	High (n)	OR	(95% CI)
Race[0]								
White	73,687	2,861	1.00	(Reference)	1,827	2,584	1	(Reference)
African American	11,220	441	1.02	(0.92-1.14)	491	607	0.75	(0.65-0.86)

●All models adjusted for age at diagnosis, year of diagnosis, marital status, insurance type, and neighborhood socioeconomic status (SES)

[0] Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

[1] Prostate-specific antigen risk category low (<20 ng/ mL) vs. high (20+ ng/ mL)

[2] Gleason grade risk category low (<8) vs. high (8+)

[3] Stage risk category low (N0, M0, and <T2b) and high (N1, M1, and/ or T2b+)

Similarly, when we added PSA as an independent variable to a model where GS was the outcome, we observed that the OR for the association of PSA with GS was 6.47 (95% CI=6.20-6.74), and in the same model, the OR for race (AA vs. NHW) was 0.97 (95% CI=0.92-1.03). When we added PSA as an independent variable to a model where stage was the outcome, we observed that the OR for the association of PSA with stage was 12.4 (95% CI=11.8-13.0), and in the same model, the OR for race (AA vs. NHW) demonstrated a statistically significant 14% reduction in high stage prostate cancer among AA men relative to NHW men after adjusting for high PSA (OR=0.86; 95% CI=0.80-0.91).

Our findings for a lack of racial/ ethnic disparities in high GS and high stage prostate cancer among AA men relative to NHW men were confirmed in robustness tests with multinomial logistic regression analyses using intermediate as the reference group. Specifically, among AA men relative to NHW men in fully adjusted models including adjustment for PSA (low, intermediate, high), the odds of high GS vs. intermediate GS was 11% lower (OR=0.89; 95% CI=0.86-0.93) and there was no difference in the odds of high stage vs. intermediate stage disease (OR=1.03; 95% CI=0.95-1.11) (**Table 7**).

Table 7: fully adjusted● multinomial logistic regression prostate cancer risk aggressiveness with outcomes of PSA[1], grade[2], and stage[3] among and African American (AA) men[0] diagnosed with first primary invasive prostate cancer between 2004 and 2013 in California, by race[0]

Prostate cancer aggressiveness outcome modeled	OR for AA men relative to White men						N†
	Low vs. intermediate			High vs. intermediate			
	OR	(95% CI)	P	OR	(95% CI)	P	
PSA[1]	0.68	(0.65-0.71)	*	1.30	(1.23-1.39)	*	117,641
Grade[2]	0.89	(0.86-0.93)	*	0.89	(0.84-0.94)	*	112,256
Stage[3]	1.27	(1.22-1.33)	*	1.03	(0.95-1.11)		115,728

●All models adjusted for age at diagnosis (y), year of diagnosis, marital status, insurance type, and neighborhood socioeconomic status (SES). Model for outcome of PSA adjusted for grade (low, intermediate, high), and stage (low intermediate, and high). Model for outcome of grade adjusted for PSA (low, intermediate, high). Model for outcome of stage adjusted for PSA (low, intermediate, high).

*P<0.001

1 Prostate-specific antigen risk category low (<10 ng/ mL), intermediate (10-20 ng/ mL), and high (20+ ng/ mL)

2 Gleason grade risk category low (<7), intermediate (7), and high (8+)

3 Stage risk category low (N0, M0, and T1/T2a), intermediate (T2b/T2c) and high (N1, M1, and/ or T3/T4)

0 Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

†Model with PSA outcome excludes cases with missing data on PSA. Model with outcome of grade excludes cases with missing data on PSA and/ or grade. Model with outcome of stage excludes cases with missing data on PSA and/ or stage.

Persistent racial/ ethnic disparities in high PSA disease among AA men

However, disparities in high PSA disease persisted across all stratified analyses (**Figure 6**), ranging from ORs of 1.55 within the high GS-stratified model to 1.85 within the low stage-stratified model. In a model that included only AA and White men diagnosed with high GS and high stage disease, AA men experienced 1.77 times the odds of high PSA prostate cancer relative to White men, after full adjustment (95% CI=1.48-2.11; **Table 6**). Furthermore, additionally adjusting models with outcome of high PSA prostate cancer for high stage and high GS resulted in comparable risk estimates as those presented in **Figure 6** (OR=1.79; 95% CI=1.69-1.90). Our finding of a persistent racial/ ethnic disparity in high PSA prostate cancer among AA men relative to NHW men was confirmed in robustness tests with multinomial logistic regression analyses using intermediate as the reference group. Specifically, among AA men relative to NHW men in fully adjusted models including adjustment for GS and stage (low, intermediate, high), the odds of high vs. intermediate PSA prostate cancer were 30% higher (OR=1.30; 95% CI=1.23-1.39) and the odds of low PSA vs. intermediate PSA prostate cancer were about 30% lower (OR=0.68; 95% CI=0.65-0.71) (**Table 7**).

High GS tumors were more likely to co-occur with high PSA tumors for AA men than NHW men; and similarly, high stage tumors were more likely to co-occur with high PSA tumors for AA men than NHW men (**Figure 7**). Approximately 2.9% of NHW men and 5.4% of AA men in our study presented with advanced prostate cancer that was high PSA but not high GS or high Stage (**Table 8**).

Table 8: Prostate cancer risk characteristics (combinations of PSA[1], grade[2], and stage[3]) among African American (AA) men and White men[0] diagnosed with first primary invasive prostate cancer between 2004 and 2013 in California, by race[0]

Prostate cancer aggressiveness	Race[0]							
	White men				African American men			
	PSA[1]				PSA[1]			
	Low	High	Missing	Total	Low	High	Missing	Total
	%	%	%		%	%	%	
Grade[2]								
Low	86.4	5.0	8.6	89,584	84.1	9.4	6.5	14,026
High	62.8	28.3	8.9	16,106	50.8	41.9	7.4	2,747
Missing	51.5	16.1	32.5	6,901	44.5	26.9	28.6	1,014
Stage[3]								
Low	86.7	5.5	7.8	97,658	84.5	10.0	5.5	15,107
High	43.7	37.6	18.7	11,877	32.1	50.9	17.1	2,175
Missing	39.3	11.1	49.6	3,056	34.1	26.1	39.8	505
Total	80.9	9.0	10.1	112,591	76.7	15.4	7.9	17,787

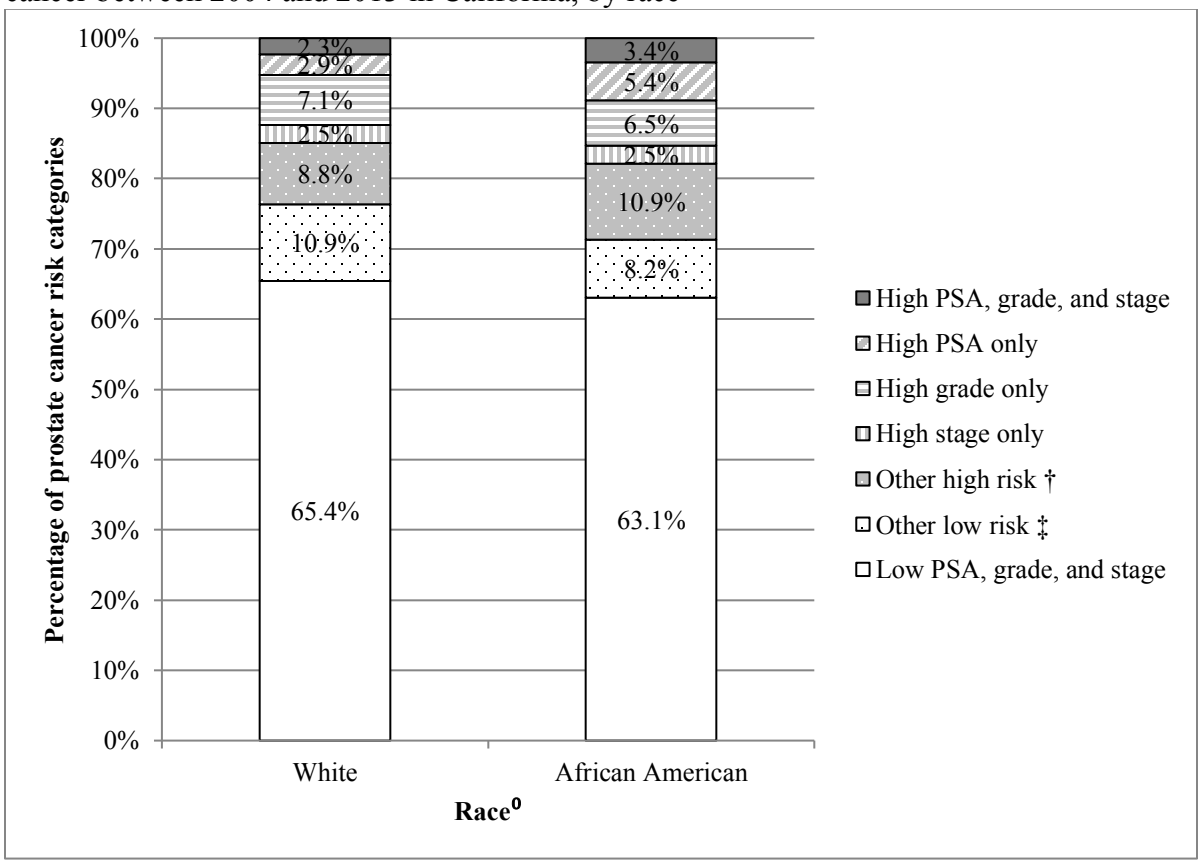
[0] Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

[1] Prostate-specific antigen risk category low (<20 ng/ mL) vs. high (20+ ng/ mL)

[2] Gleason grade risk category low (<8) vs. high (8+)

[3] Stage risk category low (N0, M0, and <T2b) and high (N1, M1, and/ or T2b+)

Figure 7: Prostate cancer risk characteristics (combinations of PSA[1], grade[2], and stage[3]) among 130,378 African American men and White men[0] diagnosed with first primary invasive prostate cancer between 2004 and 2013 in California, by race[0]



[0] Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity
[1] Prostate-specific antigen risk category low (<20 ng/ mL) vs. high (20+ ng/ mL)
[2] Gleason grade risk category low (<8) vs. high (8+)
[3] Stage risk category low (N0, M0, and <T2b) and high (N1, M1, and/ or T2b+)
† Other high risk includes all combinations of two, but not three, high risk characteristics
‡ Other low risk includes all combinations of two, but not three, low risk characteristics

Relative influence of covariables on racial/ ethnic disparities

Results from the method to assess relative influence of covariables on racial/ ethnic disparities are provided in **Figure 8** and **Figure 9**. The odds of high PSA prostate cancer among AA men with prostate cancer were 2.21 times those of NHW men in the age-adjusted model

(OR=2.21; 95% CI =2.11-2.32; **Figure 8**). A large proportion of this racial/ ethnic disparity in advanced prostate cancer was attributable to differences in neighborhood SES, which accounted for about 24.3% of the racial/ ethnic disparity in multivariable models. An additional 10.1% was explained by differences in marital status, and 5.5% was explained by differences in insurance status. Adjustment for all covariables explained 40.0% of the overall racial/ ethnic disparities in high PSA prostate cancer (**Figure 8B**). High GS prostate cancer among AA men with prostate cancer was 30% higher than among NHW men in the age-adjusted model (OR=1.30; 95% CI = 1.24-1.36; **Figure 8C**). Neighborhood SES explained the largest proportion of this racial/ ethnic disparity in prostate cancer aggressiveness in multivariable models (34.3%), followed by marital status (14.2%), and insurance type (9.4%). Adjustment for all covariables explained about 60.9% of the overall racial/ ethnic disparity in high GS prostate cancer (**Figure 8C**). High stage prostate cancer among AA men with prostate cancer was 35% higher than among NHW men in the age-adjusted model (OR=1.35; 95% CI = 1.28-1.42; **Figure 8A**). Neighborhood SES explained the largest proportion of this racial/ ethnic disparity in prostate cancer aggressiveness in multivariable models (45.1%), followed by marital status (37.6%). Adjustment for all covariables explained about 96.2% of the overall disparities in high stage prostate cancer (**Figure 8D**). The fully adjusted models for the four risk categorizations, including high NCCN risk, are provided in **Table 5**. In our application of this method using an unadjusted baseline model, we confirmed that the primary contributors to racial/ ethnic disparities in advanced prostate cancer were due to differences in neighborhood SES and age at diagnosis (**Figure 9**).

Figure 8: A, OR of advanced prostate cancer (PSA[1], grade[2], stage[3], and risk[4]) for African American men compared to White men[0], for a sequence of logistic regression models, the leftmost of which includes racial/ethnic group alone adjusted for age at diagnosis, where variables are added in the order of their univariable significance, and where the rightmost represents the full baseline model. B-E, univariable and multivariable relative influence of individual variables in the baseline model for prostate cancer aggressiveness outcomes.

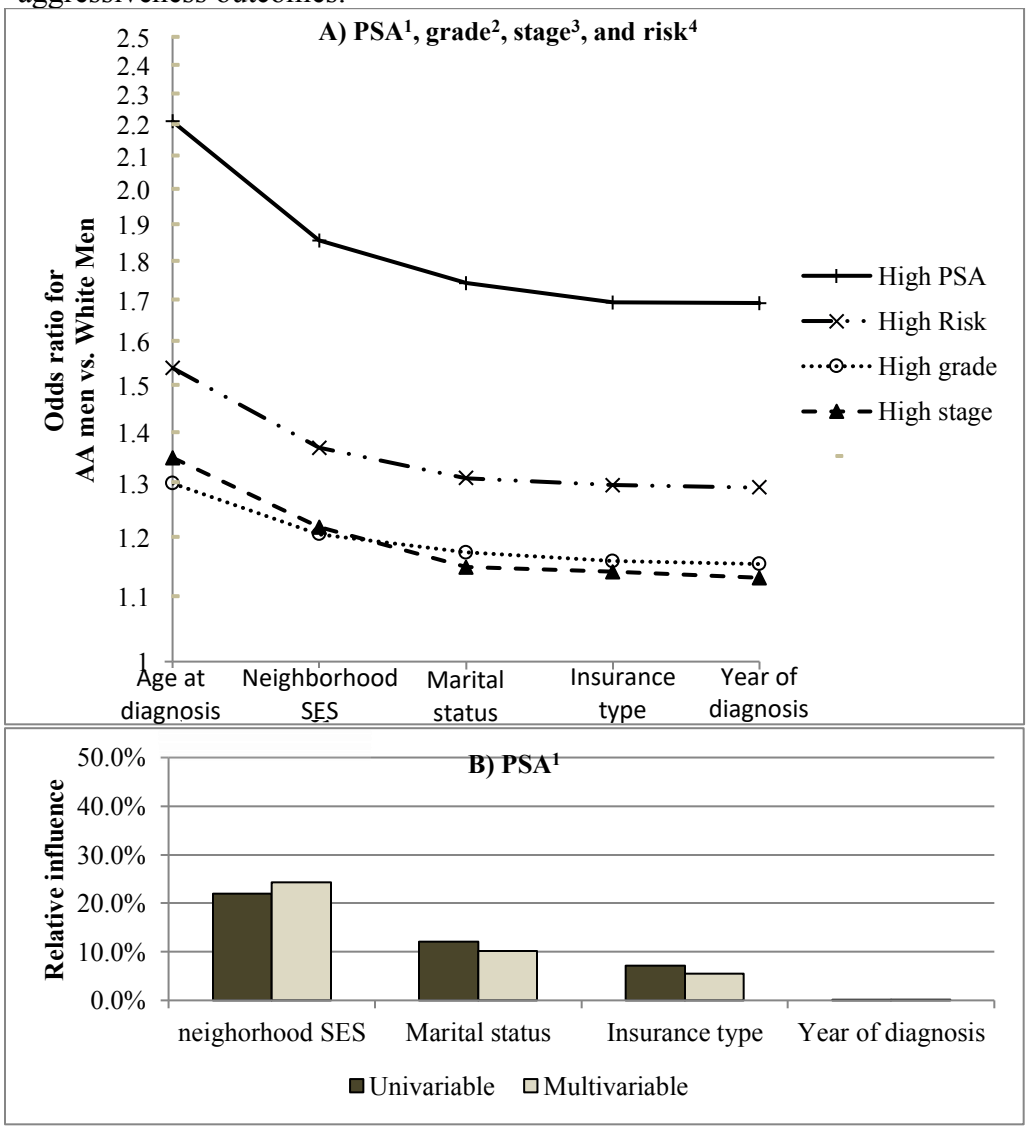
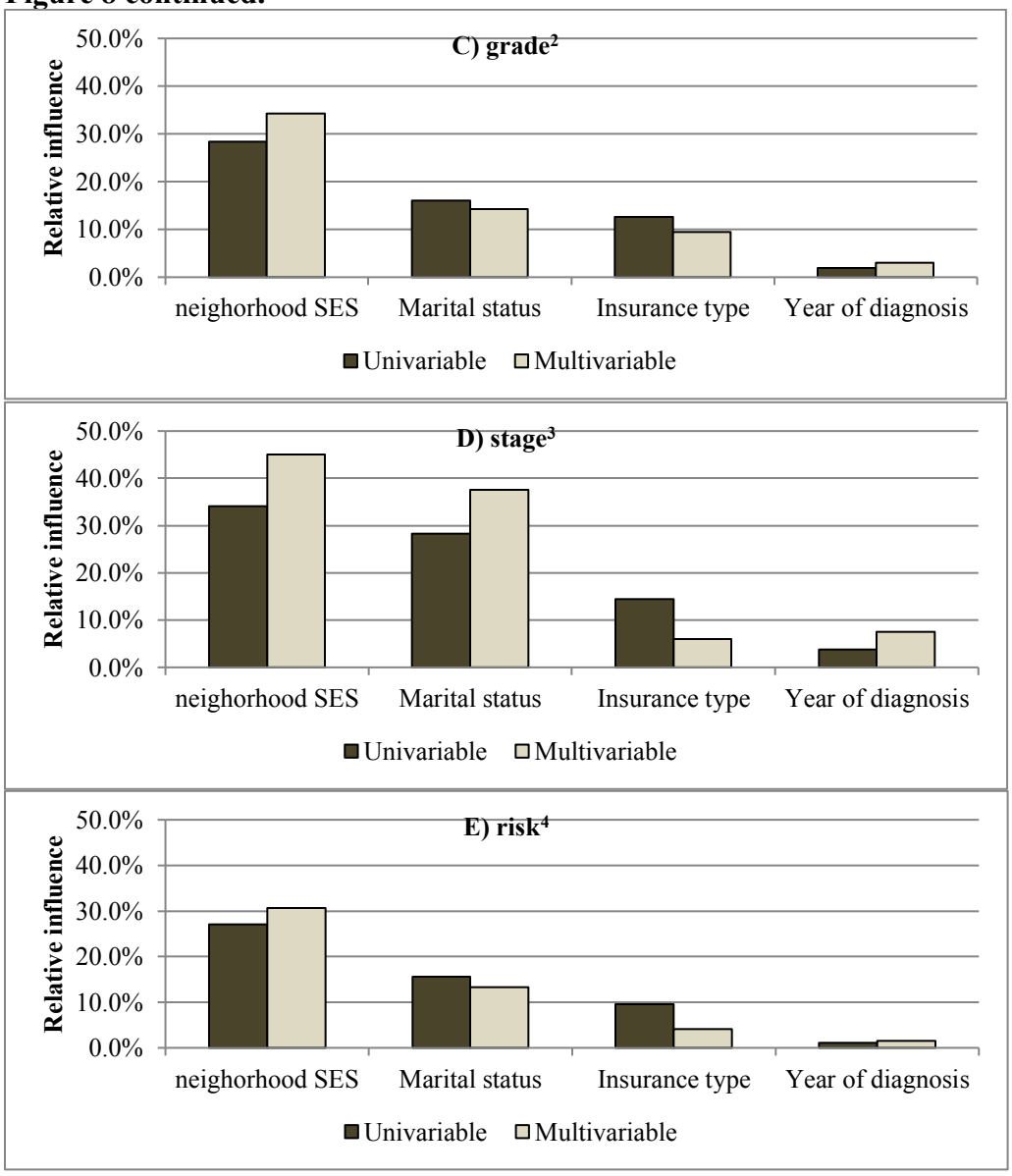


Figure 8 continued.



[0] Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

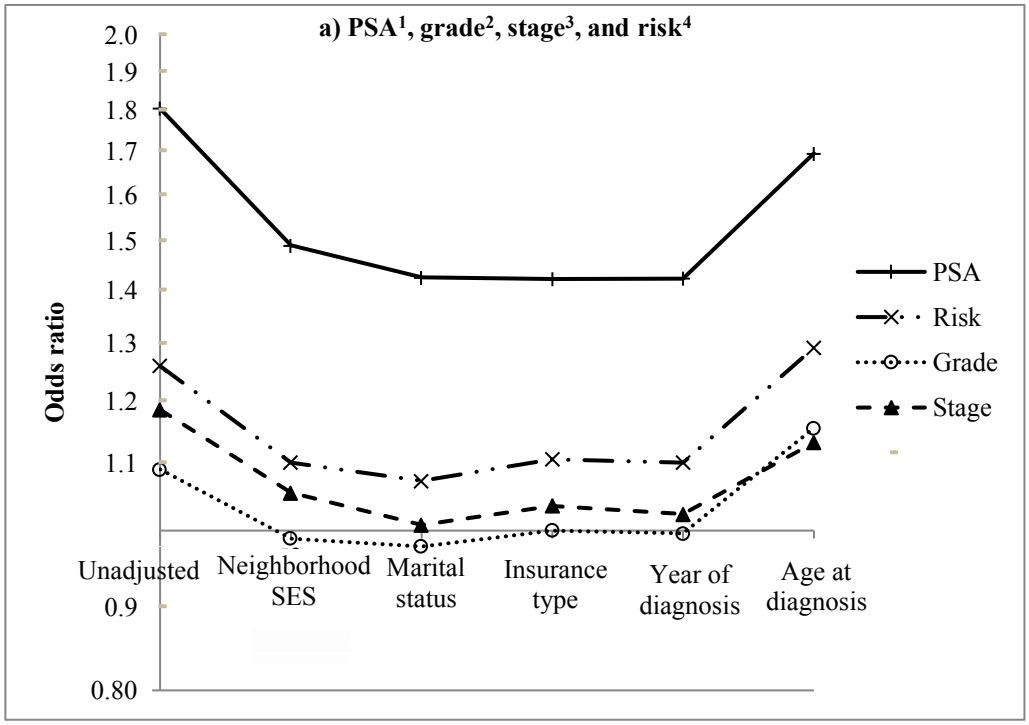
1 Prostate-specific antigen risk category low (<20 ng/ mL) vs. high (20+ ng/ mL)

2 Gleason grade risk category low (<8) vs. high (8+)

3 Stage risk category low (N0, M0, and <T2b) and high (N1, M1, and/ or T2b+)

4 Prostate cancer risk stratification criteria based on the NCCN classification using TNM stage, Gleason grade, and prostate-specific antigen (PSA) level. Low included low-risk (T1/T2a and Gleason ≤ 6 and PSA<10 ng/ml) and intermediate-risk (T2b/T2c or biopsy Gleason 7 or PSA 10-20 ng/ml); and high included high-risk (T3/T4 or Gleason 8+ or PSA>20 ng/ml or N1) and metastatic (M1).

Figure 9: OR of advanced prostate cancer (PSA[1], grade[2], stage[3], and risk[4]) for African American men compared to White men[0], for a sequence of logistic regression models, the leftmost of which includes racial/ethnic group alone, where variables are added in the order of their univariable significance, and where the rightmost represents the full baseline model.



[1] Prostate-specific antigen risk category low (<20 ng/ mL) vs. high (20+ ng/ mL)
[2] Gleason grade risk category low (<8) vs. high (8+)
[3] Stage risk category low (N0, M0, and <T2b) and high (N1, M1, and/ or T2b+)
[4] Prostate cancer risk stratification criteria based on the NCCN classification using TNM stage, Gleason grade, and prostate-specific antigen (PSA) level. Low included low-risk (T1/T2a and Gleason ≤ 6 and PSA<10 ng/ml) and intermediate-risk (T2b/T2c or biopsy Gleason 7 or PSA 10-20 ng/ml); and high included high-risk (T3/T4 or Gleason 8+ or PSA>20 ng/ml or N1) and metastatic (M1).

Age-specific incidence rates for advanced prostate cancer are presented in **Figure 10** and for non-advanced prostate cancer are presented in **Figure 11**. Advanced prostate cancer incidence rates were higher for AA men than NHW men for all age categories examined, with a

larger gap in the difference observed for high PSA prostate cancer than high GS or high stage prostate cancer. For example, the incidence rates per 100,000 men at age at diagnosis group 60-61 years were as follows: for high PSA, 26.1 NHW men and 88.6 AA men; for high GS, 43.8 NHW men and 100.0; for high stage, 34.6 NHW men and 77.0 AA men; for high risk, 74.6 for NHW men and 173.1 for AA men (**Figure 10**). No major differences in age-specific incidence rates for AA and NHW men were observed for non-advanced prostate (**Figure 11**).

Figure 10: Age-specific incidence rates of prostate cancer by race[0] among California men, 2004-2013. Panels A-E present different definitions of advanced prostate cancer. Note different axis scales.

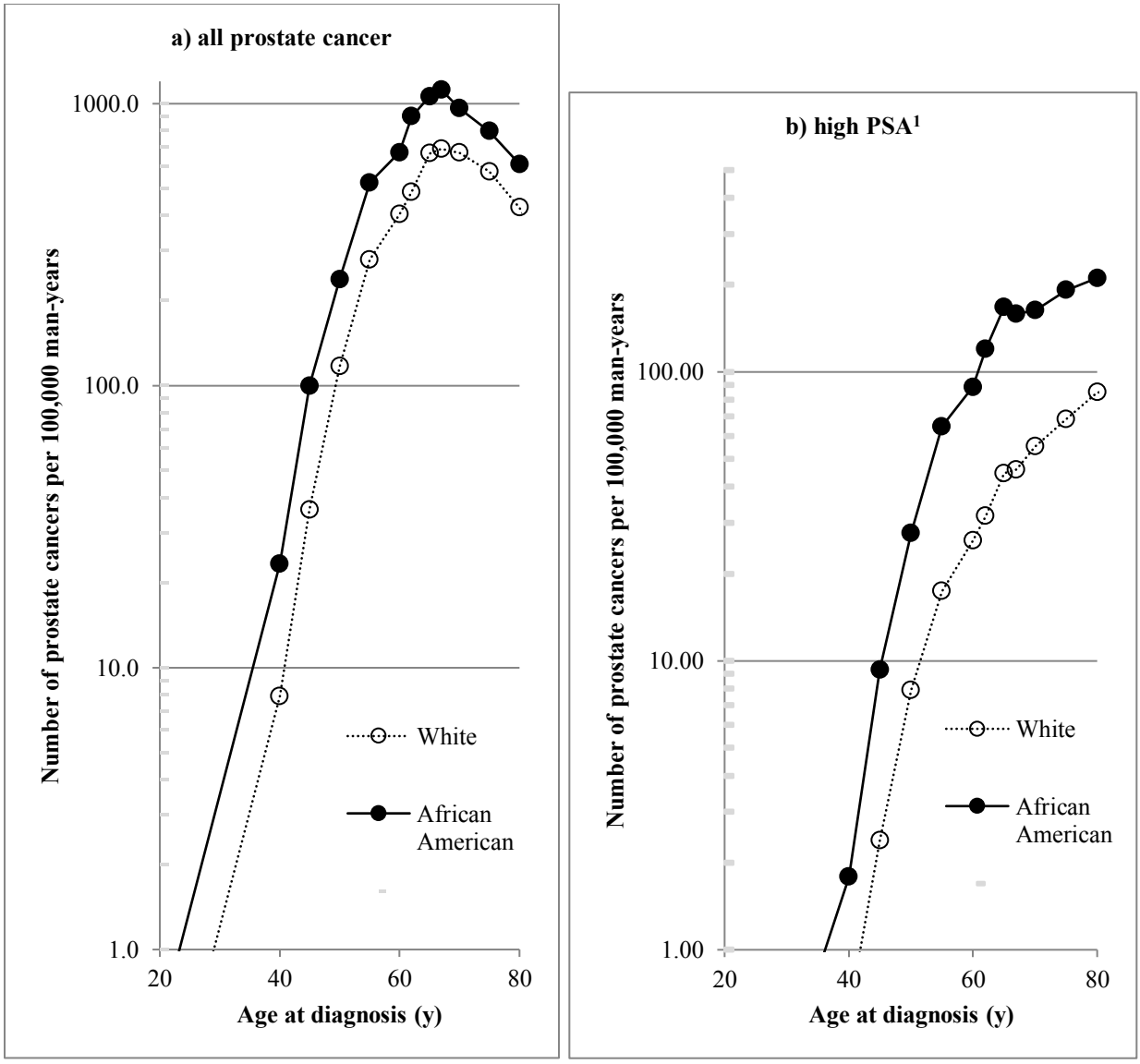


Figure 10 continued.

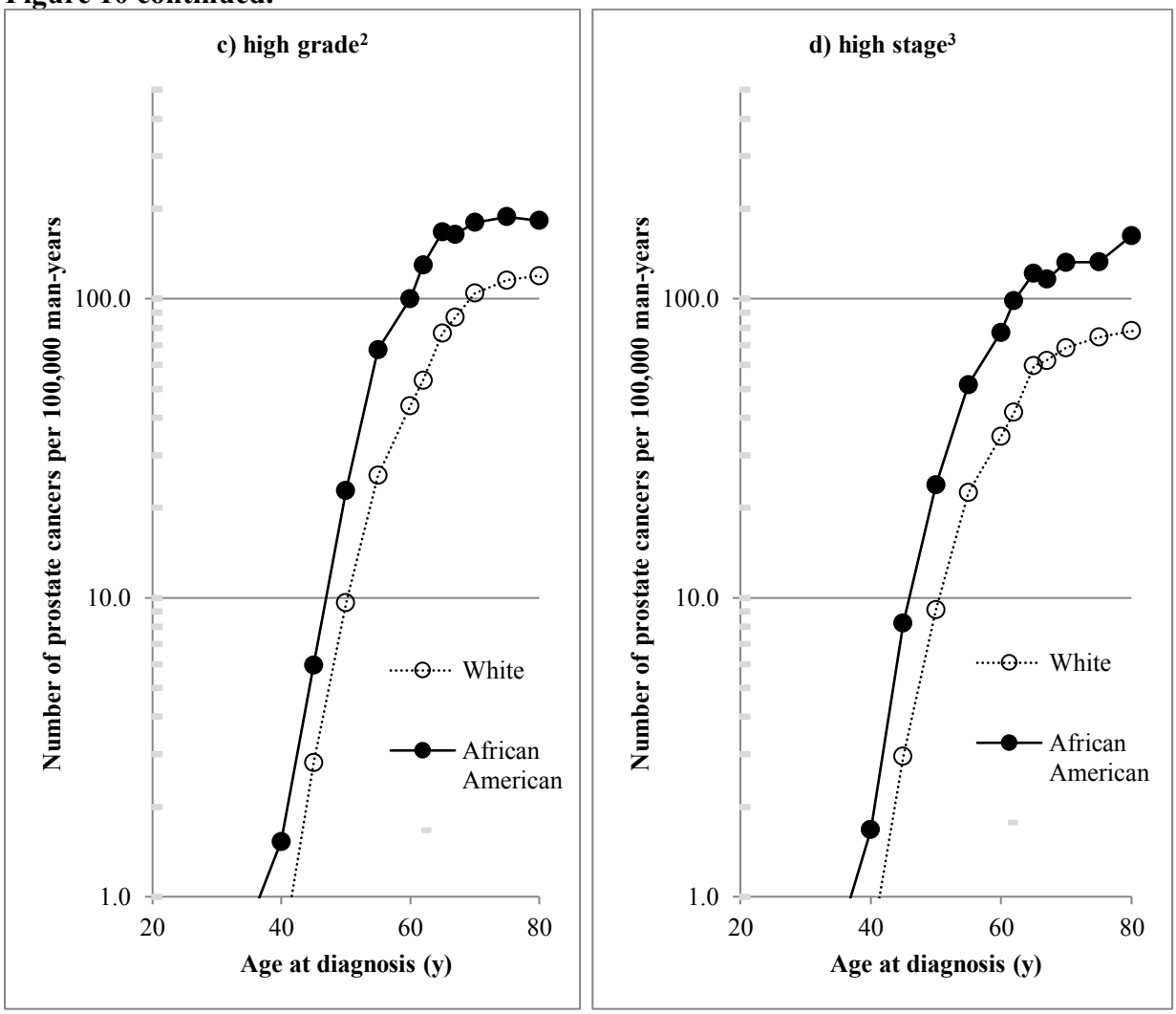
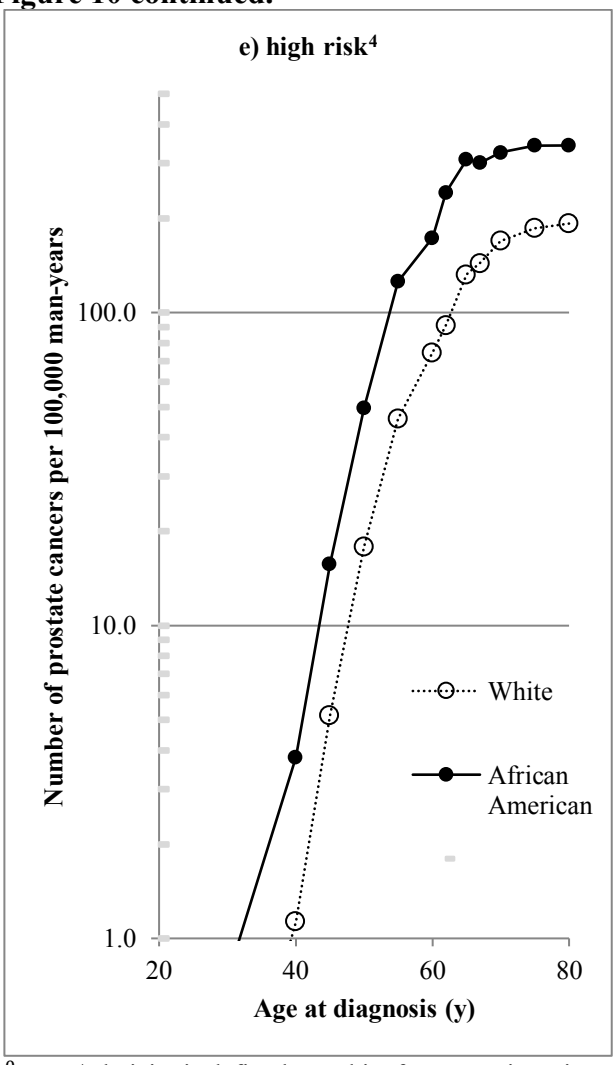


Figure 10 continued.



[0] Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

[1] Prostate-specific antigen risk category high (20+ ng/ mL)

[2] Gleason grade risk category high (8+)

[3] Stage risk category high (N1, M1, and/ or T2b+)

[4] Prostate cancer risk stratification criteria based on the NCCN classification using TNM stage, Gleason grade, and prostate-specific antigen (PSA) level. High included high-risk (T3/T4 or Gleason 8+ or PSA>20 ng/ml or N1) and metastatic (M1).

Figure 11: Age-specific incidence rates of prostate cancer by race[0] among California men, 2004-2013. Panels A-E present different definitions of prostate cancer aggressiveness.

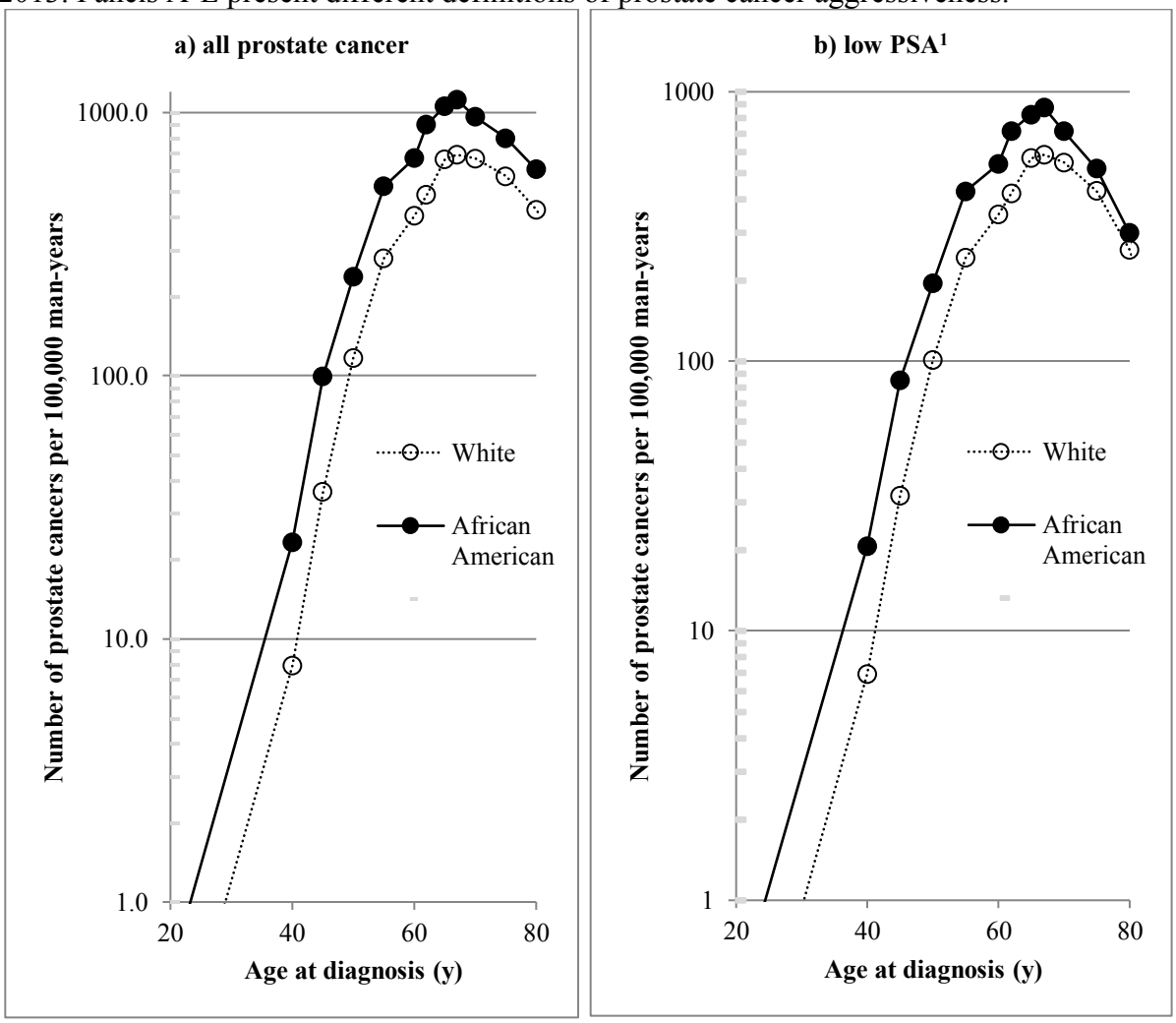
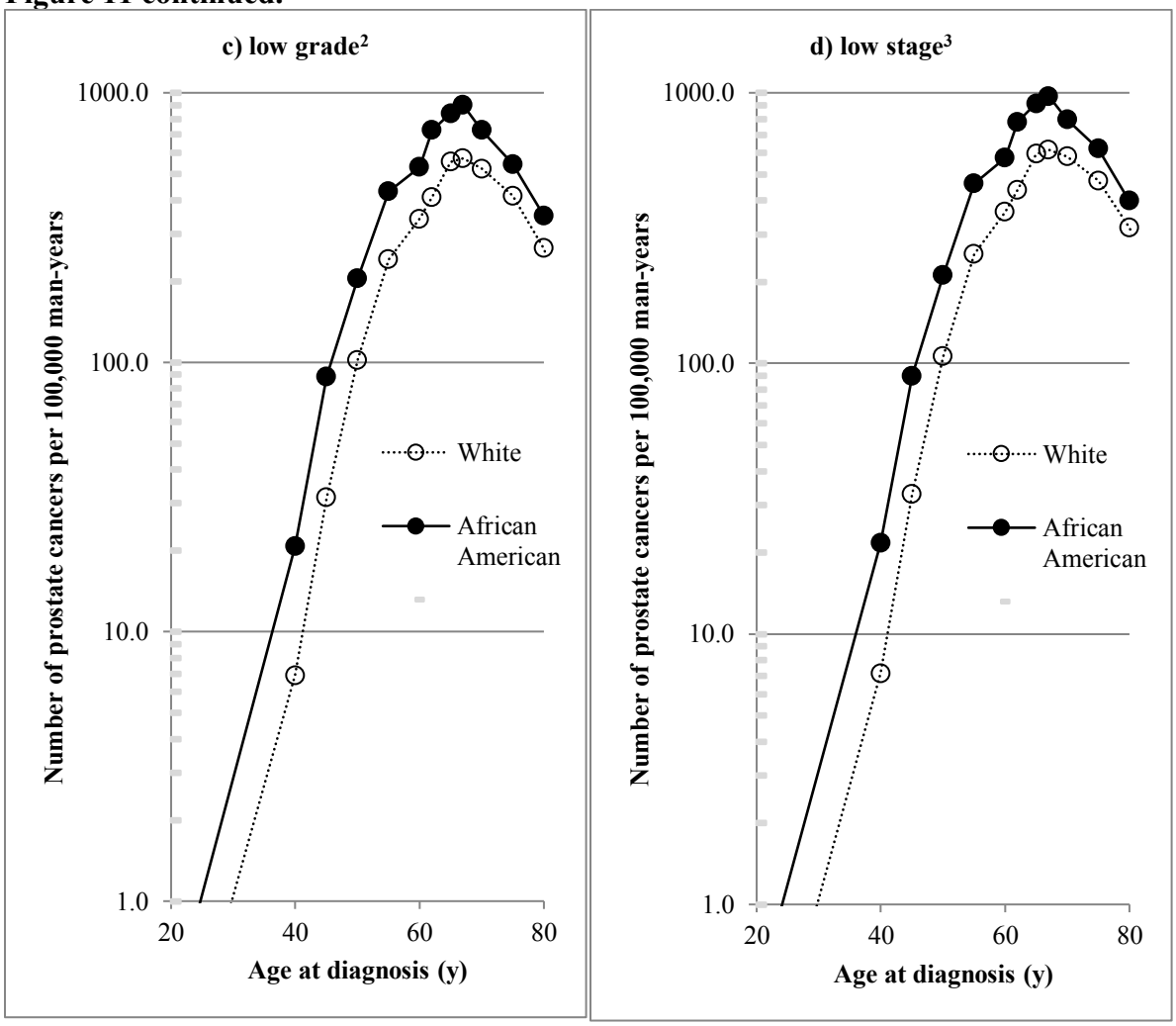


Figure 11 continued.



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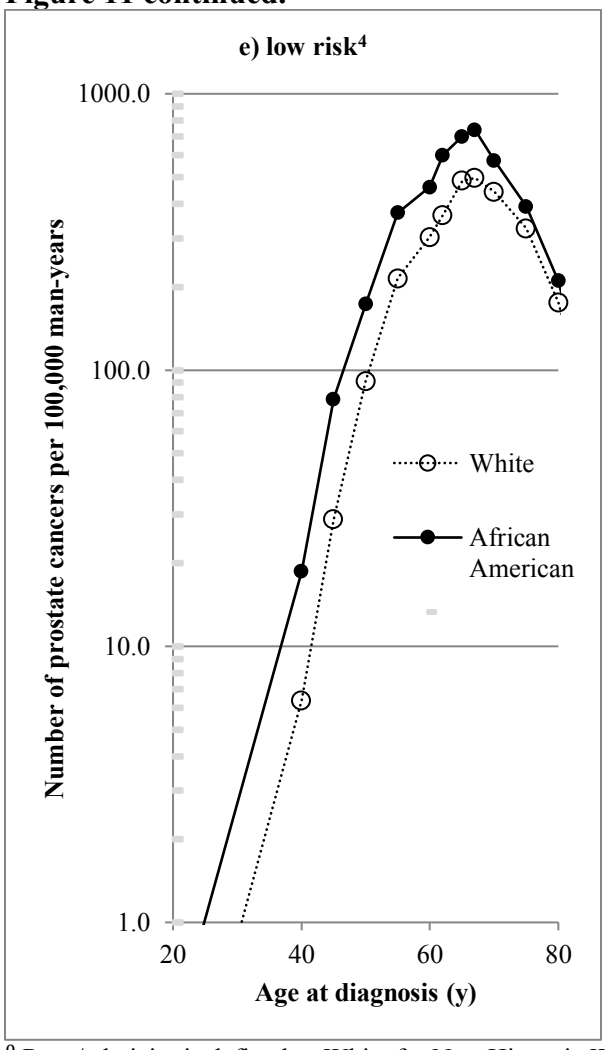


0 Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

1 Prostate-specific antigen risk category high (20+ ng/ mL)

2 Gleason grade risk category high (8+)

3 Stage risk category high (N1, M1, and/ or T2b+)

4 Prostate cancer risk stratification criteria based on the NCCN classification using TNM stage, Gleason grade, and prostate-specific antigen (PSA) level. High included high-risk (T3/T4 or Gleason 8+ or PSA>20 ng/ml or N1) and metastatic (M1).

In age-stratified multivariable regression models, we observed that AA men <60 years experienced higher odds of high PSA (OR=1.30; 95% CI=1.17-1.44) but not high GS (OR=1.01;

95% CI=0.92-1.12) or high stage (OR=0.88; 95% CI=0.79-0.98) prostate cancer relative to NHW men <60 years, after full adjustment (**Table 9**).

Table 9: Advanced prostate cancer among African American (AA) men and White men[0] diagnosed with first primary invasive prostate cancer between 2004-2013 in California, using 4 risk categorizations as separate outcomes (prostate specific antigen [PSA[1]], Gleason score grade [GS[2]], and TNM stage[3]), in separate fully adjusted models●, stratified by age

Patient characteristics	Outcome = high PSA[1]					
	Age <60 years			Age 60+ years		
	OR	95% CI		OR	95% CI	
Race[0]						
White	1.00	(Reference	)	1.00	(Reference	)
African American	1.30	(1.17 - 1.44	)	1.78	(1.68 - 1.89	)
Total (N)	29,643			87,998		
Patient characteristics	Outcome = high grade[2]					
	Age <60 years			Age 60+ years		
	OR	95% CI		OR	95% CI	
Race[0]						
White	1.00	(Reference	)	1.00	(Reference	)
African American	1.01	(0.92 - 1.12	)	1.17	(1.11 - 1.23	)
Total (N)	30,308			92,155		
Patient characteristics	Outcome = high stage[3]					
	Age <60 years			Age 60+ years		
	OR	95% CI		OR	95% CI	
Race[0]						
White	1.00	(Reference	)	1.00	(Reference	)
African American	0.88	(0.79 - 0.98	)	1.19	(1.12 - 1.27	)
Total (N)	31,373			95,444		
Patient characteristics	Outcome = high risk[4]					
	Age <60 years			Age 60+ years		
	OR	95% CI		OR	95% CI	
Race[0]						
White	1.00	(Reference	)	1.00	(Reference	)
African American	1.11	(1.03 - 1.20	)	1.31	(1.25 - 1.37	)
Total (N)	29,718			90,006		

[0] Race/ethnicity is defined as White for Non-Hispanic White men and African American for Black men regardless of Hispanic ethnicity

[1] Prostate-specific antigen risk category low (<20 ng/ mL) vs. high (20+ ng/ mL)

[2] Gleason grade risk category low (<8) vs. high (8+)

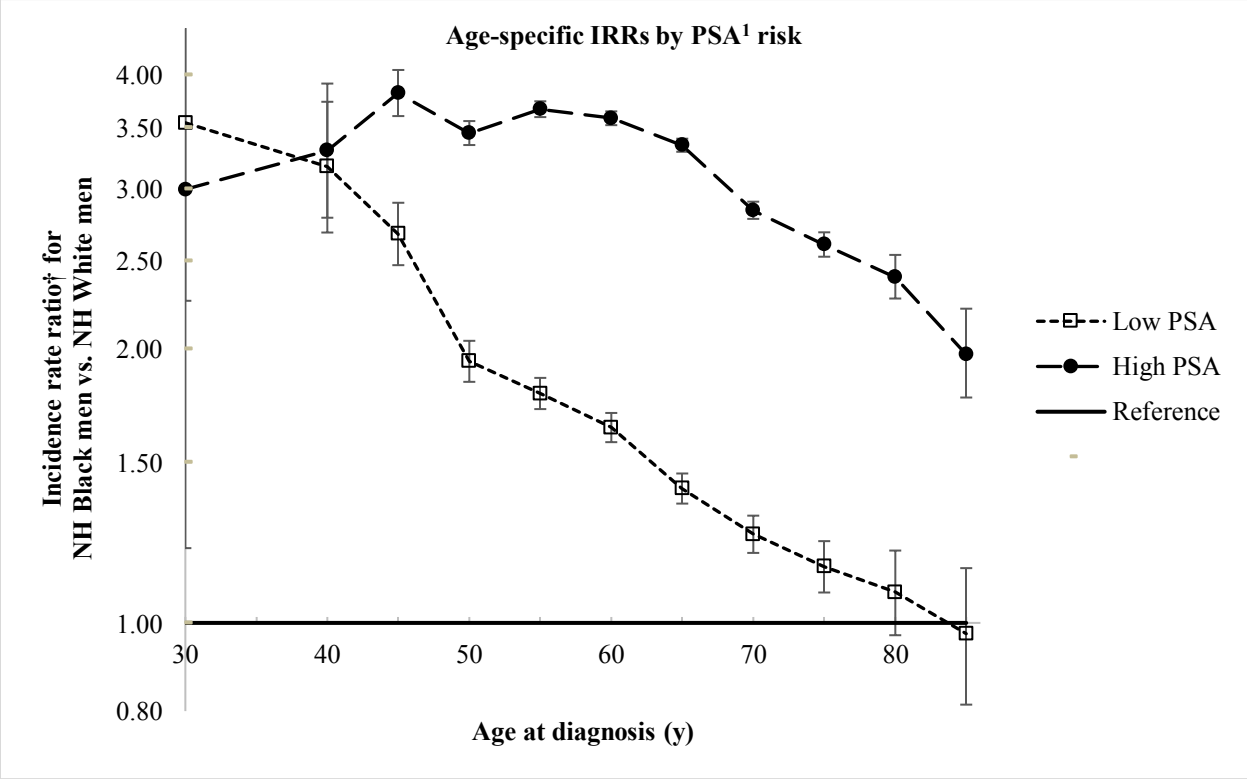
[3] Stage risk category low (N0, M0, and <T2b) and high (N1, M1, and/ or T2b+)

[4] Prostate cancer risk stratification criteria based on the NCCN classification using TNM stage, Gleason grade, and prostate-specific antigen (PSA) level. Low included low-risk (T1/T2a and Gleason ≤ 6 and PSA<10 ng/ml) and intermediate-risk (T2b/T2c or biopsy Gleason 7 or PSA 10-20 ng/ml); and high included high-risk (T3/T4 or Gleason 8+ or PSA>20 ng/ml or N1) and metastatic (M1).

Incidence rate ratios examining PSA risk

Age-specific IRRs, stratified by advanced PSA, among 124,203 AA men and NHW men diagnosed with first primary invasive prostate cancer from 2004-2013 in California using the SEER*Stat database are presented in **Figure 12**. The age-adjusted incidence rates for AA men were statistically significantly higher than those for NHW men for both low PSA prostate cancer (IRR=1.49; 95% CI=1.46-1.51) and high PSA prostate cancer (IRR=2.90; 95% CI=2.77-3.02). A statistically significant higher incidence of high PSA prostate cancer was observed for all age groups examined, with a general decrease in the IRRs for older age groups. Specifically, relative to the incidence of high PSA prostate cancer observed among NHW men in the respective age groups, incidence among AA men was approximately 4 times at ages 45-49 years (IRR=3.82; 95% CI=3.61-4.05) and 2 times at ages 85+ years (IRR=1.97; 95% CI=1.77-2.21). A steeper decrease in age-specific low PSA prostate cancer than high PSA prostate cancer IRRs was observed, with incidence of low PSA prostate cancer among AA men ages 45-49 years nearly 3 times that among NHW men of those ages (IRR=2.68; 95% CI=2.47-2.90) and no difference among men 85+ years (IRR=0.97; 95% CI=0.81-1.15). The age-specific IRRs comparing AA men to NHW men for high PSA prostate cancer exceeded those for low PSA prostate cancer for all age categories 45+ years. The largest absolute difference in IRRs between AA men and NHW men were observed for prostate cancer incidence at ages 60-64 years, with an IRR=1.64 (95% CI=1.58-1.70) for low PSA disease and an IRR=3.58 (95% CI=3.52-3.65) for high PSA disease.

Figure 12: Age-specific incidence rate ratio (IRR)†, stratified by advanced PSA prostate cancer for African American men relative to White men[0] among N=124,203 men diagnosed with first primary invasive prostate cancer between 2004 and 2013 in California



[0] Race/ ethnicity is defined as African American for NH Black men and White for NH White men
[1] Prostate-specific antigen risk category low (<20 ng/ mL) vs. high (20+ ng/ mL)
† Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard; Confidence intervals (Tiwari mod) are 95% for rates and ratios.
Database reference- California Cancer Registry (www.ccrcal.org), California Department of Public Health. SEER*Stat Database: Incidence - California, Dec 2018 (1988-2016), 04/19/2019; NAACCR 3339 Version. Benchmarked 1988-1989 DOF population estimates, 6/12/2006; NCHS population estimates 1990-2016.

Age-adjusted neighborhood SES-specific IRRs, stratified by advanced PSA among 59,686 AA men and NHW men in California diagnosed with first primary invasive prostate cancer in peri-censal years 2008-2012 are presented in **Figure 13**. No major differences were observed in the magnitude of neighborhood SES-specific IRRs for AA men relative to NHW men across categories of neighborhood SES for either low PSA or high PSA prostate cancer

(**Figure 13A**). However, among all men regardless of race/ ethnicity we observed modest differences in the magnitude of neighborhood SES-specific IRRs relative to the highest SES neighborhood quintile 5. Specifically, we observed a lower incidence rate of low PSA prostate cancer among men in the lowest SES neighborhood quintile 1 vs. quintile 5 (IRR=0.86; 95% CI=0.83-0.88) and a higher incidence of high PSA prostate cancer (IRR=1.92; 95% CI=1.77-2.10) (**Figure 13B**). A general increase in the proportion of the population denominators comprised by AA men was observed from the highest neighborhood SES quintile 5 (4.0%) to the lowest neighborhood SES quintile 1 (30.5%) (**Figure 13C**). Taken together, panels B and C of **Figure 13** reflect a modest disparity in advanced PSA prostate cancer for AA men by neighborhood SES quintiles, since AA men disproportionately resided in low vs. high neighborhood environments relative to NHW men.

Figure 13: A, neighborhood socioeconomic status (SES)-specific incidence rate ratio (IRR)† for African American men relative to White men. B, neighborhood SES-specific IRR† with neighborhood SES Quintile 5 (Highest) as the Reference group, stratified by advanced PSA[1] among N=59,686 African American men and White men diagnosed with first primary invasive prostate cancer in peri-censal years from 2008 to 2012 in California. C, % race/ ethnicity[0] of population denominators by neighborhood SES quintile in California.

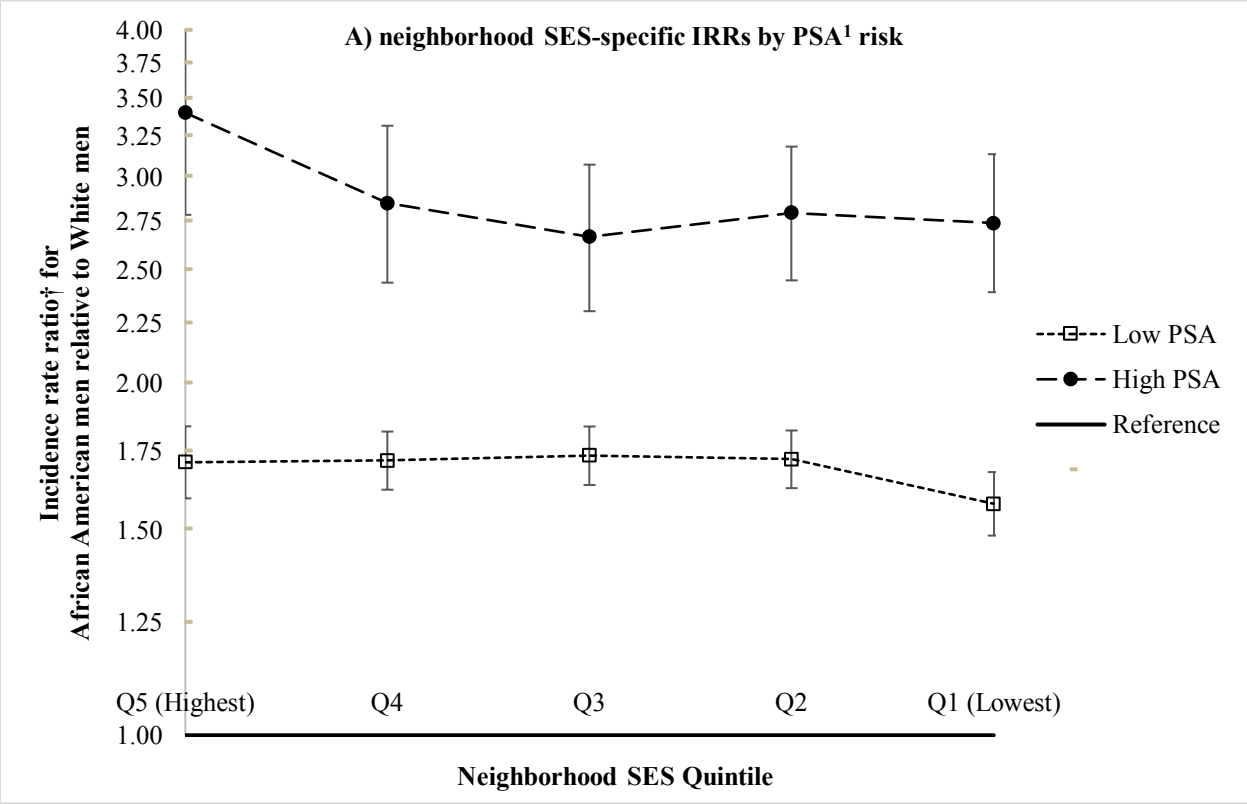
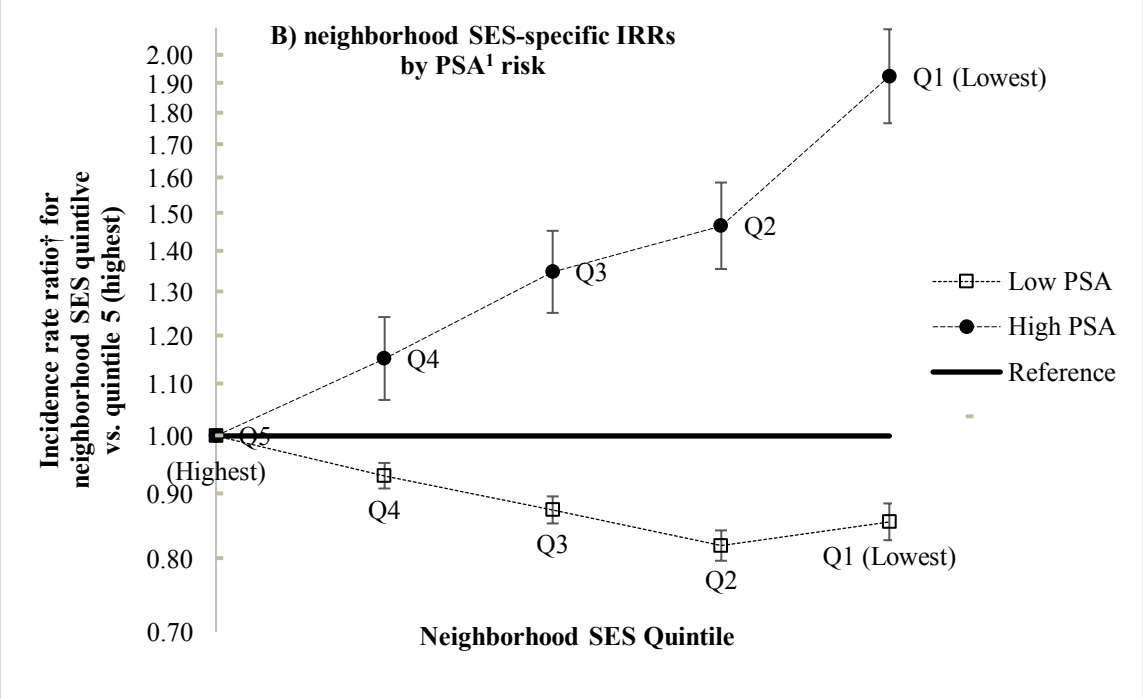
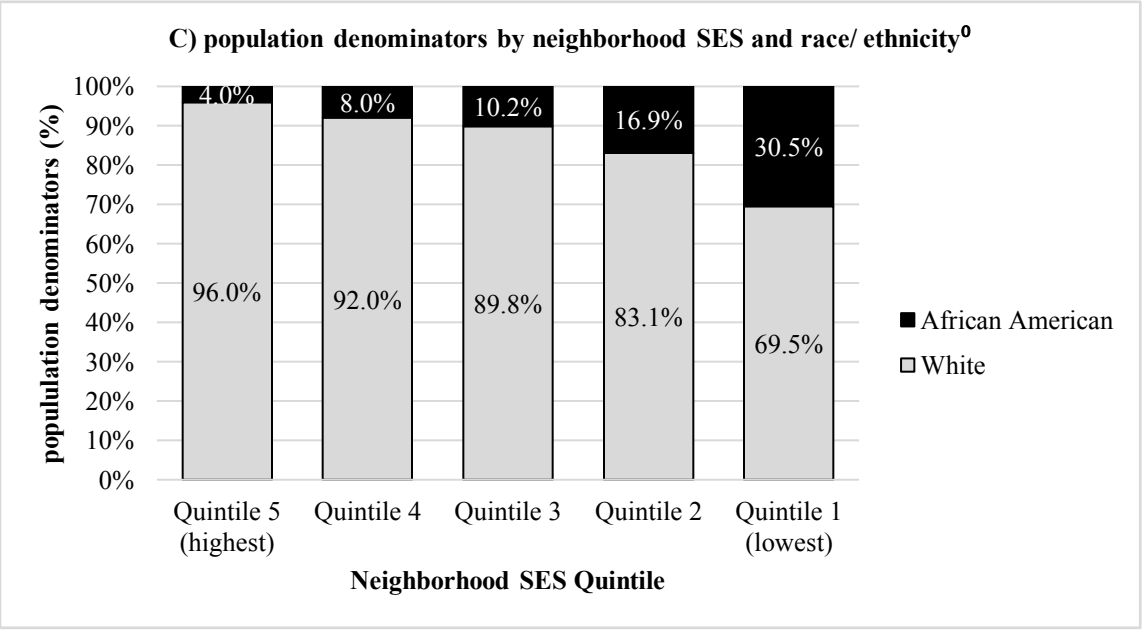


Figure 13 continued.





[0] Race/ ethnicity is defined as African American for NH Black men and White for NH White men

† Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard; Confidence intervals (Tiwari mod) are 95% for rates and ratios.

Database reference - Statewide CCR data received November 2014. 1990 and 2000 Census Population counts and 2007-11 ACS Populations at CT level from SEER*Stat. Nativity based on Birthplace (all races); for Hispanics and selected Asian subgroups, SSN Yr/ Age Issued or by random assignment

DISCUSSION

Relative to NHW men, AA men present with prostate cancer at an earlier age, with adverse patho-clinical characteristics (high stage, GS, and PSA), a higher likelihood that a preclinical prostate tumor will spread, larger tumor volumes per ng/ mL of serum PSA, and a higher incidence of and mortality from prostate cancer [32-35, 57]. In order to examine racial/ ethnic disparities in prostate cancer aggressiveness, we conducted a population-based study of all AA men and NH White men diagnosed with first primary invasive prostate cancer in California from 2004 to 2013 with sufficiently detailed data on PSA, GS, and stage to risk stratify prostate cancer aggressiveness. We observed that disparities in prostate cancer aggressiveness among AA men were independently apparent for high PSA prostate cancer, but not GS and/ or stage. We identified that age at diagnosis and neighborhood SES were the most influential covariables to racial/ ethnic disparities in prostate cancer aggressiveness. In incidence-based analyses, we observed that racial/ ethnic disparities in high PSA prostate cancer were present among AA men relative to NHW men for all ages at diagnoses 45+ years. Disproportionate residence in the lowest neighborhood SES environments appeared to exacerbate racial/ ethnic disparities in high PSA prostate cancer for AA men. Future work may help to inform whether high PSA prostate cancer drives racial/ ethnic disparities in prostate cancer mortality among AA men relative to NHW men.

Increased serum PSA, an androgen-regulated glycoprotein molecule involved in liquefaction of seminal fluid, is a strong predictor of subsequent lethal prostate cancer risk [58-60]. However, other clinical correlates of increased serum PSA include increasing age, larger prostate volume, inflammation or infection or trauma to the prostate, and medical procedures that

interfere with the prostate gland [61-65]. It is therefore unclear whether the racial/ ethnic differences in occurrence of high PSA prostate cancer observed in our study were due to differences in biology and/ or may have reflected PSA as a general marker of male health. However, we were able to partially account for the possibility that the racial/ ethnic disparities presented here were unlikely to be due to changes in screening behavior coinciding with the 2012 United States Preventives Services Task Force (USPSTF) recommendation limiting PSA-based screening for prostate cancer [66]. We observed fewer cases of prostate cancer, and proportionally more advanced prostate cancers, diagnosed in 2012-2013 than in preceding years. However, the results presented here did not differ when separately examining multivariable logistic regression models stratified by year of diagnosis 2004-2011 and 2012-2013.

Our results contribute to the literature by providing population-based estimates to inform the timing of divergence of prostate cancer aggressiveness by race/ ethnicity among AA men relative to NHW men. The USPSTF, NCCN, American Cancer Society (ACS) and American Urological Association (AUA) all currently recommend shared decision-making in prostate cancer screening that includes patient race/ ethnicity as an aspect of the decision-making process. However, these guideline recommendations differ with respect to target age groups for PSA screening and populations to test [67-70]. In our study, the divergence in high PSA prostate cancer for AA men appeared at ages 45+ years, with no difference between low/ high PSA prostate cancer risk for AA men <45 years and high PSA IRRs that exceeded those for low PSA in all ages 45+ years. Our results are potentially consistent with previous research that has identified higher PSA distributions among young AA men than young NH White men (<40 years) without prostate cancer [33]. Although early adulthood PSA concentrations predict later

incidence of aggressive and lethal prostate cancer [71, 72], it remains unclear whether increased PSA testing among AA men in their 40s or 50s may be an appropriate risk-based screening strategy for reducing racial/ ethnic disparities in prostate cancer mortality. Importantly, specificity of serum PSA in predicting prostate cancer is worse for AA men than NHW men [73].

Rather, as demonstrated in recent studies examining racial/ ethnic disparities in prostate cancer-specific mortality, unequal access to treatment appears to explain mortality disparities experienced by AA men relative to NHW men. Specifically, in a recent study of 306,100 prostate cancer patients in SEER, Veterans Affairs, and randomized clinical trials cohorts, differences in stage-for-stage prostate cancer-specific mortality were observed for AA men relative to NHW men in the SEER cohort, but not the other two cohorts with equal access to treatment [74]. Findings from this Dess et. al. study, and others, imply that equal treatment among equal patients provide equal outcomes, without regard to race/ ethnicity [74-77]. Our recent report in California demonstrates that the 60% higher age-adjusted prostate cancer-specific mortality among AA men relative to NHW men was reduced to the null after full adjustment for tumor, sociodemographic, institutional, and neighborhood characteristics, with evidence that stage, marital status, and neighborhood SES were the major contributors to prostate cancer mortality disparities [23]. Findings from the present study contribute to the literature by suggesting that racial/ ethnic disparities in prostate cancer aggressiveness at diagnosis among AA men are likely driven by differences in PSA rather than by GS and/ or stage independent of PSA. High PSA tends to be associated with increased odds of high GS, as reported in our study. Specifically, we observed that high PSA increased the odds of high stage by a factor of 12.4, and high stage prostate cancer

in the absence of high PSA was more likely among NHW men than AA men. We observed that co-occurrence of high GS and high PSA, and high stage and high PSA tumors, was more frequent for AA men than NHW men. Presumably, less differentiated prostate tissue may produce less PSA. However, we also observed high GS tumors with low PSA. This finding is consistent with a recent study of Japanese men that found co-occurence of high GS and high stage prostate cancer among patients with very low PSA (<3.5 ng/ mL) disease [78]. Future work may elucidate whether adverse PSA profiles, rather than stage and/ or grade, among AA men may be responsible for the mortality disparities previously reported.

We did not assess potential racial/ ethnic disparities in prostate cancer aggressiveness within more granular categorizations than our definitions of low, intermediate, and high PSA, GS and stage prostate cancer. Treatment decisions within each of these categories may have clinical significance [53,69,78]. This has been demonstrated in a recent evaluation that observed heterogeneous outcomes within the intermediate- and high-risk NCCN prostate cancer risk classification scheme [69]. We were able to confirm our binary findings within low, intermediate, and high risk categories, but we did not perform more granular analyses. Future work may further elucidate potential racial/ ethnic disparities for men diagnosed with low and intermediate risk disease, and outcome heterogeneity within risk categories.

We observed that age at diagnosis, neighborhood SES, and insurance type contributed to racial/ ethnic disparities in prostate cancer aggressiveness for AA men relative to NHW men. These findings are consistent with previous findings of adverse prostate cancer risk profiles among men in the lowest neighborhood SES quintile, those who are not married, and uninsured [26]. We interpret our findings in light of emerging evidence suggesting that prostate cancer

develops through complex interactions at the biologic, individual, and social levels [2, 24, 25, 79, 80].

Our study is strengthened by the legal mandate in California for routine collection of tumor and patient characteristics on all cancer cases in California. Hence, our study is less prone to reporting and selection biases than studies within specific health care systems and/ or patient populations. Our study was subject to several limitations common to cancer registry-based analyses including the lack of individual-level data on SES, lifestyle factors, and exposures. In particular, we were unable to control for obesity, which is positively associated with grade [81], negatively associated with PSA [82], and disproportionately high in California for AA men relative to NHW men (35.4% vs. 25.2%, respectively) [83]. Furthermore, our findings for neighborhood SES may be a proxy for individual SES. Additionally, neighborhood SES may be misclassified for subjects with residential mobility. Another limitation is that we lacked data on tumor volume, prostate size, and the number and involvement of biopsy cores. Additionally, our single PSA test result lacked potentially important information such as PSA kinetics (PSA velocity and doubling time) and free-to-total PSA ratio, which are potentially important predictors of prostate cancer aggressiveness [59, 60, 84]. Nevertheless, the available data were sufficient to stratify men into binary risk groups based on NCCN guidelines that guide the initial management [53].

Conclusions

Relative to NHW men, AA men currently experience a racial/ ethnic disparity in prostate cancer-

specific mortality. Since most prostate tumors are indolent, it is particularly important to risk stratify subjects to guide treatment decisions. Further research is needed to assess whether the poor risk profiles observed specifically for AA men with high PSA translate to worse clinical outcomes.

CHAPTER 3

ChicagO Multiethnic Prevention And Surveillance Study (COMPASS): increased response rates among African American residents in low socioeconomic status neighborhoods

ABSTRACT

BACKGROUND: Previous studies examining determinants of bio-specimen research participation among minority participants have focused on individual-level barriers and facilitators. Neighborhood-level contextual factors may inform bio-specimen research participation, possibly through social norms and the influence of social views and behaviors on the perspectives of neighbors.

METHODS: In a Chicago study of predominantly African American (AA) participants that utilized door-to-door recruitment by predominantly minority status interviewers and $50 compensation for research participation including bio-specimen collection, we examined associations between census tract-level socioeconomic status (SES) on bio-specimen research participation at the address level, after adjustment for summarized address-level data on households, interviewers, and design characteristics.

RESULTS: We achieved response rates of 30.4% for non-AA addresses and 58.0% for AA addresses, with as high as 80.3% response among AA addresses in low SES neighborhoods. In fully adjusted models of AA addresses in the original target sample, we observed 3.06 times the odds of participation for AA addresses in low SES neighborhoods relative to AA addresses in average SES neighborhoods (odds ratio(OR)=3.06; 95% confidence interval (CI)=2.20-4.24).

Conversely, for non-AA addresses we observed no difference in the fully adjusted odds of participation in low vs. average SES neighborhoods (OR=0.94; 95% CI=0.71–1.25).

CONCLUSIONS: Our findings suggest that door-to-door recruitment and financial compensation may be effective strategies to recruit traditionally under-represented racial/ethnic minorities for bio-specimen research in low SES neighborhoods in Chicago. Future studies may further elucidate best practices to improve bio-specimen research participation among minority populations.

BACKGROUND

Minority representation of participants and bio-specimens in clinical and epidemiological research is a growing national priority in the United States [85]. The African American (AA) population comprises 14% of the US population [86], is characterized by greater levels of genetic diversity than non-African populations [87], and continues to experience health disparities across the lifespan relative to non-Hispanic (NH) White populations; including higher mortality from cancer, cerebrovascular and heart disease [88-92]. However, AA participants and bio-specimens are under-represented in medical research involving genetics, including approximately 6.0% of cancer clinical trials enrollees in ClinicalTrials.gov [93], and <10% of bio-samples in The Cancer Genome Atlas [94-96]. Observational research involving bio-specimens is hampered by low response rates among AA participants [97-99], which precludes stratified analyses, and may provide a potential threat of non-response bias. Recent cross-sectional studies among AA participants that have examined willingness to participate in

biobanking or genetics studies have also suffered from low response rates ranging from 10% to 32% [97, 100].

Individual-level factors previously found to be associated with bio-specimen research participation include degree of trust towards researchers, cash remuneration, discomfort with needles, altruism, and personal salience of medical research [94, 97-99, 101-106]. Individual-level factors previously found to decrease the likelihood of bio-specimen research participation include AA race/ethnicity, younger ages, and limited knowledge about bio-specimen research [98, 99, 103]. However, evidence regarding race/ethnicity has been mixed [94, 106]. Mistrust of medical professionals among AA persons due to historical racism and institutional discrimination are perceived barriers for AA representation in bio-specimen research [96, 98, 104]. However, a study conducted in Washington, DC found that the association between AA race/ethnicity and research participation was explained by bio-specimen knowledge, which was the only statistically significant determinant after multivariable adjustment; suggesting that race/ethnicity may cease to be associated with bio-specimen research participation after accounting for bio-specimen knowledge [103]. Moreover, bio-specimen research participation rates may be improved by tailoring recruitment strategies to specific racial/ethnic groups, including concordance of interviewer race/ethnicity and providing bio-specimen education to community residents [103, 107].

Neighborhood contextual factors underlie many health behaviors and health disparities, which may extend to disparities in bio-specimen research participation [2, 80, 108-116]. As one possible mechanism for how neighborhood-level social determinants of health may impact bio-specimen research participation, psychological research posits that behavioral norms may be

developed and transferred through observation and verbal communication including positive or negative reinforcement [117], and these social interactions/ behavioral norms occur within neighborhoods where individuals reside [118, 119]. One previous study of predominantly white participants (<4% AA) found that residence in high level educational attainment zip codes is associated with increased willingness to participate in a bio-specimen study [120]. However, it is unclear whether this finding is applicable to potential AA participants. In order to examine the potential association of neighborhood-level factors and bio-specimen research participation, we conducted a cross-sectional study in the context of recruitment for a new cohort in predominantly AA communities in Chicago. The study used door-to-door recruitment by predominantly minority status interviewers, provided $50 compensation for participation, and gathered data on responders and non-responders at an address level.

METHODS

The Chicago Multiethnic Prevention And Surveillance Study (COMPASS) is a population-based longitudinal cohort study with ongoing recruitment. COMPASS is designed to identify etiologic associations and opportunities for disease prevention – including exposure assessment, early detection, screening, interventions, and survivorship evaluations [27]. The present study summarizes a COMPASS Phase I recruitment assessment of study feasibility and recruitment strategies for the larger cohort study using a predominantly minority status interviewer team and community engagement activities. The census tract was the primary sampling unit (PSU). Census tracts, by design, are generally homogenous with respect to

population size. The original study design included approximately 120 census tract study areas (~15% of Chicago census tracts). We selected specific census tracts in order to confer the racial/ethnic distribution desired for recruitment (including over-sampling of AA participants). A two-stage cluster sampling approach was used: sampling at the census tract level in the first stage to sample tracts that would allow interviewers to efficiently contact households by minimizing travel time and cost; and randomly sampling households within tracts in the second stage to maximize study efficiency while minimizing costs. We used the Stata module *gsample* (Jann, B. 2006) to randomly select the census tracts and addresses within blocks.

Trained interviewers were provided with a list of potentially eligible participants compiled from commercially available address lists from the United States Postal Service's Address Management System and demographic data for addresses from commercial sources: NFocus Consulting Inc© [121] and Valassis® [122]. The lists of potentially eligible participants provided partial coverage within the selected census tracts. The recruitment approach was not nested and potential participants at identified addresses were recruited even if they were not on the original vendor list. Within buildings, multiple potential households and units were recruited. Within households, multiple potential participants were approached. Within and across households, multiple interviewers conducted recruitment. In addition to recruitment from the compiled sampled list of addresses, there was a supplementary snowball sample, in which participants were able to refer friends and family who may have been interested.

Interviewers went door-to-door during the daytime, Mondays through Fridays and select Saturdays, and would recruit all eligible persons within a given household or set of households from a given address. Interviewers recorded the approach date, approach outcome (no contact

made, refused participation, revisit planned, all scheduled interviews completed, and no one eligible), notes on refusal and/ or eligibility, and approach date. Individuals were considered eligible for inclusion in COMPASS if they were a resident of the Chicago metropolitan area, age 35 years or older, male or female, English or Spanish speaking, competent to give consent, and permanent resident or citizen of the US. For the purposes of this Phase I study, we only considered addresses with completed contact attempts, which we defined as addresses where at least 3 approaches were made and/ or an interview that included bio-specimen contribution was successfully completed. COMPASS was approved by the institutional review board (IRB) of the University of Chicago Biological Sciences Division [http://bsdirb.bsd.uchicago.edu]. The $50 compensation, also approved by the IRB, was consistent with studies that have required similar and substantial time input and bio-specimen collection from participants.

Interviewer, household, and design characteristics

We consolidated our dataset to the addresses for all building types (single family, multi-unit, etc.) using a long-to-wide transform. This transformation generated summarized data for interviewer-, household-, and design factors at the address level. Interviewer-level factors were based on the interviewer with the most approaches to the address (age, sex, race/ethnicity). Household-level factors were the potential participant characteristics from both the vendor list and the participant data from recruited subjects, which were summarized as the average household data at the address unit level (mean age [continuous], predominant race/ethnicity [categorical], majority interviewer-household concordant on race/ethnicity [yes, no, no majority

for household and/or interviewer]). Design factors were the household units within an address (1, 2-3, and 4+), and whether the address was in the original target sample from the vendor contact or part of the snowball sample.

Neighborhood characteristics

Neighborhood SES was defined as a time-invariant measure of neighborhood SES developed and made publicly available by the authors of Miles et al. For this measure, neighborhood SES was defined at the census tract level on a scale from 0 to 100 with 50 being the national average. An unconstrained single factor model was used, according to the equation (1 x [ln{Median Household Income}]) + (-1.129 x [ln{% Female-Headed Households}]) + (-1.104 x [ln{% Workers 16 years or older who are unemployed}]) + (-1.974 x [ln{% of households in poverty}]) + 0.451 x (1 x[%high school grads but not bachelors holders] + 2 x [%bachelors holders]) [123]. We categorized these census tract-level neighborhood SES data into quintiles of neighborhood SES at the Chicago area level. We separately defined neighborhood SES categories based on cores/clusters of neighborhood SES as average, low, and high using the local Getis-Ord G* statistic [124]. The local G* statistic represents the degree to which the neighborhood characteristic of that tract is more similar (high or low) to the characteristics of the neighboring tracts than would be the case under spatial randomness [125]. Tracts were considered neighboring if they shared an edge with the focal tract. We defined neighborhood SES categories with different levels of statistical significance: a pseudo P-Value<0.05 with randomization of 999 permutations as the analytical measure; and a separate

measure with 99,999 permutations and a pseudo P-value<0.0001 for a robustness check. Local G* statistics for each tract were calculated and neighborhoods were categorized using GeoDa 1.12 [125].

Outcome

Our outcome was defined as whether one or more participant was enrolled at the address (yes/no). Participants completed a ~1-hour interview and contributed bio-specimens, including blood, urine, and saliva.

Statistical Analyses

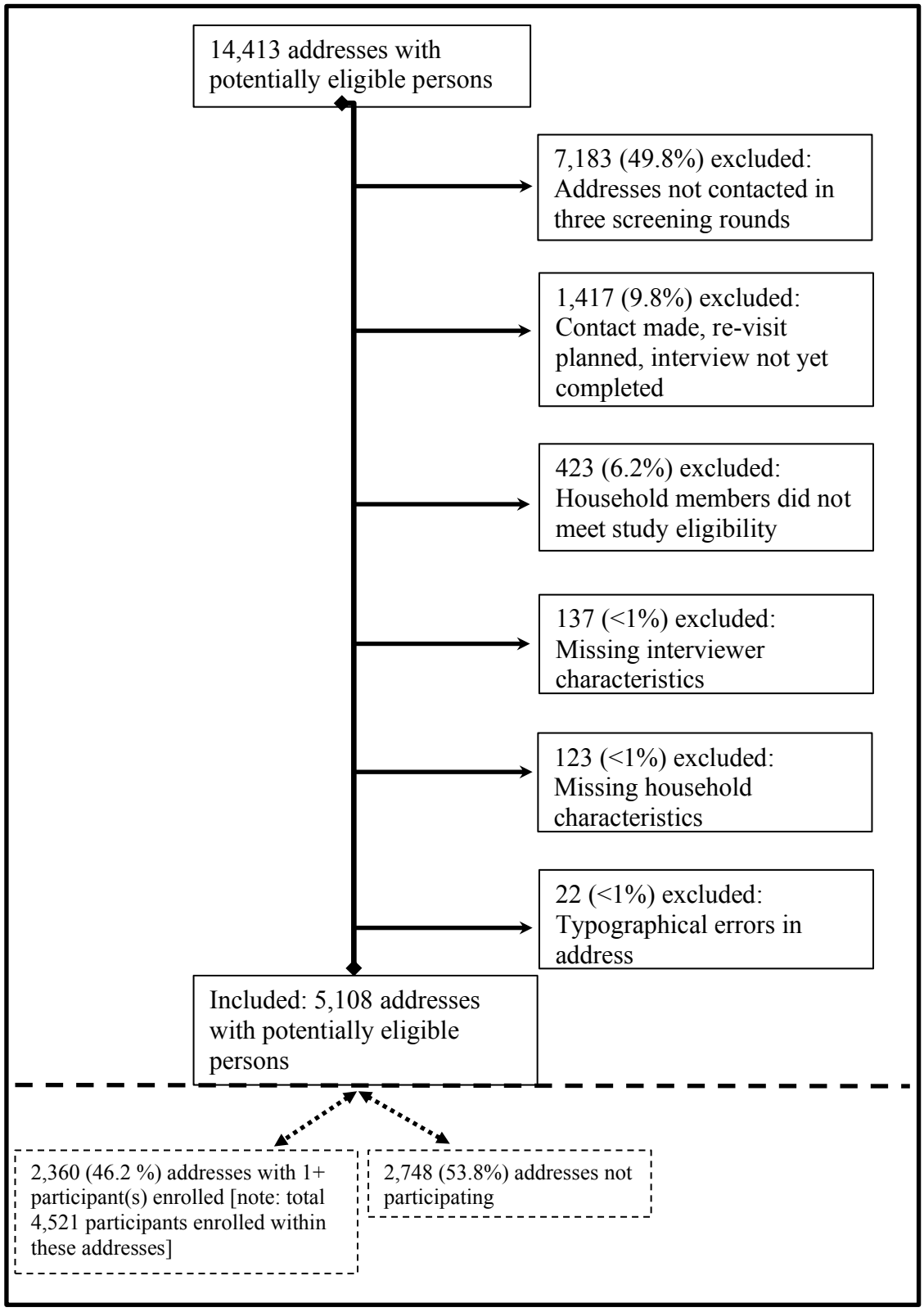
We used chi-square statistics to generate descriptive characteristics by household-, interviewer-, and design factors, for whether 1+ participant was enrolled at the address or not. We also used multivariable logistic regression analyses to examine the association between neighborhood-level factors (separately and combined) and bio-specimen research participation, adjusting for design, interviewer, and household factors. To examine the robustness of our main neighborhood-level findings to different classifications of neighborhood level measures, we performed sensitivity analyses of our final models using the three neighborhood SES classifications described above. To assess whether measured characteristics modified the neighborhood level effects of interest, we performed sensitivity analyses by separately stratifying our full model according to predominant interviewer age (<40, 40+ years), predominant

interviewer race/ethnicity (AA, NH White, and Hispanic), predominant household age (<55, 55+ years), predominant household race/ethnicity (AA, NH White, and Hispanic), and whether the address was in the original sample (yes/ no). In our multivariable logistic regression models, we calculated odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was defined at a nominal $P < 0.05$. All analyses were conducted in SAS 9.4 (Cary, NC).

RESULTS

A flow diagram of the study sample is presented in **Figure**. Of 14,413 addresses with potentially eligible participants from two commercial vendors and participant referral, we excluded: 7,183 (49.8%) not contacted by interviewers in three screening rounds; 1,417 (9.8%) with contact made and re-visit planned, but interview not yet completed; 423 (6.2%) with household members who did not meet eligibility criteria; 137 (<1%) with missing information on interviewer; and 22 (<1%) with typographical errors in address. Our study included 5,108 addresses with potentially eligible persons. Of those addresses, 2,748 (53.8%) refused actively or passively and 2,360 (46.2%) had 1 or more participants enrolled. All 5,108 addresses were included in our analysis, with 4,521 participants total within those participating addresses. Differences in addresses approached in all three screening rounds vs. less than three screening rounds were observed by neighborhood SES category, with the lowest inclusion among addresses in high SES neighborhoods (24.6%) and the highest inclusion among addresses in low SES neighborhoods (47.8%) (P<0.001).

Figure 14: Flow diagram of study sample



The 19 interviewers were of mean age 44.1 (standard deviation=15.5), with 11 females (57.9%), and a diverse racial/ ethnic composition of predominantly minority status (11 AA (57.9%), 6 Hispanic (31.6%), 1 Asian (5.2%), and 1 NH White (5.2%)). Descriptive characteristics of the study sample are presented in **Table 10**. Of the 5,108 addresses approached, 2,923 (57.2%) were comprised of predominantly AA households. Descriptive household, interviewer, design and neighborhood characteristics of addresses by whether at least one participant was enrolled within addresses were statistically significantly different for each factor included in the analysis (all p-values <0.001). Of note, response rates varied across predominant household race/ethnicity, with 58.0% of AA addresses and 30.4% of non-AA addresses enrolling 1+ participant. Response rates also varied by neighborhood SES, with 57.3% of low neighborhood SES addresses, 41.4% of average neighborhood SES addresses and 32.2% of high neighborhood SES addresses enrolling 1+ participant. Approximately 80.3% of AA addresses in low SES neighborhoods participated.

Table 10: Descriptive household, interviewer and design characteristics of 5,108 addresses in Chicago study, by whether one or more participant was enrolled in the study

Address level characteristics	1+ participant enrolled at address				Total
	No		Yes		
	n	Row%	n	Row%	
Design characteristics					
Address units (apartments) approached					
1	1,385	54.6	1,153	45.4	2,538
2-3	1,183	57.8	863	42.2	1,513
4+	180	34.4	344	65.7	1,057
$\chi 2$ P-value	<0.001				
Original target sample					
Yes	555	25.3	1,639	74.7	2,194
No	2,193	75.3	721	24.7	2,914
$\chi 2$ P-value	<0.001				

Table 10 continued.

Address level characteristics	1+ participant enrolled at address				Total
	No		Yes		
	n	Row%	n	Row%	
Interviewer characteristics					
Predominant interviewer age (majority; years)					
<30	664	73.5	239	26.5	903
30 to <40	899	60.4	589	39.6	1,488
40 to <50	247	35.5	448	64.5	695
50 to <60	401	41.4	567	58.6	968
60+	537	51.0	517	49.1	1,054
χ2 P-value	<0.001				
Predominant interviewer sex (majority)					
Female	1,598	51.7	1,492	48.3	3,090
Male	1,003	55.3	810	44.7	1,813
No majority	147	71.7	58	28.3	205
χ2 P-value	<0.001				
Predominant interviewer R/E (majority)					
African American	1,609	51.4	1,524	48.6	3,133
Non-Hispanic White	165	37.3	277	62.7	442
Hispanic	835	64.6	457	35.4	1,292
Asian	10	19.6	41	80.4	51
No majority	129	67.9	61	32.1	190
χ2 P-value	<0.001				
Household characteristics					
Household age (mean; years)					
<30	<10	~	<10	~	17
30 to <40	150	31.5	326	68.5	476
40 to <50	719	52.6	647	47.4	1,366
50 to <60	640	45.5	768	54.6	1,408
60+	1,231	66.9	610	33.1	1,841
χ2 P-value	<0.001				
Household race/ ethnicity (majority)					
African American	1,227	42.0	1,696	58.0	2,923
Non-Hispanic White	796	71.4	319	28.6	1,115
Hispanic	472	66.9	234	33.1	706
Asian	63	91.3	<10	8.7	69
Other/unknown	19	39.6	29	60.4	48
No majority	171	69.2	76	30.8	247
χ2 P-value	<0.001				
Interviewer and household concordant on race/ ethnicity (majority)					
No	1,093	55.9	861	44.1	1,954
Yes	1,366	50.0	1,367	50.0	2,733
No majority	289	68.7	132	31.4	421
χ2 P-value	<0.001				

Table 10 continued.

Address level characteristics	1+ participant enrolled at address				Total
	No		Yes		
	n	Row%	n	Row%	
Neighborhood characteristics					
Neighborhood socioeconomic status (SES)◦					
Average	1,884	58.6	1,333	41.4	3,217
Low	710	42.7	954	57.3	1,664
High	154	67.8	73	32.2	227
$\chi 2$ P-value	<0.001				
Total	2,748	53.8	2,360	46.2	5,108

◦ Categories defined as cores or clusters of similar census tracts in geographic and feature space by Local G* statistic at the Chicago area level using 999 permutations test with pseudo P-value <0.05 and queen contiguity, using 2010 Census tract boundaries

~ Statistic suppressed due to cell frequency <10

Table 11 presents results from the multivariable logistic regression analyses for neighborhood characteristics with outcome of bio-specimen research participation within addresses (yes/no), among the 5,108 addresses. In fully adjusted models, AA addresses had 2.19 times the odds of participation as NH White addresses (OR= 2.19; 95% CI=1.91-2.60). Relative to addresses located in average SES neighborhoods, addresses in low SES neighborhoods had 2.23 times the odds of participation (95% CI=3.50–7.78), and addresses in high SES neighborhoods had 0.30 times the odds of participation (95% CI=0.21–0.42), after full adjustment for household, interviewer, and design factors.

Table 11: Logistic regression analyses with outcome of bio-specimen research participation within addresses (yes/no) among addresses approached in Chicago study sample, adjusting for design, interviewer, household, and other neighborhood-level factors. Models are stratified by address type (predominantly African American [AA] households and/ or not predominantly AA households) and only include addresses in the original target sample●

Characteristics of addresses	Only predominantly AA addresses, original target sample only			
	1+ participant enrolled at address		OR	(95% CI)
	No	Yes		
Design characteristics				
Address units (apartments) approached				
1	518	66	1.00	(Reference)
2-3	380	197	3.52	(2.46-5.02)
4+	29	98	17.4	(10.1-29.8)
Interviewer characteristics				
Predominant interviewer age (majority; years)	[continuous]		1.00	(0.98-1.01)
Predominant interviewer sex (majority)				
Male	113	110	1.00	(Reference)
Female	737	232	0.35	(0.22-0.54)
No majority	77	19	0.20	(0.10-0.41)
Predominant interviewer race/ ethnicity (majority)				
Non-Hispanic White	46	35	1.00	(Reference)
African American	760	218	1.25	(0.63-2.49)
Hispanic	89	75	2.72	(1.23-6.01)
Asian	<10			~
No majority	28	20	2.27	(0.89-5.79)
Household characteristics				
Predominant household age (mean; years)	[continuous]		0.99	(0.98-1.00)
Neighborhood characteristics				
Neighborhood SES◦				
Average	774	171	1.00	(Reference)
Low	153	190	3.06	(2.20-4.24)
High	<10			~

Table 11 continued.

Characteristics of addresses	Predominantly non-AA addresses, original target sample only			
	1+ participant enrolled at address		OR	(95% CI)
	No	Yes		
Design characteristics				
Address units (apartments) approached				
1	630	93	1.00	(Reference)
2-3	552	206	2.80	(2.10-3.70)
4+	84	61	4.59	(2.97-7.09)
Interviewer characteristics				
Predominant interviewer age (majority; years)	[continuous]		1.00	(0.99-1.01)
Predominant interviewer sex (majority)				
Male	799	168	1.00	(Reference)
Female	403	181	2.13	(1.43-3.16)
No majority	64	11	1.27	(0.55-2.90)
Predominant interviewer race/ ethnicity (majority)				
Non-Hispanic White	117	50	1.00	(Reference)
African American	362	149	0.51	(0.26-1.02)
Hispanic	690	136	0.49	(0.24-0.98)
Asian	<10			~
No majority	91	12	0.15	(0.05-0.39)
Household characteristics				
Predominant household age (mean; years)	[continuous]		1.01	(1.00-1.02)
Neighborhood characteristics				
Neighborhood SES◦				
Average	739	241	1.00	(Reference)
Low	488	104	0.94	(0.71-1.25)
High	39	15	0.77	(0.40-1.48)
Total	927	361		

◦ Categories defined as cores or clusters of similar census tracts in geographic and feature space by Local G* statistic at the Chicago area level using 999 permutations test with pseudo P-value <0.05 and queen contiguity, using 2010 Census tract boundaries

~ Statistic suppressed due to cell frequency <10

Table 12 presents results from the fully adjusted multivariable logistic regression analyses jointly stratified by whether the address was part of the original or snowball sample, and whether the address was or was not a predominantly AA address. Statistically significantly high odds of participation in low SES neighborhoods relative to average SES neighborhoods were driven by predominantly AA addresses (OR=4.13; 95% CI=3.30-5.16), with statistically

significantly high odds in both the original and snowball samples (all P-values <0.01). However, no difference in odds of participation were observed among predominantly non-AA addresses in low SES neighborhoods relative to those in average SES neighborhoods after full adjustment (OR=1.02; 95% CI=0.81-1.29). In fully adjusted models including only AA addresses in the original target sample, we observed 3.06 times the odds of participation in low SES neighborhoods relative to AA addresses in average SES neighborhoods (OR=3.06; 95% CI=2.20-4.24). In fully adjusted models including only non-AA addresses in the original target sample, we observed no difference in the fully adjusted odds of participation in low vs. average SES neighborhoods (OR=0.94; 95% CI=0.71–1.25). Conversely, statistically significantly low odds of participation for addresses in high SES neighborhoods were driven by addresses that were not predominantly AA, with 0.20 times the odds of participation relative to predominantly non-AA addresses in average SES neighborhoods (95% CI=0.14-0.31).

Table 12: Logistic regression analyses with outcome of bio-specimen research participation within addresses (yes/no), among addresses approached in Chicago study sample. Models are adjusted for design, interviewer, household, and other neighborhood-level factors

Characteristics of addresses	Only predominantly AA addresses, original target sample only			
	1+ participant enrolled at address		OR	(95% CI)
	No	Yes		
Design characteristics				
Address units (apartments) approached				
1	518	66	1.00	(Reference)
2-3	380	197	3.52	(2.46-5.02)
4+	29	98	17.4	(10.1-29.8)

Table 12 continued.

Characteristics of addresses	Only predominantly AA addresses, original target sample only			
	1+ participant enrolled at address		OR	(95% CI)
	No	Yes		
Interviewer characteristics				
Predominant interviewer age (majority; years)	[continuous]		1.00	(0.98-1.01)
Predominant interviewer sex (majority)				
Male	113	110	1.00	(Reference)
Female	737	232	0.35	(0.22-0.54)
No majority	77	19	0.20	(0.10-0.41)
Predominant interviewer race/ ethnicity (majority)				
Non-Hispanic White	46	35	1.00	(Reference)
African American	760	218	1.25	(0.63-2.49)
Hispanic	89	75	2.72	(1.23-6.01)
Asian	<10			~
No majority	28	20	2.27	(0.89-5.79)
Household characteristics				
Predominant household age (mean; years)	[continuous]		0.99	(0.98-1.00)
Neighborhood characteristics				
Neighborhood SES◦				
Average	774	171	1.00	(Reference)
Low	153	190	3.06	(2.20-4.24)
High	<10			~

Characteristics of addresses	Predominantly non-AA addresses, original target sample only			
	1+ participant enrolled at address		OR	(95% CI)
	No	Yes		
Design characteristics				
Address units (apartments) approached				
1	630	93	1.00	(Reference)
2-3	552	206	2.80	(2.10-3.70)
4+	84	61	4.59	(2.97-7.09)
Interviewer characteristics				
Predominant interviewer age (majority; years)	[continuous]		1.00	(0.99-1.01)
Predominant interviewer sex (majority)				
Male	799	168	1.00	(Reference)
Female	403	181	2.13	(1.43-3.16)
No majority	64	11	1.27	(0.55-2.90)
Predominant interviewer race/ ethnicity (majority)				
Non-Hispanic White	117	50	1.00	(Reference)
African American	362	149	0.51	(0.26-1.02)
Hispanic	690	136	0.49	(0.24-0.98)
Asian	<10			~
No majority	91	12	0.15	(0.05-0.39)

Table 12 continued.

Characteristics of addresses	Only predominantly AA addresses, original target sample only			
	1+ participant enrolled at address		OR	(95% CI)
	No	Yes		
Household characteristics				
Predominant household age (mean; years)	[continuous]		1.01	(1.00-1.02)
Neighborhood characteristics				
Neighborhood SES◦				
Average	739	241	1.00	(Reference)
Low	488	104	0.94	(0.71-1.25)
High	39	15	0.77	(0.40-1.48)
Total	927	361		

◦ Categories defined as cores or clusters of similar census tracts in geographic and feature space by Local G* statistic at the Chicago area level using 999 permutations test with pseudo P-value <0.05 and queen contiguity, using 2010 Census tract boundaries
~ Statistic suppressed due to cell frequency <10

Upon further investigation, recruitment within high SES neighborhoods was found to be mostly comprised of addresses that were part of the snowball sample (73.0%). Robustness checks based on different measures of neighborhood-level factors produced broadly similar results (**Table 13**). Removing leverage points and large residuals did not substantively affect findings.

Table 13: Logistic regression analyses for neighborhood characteristics with outcome of bio-specimen research participation within addresses (yes/no), among 5,108 addresses approached in Chicago study sample. Models are adjusted for design, interviewer, household, and other neighborhood-level factors ●

Characteristic	1+ participant within the address		OR	(95% CI)
	No	Yes		
Local G at Chicago level using 99,999 permutations; pseudo P-value <0.0001*				
Neighborhood socioeconomic status (SES)[1]				
Average	2,484	1,944	1.00	(Reference)
Low	264	407	1.79	(1.46-2.20)
High	-	<20		~
Local G at Chicago level using 999 permutations; pseudo P-value <0.05*				
Neighborhood SES [2]				
Average	1,884	1,333	1.00	(Reference)
Low	710	954	2.23	(1.91-2.60)
High	154	73	0.30	(0.21-0.42)
Quintiles at the Chicago level				
Neighborhood SES [3]				
Quintile 1 (Low)	264	424	1.00	(Reference)
Q2	578	771	1.23	(0.96-1.57)
Q3	1,617	933	0.38	(0.30-0.47)
Q4	289	217	0.51	(0.37-0.69)
Q5 (High)	-	<20		~
Total	2,748	2,360		

● Interviewer-level factors: interviewer with the majority approaches at the address unit level (age (continuous), sex, race/ ethnicity). Household-level factors: average potential participant characteristics at the address unit level (mean age (continuous), predominant race/ ethnicity (categorical), majority interviewer-household concordant on R/E (yes, no, no majority for household and/or interviewer)). Design factors: potential participants within addresses (continuous) and whether the address was in the original target sample from the vendor contact list (yes/no), using 2010 Census tract boundaries

1. Categories defined as cores or clusters of similar census tracts in geographic and feature space by Local G* statistic at the Chicago area level using 999 permutations test with pseudo P-value <0.05 and queen contiguity, using 2010 Census tract boundaries

2. Categories defined as cores or clusters of similar census tracts in geographic and feature space by Local G* statistic at the Chicago area level using 999 permutations test with pseudo P-value <0.05 and queen contiguity, using 2010 Census tract boundaries

3. Categories defined as quintiles of nSES at Chicago area level, using 2010 Census tract boundaries

~ Statistic suppressed due to cell frequency <20

DISCUSSION

There is longstanding concern about low research study participation rates in epidemiological studies in general [101, 107, 126] and for bio-specimen research among AA participants in particular [103]. In order to examine determinants of bio-specimen research participation among potential AA participants, we conducted a study of an ongoing population-based cohort in Chicago that used a door-to-door recruitment strategy by predominantly minority status interviewers during the day-time and provided $50 in compensation, which was considered an appropriate and non-coercive compensation by the IRB. We examined associations between neighborhood-level factors on bio-specimen research participation within addresses, adjusting for interviewer, household, and design characteristics. In our fully adjusted models, we observed that residence in addresses within neighborhoods of low SES was associated with increased odds of bio-specimen research participation for AA addresses. Findings from our study suggest that it may be possible to recruit traditionally under-represented racial/ethnic minorities for bio-specimen research in Chicago, with door-to-door recruitment and financial compensation to participants.

To our knowledge, this is the first study to examine the association between small-area level (census tract or block group) features of the neighborhood context and bio-specimen research participation, as well as the first study of its kind among predominantly AA addresses. In our study, which provided $50 compensation to participants, we observed higher response rates for AA addresses in low SES neighborhoods. This result differs from a recent study in which higher self-reported willingness to participate in a bio-specimen research study was observed among respondents within Zip codes of higher educational attainment. Several design

features differed between this San Diego Blood Bank study and ours: the sociodemographic characteristics of the population base (predominantly White population vs. predominantly AA population); the method of recruitment (email vs. door-to-door in-person recruitment); financial compensation ($0 vs. $50); demands of time (5 minutes vs. ~1 hour); demands of bio-specimen collection (no vs. yes); demands of sensitive information (limited sensitive information vs. detailed sensitive information) [120]. Further work is necessary to inform potential differences in determinants of bio-specimen research participation between predominantly White and predominantly AA populations.

Our findings may help to clarify the previously mixed evidence for the individual-level effect of AA race/ethnicity on bio-specimen research participation [94, 98, 99, 103, 106]. According to previous qualitative research, some AA persons hold the view that bio-specimen research "[benefits] white populations, while minority groups have been unjustly used as "lab rats""[98] – possibly reflecting mistrust following mainstream media coverage about the development of the HeLa cell line [127]. However, previous evidence also suggests that bio-specimen knowledge moderates racial/ ethnic disparities in bio-specimen research participation [103]. A recent qualitative examination of interviewer-reported factors of research participation in this COMPASS Phase I study found that interviewer race and skills were interviewer-perceived facilitators and that fear of the blood draw and mistrust of medical researchers were interviewer-perceived barriers [27, 28]. These perceptions from our field staff are consistent with findings from the present study, which together suggest that culturally competent door-to-door recruitment with financial compensation and education to community members and potential participants may be an effective strategy for bio-specimen research participation among AA

participants. Additional research in other regions and with other design features may help to confirm and clarify the results presented here.

One possible mechanism for our observed results could be that low neighborhood SES served as a surrogate for low individual SES and hence potential participants residing in low SES neighborhoods were more motivated by the $50 compensation than potential participants residing in neighborhoods of average neighborhood SES. This is a sensitive issue that is ethically complex. Importantly, our recruitment strategy incorporated bio-specimen research education within both the community engagement and individual participant levels as integral aspects of protecting the welfare, rights and privacy of human subjects. The $50 compensation in our study was approved by the IRB as consistent with studies that have required similar time input and bio-specimen collection from participants. A related but possibly distinct mechanism for our observed findings may be the increased availability of unemployed potential participants physically located at the address during the day/ time of interviewer approaches. Low SES neighborhoods may also be a surrogate for population bases with low employment. Among COMPASS Phase I participants, approximately 81% self-reported that they were not currently working full-time. Moreover, increased potential participant availability to interviewers in low SES neighborhoods presumably increased the opportunities for recruitment contact relative to potential participants who were full-time employees in average and high SES neighborhoods. An additional proposed mechanism is the possibility that social interactions and behavioral norms that occurred within neighborhoods where individuals resided had an impact on the willingness for bio-specimen research participation.

Our study is strengthened by the geographically and socio-culturally diverse Chicago setting with address information that was used to link participants and non-participants with geo-spatial data at a small-area census tract level. Furthermore, our recruitment strategy emphasized cultural competence training and implementation of interviewers alongside active community engagement from our institution including conversations with community block clubs, Aldermen, and community-based police in targeted tracts. Chicago is the third largest city in the US, with approximately 2.7 million residents in 2014 [80]. While our findings are provocative, we suggest that they be interpreted as specific to our recruitment strategy, compensation, time/ bio-specimen demands for participants, and population base. Chicago has been characterized by unique historical, cultural, and social conditions, as well as specific geospatial differences, particularly for segregated AA neighborhoods [8, 14].

A limitation of studies examining research study participation is the lack of individual-level data from non-responders [114]. Our study lacked individual-level data from non-responders, as well as household-level data on potentially important characteristics such as SES. Our measures may be a surrogate for individual- and/or household-level unmeasured income and employment status. Nevertheless, geospatial methods to elucidate features of the small-area level social environment are useful in research when a population is non-responsive, hard to find, and/or to help quantify potential self-selection bias [114-116, 128]. An additional limitation of our study is that we did not collect information on point of contact for referrals ("who referred who"), which may have been used to inform a network analysis of social connections within communities. Additionally, our reported response rates were at an address level and do not reflect response rates at an individual level.

Another limitation of our study is our inability to completely control for interviewer-level features of the research recruitment strategy and successes that are missing or not captured in the COMPASS household database. In particular, we were unable to measure interviewer's recruitment perceptions in different communities or tracts in order to examine how such perceptions may have impacted interviewer recruitment strategies. These implicit factors may have impacted the interviewer approach and communications, as well as the communities where interviewers focused their efforts. By anecdote there was an incident where a COMPASS interviewer of minority race/ethnicity was approached by the police in a more affluent community because of a call by a concerned resident who was suspicious about the interviewer's door-to-door activity. This suggests that the mechanism by which contextual factors may have improved research participation in minority communities may have been complex and due to the interplay of individual-, household-, interviewer-, and contextual factors. Furthermore, our household database relied on interviewers for quality data collection. Our method of consolidating interviewer-level factors to the address and tract level partially reduced the threat of potential differential bias by interviewer data collection.

Our study is limited by the choice of census tracts to define neighborhoods in our analysis. Sociodemographic features such as SES impact outcomes at various levels of spatial aggregation from household, street, block group, tract, and above, and may vary for different communities, risk factors, and outcomes [80]. It is possible that the administrative geographic units in our study may not have effectively captured neighborhood boundaries. We partially minimized the threat this posed to our estimates by smoothing the analytical contextual measures based on the characteristics of the neighborhood features in a census tract's neighbors.

Nevertheless, further work may elucidate whether contextual features impact bio-specimen research participation at differing levels of geographic detail. Additionally, the time-invariant measure of neighborhood SES variable that we used was originally designed for use with 2000 census boundaries [123], which differ slightly from the 2010 boundaries in our study. We did not deem these changes to substantively impact our analysis.

Our findings suggest that characteristics of the neighborhood SES context, possibly as a surrogate for individual SES, influence bio-specimen research participation in Chicago. Efforts to include a sufficient representation from minority populations in clinical research [2, 85] would benefit from careful attention to study design, sampling frame and potential differential sociodemographic and contextual-level factors [2]. Our study suggests that enriching research studies with information on the small-area level neighborhood context may elucidate bio-specimen research participation and help to tailor effective recruitment strategies to specific households and neighborhoods. Results from this study may fuel future work on bio-specimen research to elucidate best practices for improving bio-specimen research participation among minority populations.

CHAPTER 4

Cigarette smoking history, current use of other tobacco products including e-cigarettes, and current use of marijuana impact serum prostate-specific antigen levels among African American men of predominantly low socioeconomic status in Chicago

ABSTRACT

BACKGROUND: Prostate specific antigen (PSA) is a well-established predictor of aggressive prostate cancer. African American (AA) men experience disparities in prostate cancer aggressiveness and outcomes, yet are under-represented in research involving PSA. Factors that impact increased serum PSA among AA men are largely unknown. In particular, we were interested in the associations between cigarette smoking history, other current tobacco use including e-cigarettes, and current marijuana use on PSA levels.

METHODS: We conducted a cross-sectional study among 928 AA men of predominantly low socioeconomic status (SES) with clinical laboratory testing of serum PSA from COMPASS (Chicago Multiethnic Prevention And Surveillance Study). We examined the associations between self-reported cigarette smoking pack-years, current use of other tobacco products, and current regular marijuana use on PSA in multivariable logistic regression models with outcome of PSA 4.0+ ng/ mL (yes/ no) and linear regression models with outcome of increasing PSA (continuous), adjusting for age, marital status, individual and neighborhood SES, self-reported health, hypertension medication, body mass index (BMI), health insurance type, and visits to

doctor in last 12 months (quintiles). Additionally, we stratified fully adjusted models by age (40 to 55 years and >55 years).

RESULTS: Our sample was comprised of AA men who were predominantly not working full-time (81.9%), earning <$20,000 (73.3%), on Medicaid, other government supported insurance or uninsured (87.2%), and residing in the three lowest quintiles of neighborhood SES (90.1%). Among participants, 13.5% reported >1 pack-years of cigarette smoking, 9.8% reported other current tobacco use, and 20.2% reported current regular marijuana use. In fully adjusted multivariable logistic regression models including 430 men aged 55+ years with reference groups of never cigarette smokers, and not currently using other tobacco products and marijuana, respectively, we observed suggestive evidence that odds of elevated PSA was increased five-fold among cigarette smokers with >1 pack-years (odds ratio [OR]=5.03; 95% confidence interval [CI]=1.56-16.20; P=0.007), increased two-fold among other current tobacco users (OR=2.49; 95% CI=0.83-7.50; P=0.105); and decreased three-fold among current marijuana users (OR=0.28; 95% CI=0.08-0.99; P=0.047).

CONCLUSIONS: Cigarette smoking pack-years, other current regular tobacco use, and current regular marijuana use may impact serum PSA in AA men. Serum PSA may be an inappropriate bio-marker for prostate cancer risk among current marijuana users. Future longitudinal cohort studies with sufficient representation from AA men, multi-level exposure assessment of individual and neighborhood factors, and outcomes data may elucidate whether cigarettes, other tobacco products and/ or marijuana impact prostate cancer pathogenesis.

BACKGROUND

Prostate-specific antigen (PSA) is a glycoprotein molecule involved in liquefaction of seminal fluid [58]. Sociodemographic and anthropometric factors associated with increasing PSA include advanced age, AA race, low body mass index (BMI) and larger height [82]. Known clinical correlates of serum PSA include larger prostate volume, as well as inflammation, infection, trauma, and medical procedures involving the prostate gland [61-66]. Increased PSA is a strong predictor of aggressive prostate cancer [59, 60, 129-131]. Relative to non-Hispanic White (NHW) men, African American (AA) men with prostate cancer have higher PSA [32-34], greater overall tumor volumes per ng/mL of serum PSA [35], and experience more than twice the prostate cancer mortality [30]. Despite prostate cancer disparities, AA men are less likely to be informed about the option of a PSA test, less likely to report a PSA test in the past year [132], less likely to use primary care [133], and are under-represented in academic research involving PSA measurements [73, 129, 131, 134, 135]. AA men are exposed to disproportionately high levels of comorbid conditions that impact PSA levels including obesity [136], hypertension and hypertension medication such as statins, thiazide diuretics [137], as well as social and environmental stressors such as low SES and residence in resource poor communities [1, 45, 138].

Prostate cancer disparities among the AA population are likely due to complex biological, socioeconomic, and socio-cultural determinants underlying disparities in presentation, diagnosis, treatment, and survival [36]. A recent population-based cancer registry study of 17,787 AA and 112,591 NHW men diagnosed with prostate cancer from 2004-2013 in California suggested that disparities in prostate cancer aggressiveness at diagnosis were due to high PSA

rather than Gleason grade or clinical stage, with evidence that age at diagnosis and neighborhood socioeconomic status (SES) were the primary contributors to racial/ ethnic disparities. However, this study lacked exposure data on individual SES and behavioral risk factors. Hence, it is unclear whether disparities in prostate cancer aggressiveness at diagnosis reflected differences in biology as opposed to differences in general male health, and/ or risk factors among men residing in low SES neighborhoods (chapter 2).

Americans of low individual SES and those residing in lower SES neighborhoods are more likely than those of higher individual and/ or neighborhood SES to smoke cigarettes heavily [139, 140], less likely to use electronic cigarettes (e-cigarettes) or premium cigars [141], and more likely to use marijuana [142, 143]. These factors may have an impact on prostate cancer risk [144-147]. However, to our knowledge, no previous studies have examined the impact of these behavioral factors on PSA levels in a non-screening population among a sample with sufficient representation from AA men of predominantly low SES. In order to examine the association between cigarette smoking, other tobacco use, and marijuana use on serum PSA levels among 928 AA men of predominantly low SES, we conducted a cross-sectional study with clinical laboratory testing of serum PSA in Chicago Multiethnic Prevention And Surveillance Study (COMPASS).

METHODS

COMPASS is a population-based longitudinal cohort study with ongoing recruitment. COMPASS is designed to accrue multiple decades of follow up to identify etiologic questions

and opportunities for disease prevention [27]. We previously reported on features of research study participation in COMPASS. Recruitment strategies included a predominantly minority status interviewer team and the census tract as the primary sampling unit (PSU). We previously reported that COMPASS participants were more likely than non-participants to reside in census tracts of lower neighborhood SES (chapter 3).

We conducted clinical laboratory testing of bio-specimens (including total PSA) using 0.5cc of blood stored in gold top vacutainer tubes (SST-Serum separator) using blood samples collected from the first 954 AA men enrolled in COMPASS. We excluded 2 participants with previous prostate surgery (<1%), 3 with very high PSA values above 25 ng/ mL that skewed the distribution (<1%), 4 who reported use of asterides (<1%), and 15 who resided in census tracts outside of the City of Chicago (1.6%). In total, we included 928 AA men in our analysis. Our human subjects research study protocol was approved by the institutional review board (IRB) of the Biological Sciences Division at the University of Chicago.

Participant characteristics

Participant characteristics were obtained based on self-report, direct measurement, and indirect measurement. Self-reported characteristics included exposure variables for behavioral factors (cigarette smoking history, other tobacco use, and current marijuana use), and co-variables previously suggested to be associated with PSA levels and/ or exposure variables including age, sociodemographic factors (marital status, SES), healthcare utilization factors (health insurance provider type and visits to doctor in last 12 months), and co-morbidities (self-

reported health and hypertension medication). Additional co-variables included BMI, which was obtained by direct height and weight measurement, individual SES, and neighborhood SES, which was assigned to participants based on the census tract of their residential address.

Neighborhood SES was defined as a time-invariant measure of neighborhood SES developed and made publicly available by the authors of Miles et al. For this measure, neighborhood SES was defined at the census tract level on a scale from 0 to 100 with 50 being the national average. An unconstrained single factor model was used, according to the equation (1 x [ln{Median Household Income}]) + (-1.129 x [ln{% Female-Headed Households}]) + (-1.104 x [ln{% Workers 16 years or older who are unemployed}]) + (-1.974 x [ln{% of households in poverty}]) + 0.451 x (1 x[%high school grads but not bachelors holders] + 2 x [%bachelors holders]) [123]. The analytical measure was defined as quintiles of neighborhood SES based on the distribution of the Chicago metropolitan area level.

Individual SES was defined using a composite of education, employment status, and income developed by the US Department of Justice [148]. We ascertained visits to doctor in last 12 months based on response to three items, which we combined and categorized into quintiles ('during the past 12 months, how many times have you seen a doctor or other health care professional about your health at a... doctor's office or clinic', '…hospital emergency room', '…home or some other place'). We ascertained hypertension medication based on a detailed questionnaire and interviewer request for the participant to show medications and supplements. Hypertension medication was defined as generic blood pressure medication terms, as well as specific hypertension medications such as Hydrochlorothiazide and Lisinopril. We ascertained

health insurance type based on response to a single item measure ('what kind of health insurance or health care coverage do you have?').

We ascertained cigarette smoking history based on response to 13 items, including 2 items on smoking history ('Do you currently smoke cigarettes [NOT including pipes, snuff, chewing tobacco, or any other forms of tobacco besides cigarettes]?' and 'did you ever smoke cigarettes regularly?') and 11 items on pack-years for ever smokers that included average per day cigarette consumption currently and in the past. We ascertained current marijuana use based on response to a single item measure ('do you currently smoke marijuana?'). We ascertained other current tobacco use based on response to a single item measure ('do you use any of the other following tobacco products regularly now? (select all that apply)', separately including 6 categories of 'Cigar', 'E Cigarette' (the two most common responses), 'Pipe', 'Snuff', 'Chewing Tobacco', and 'Hookah').

Statistical analyses

We conducted analyses for two outcomes: 1) binary PSA as <4 or 4+ ng/ mL and 2) continuous PSA. Descriptive analyses were conducted to assess the relationship between each exposure variable and co-variable and PSA, using chi-squared p-values for binary PSA and one-way analysis of variance (ANOVA) for continuous PSA. We examined the associations between self-reported cigarette smoking history, current use of other tobacco products, and current use of marijuana on PSA, controlling for co-variables in multivariable logistic regression models with outcome of binary PSA and general linear models (GLMs) with outcome of PSA. Models were

fully adjusted for age, marital status, individual and neighborhood SES, self-reported health, hypertension medication, BMI, health insurance type, and visits to doctor in last 12 months. Given the latency of known smoking factors on disease risk later in life, we stratified our models by age (40 to 55 years and >55 years). Age 55 years was selected for stratification due to PSA screening guidelines that consider this age cutoff to be clinically significant. We further conducted sensitivity analyses examining different age cutoffs (<45 and 45+, <50 and 50+, and <55 and 55 to 69 years). Additionally, for robustness tests, we developed a third set of analyses with natural log-transformed PSA as the outcome (continuous) using the same approach as for untransformed PSA as the outcome. We considered a nominal $P<0.05$ as statistically significant for all analyses. All regression analyses were conducted using SAS version 9.4 (Cary, NC).

RESULTS

The study sample of AA men was predominantly low SES (77.6%), on Medicaid, other government supported insurance or uninsured (87.2%), and residing in the lowest three quintiles of neighborhood SES (90.1%). Elevated PSA 4+ ng/ mL was observed for 68 AA men (7.3%). Mean PSA for the study sample was 1.51 (standard deviation[SD]=2.28). Statistically significant differences in elevated PSA 4+ ng/ mL were observed across categories of age ($P<0.001$) and cigarette smoking history ($P<0.01$). Among never smokers, <5% had elevated PSA whereas 13.6% of smokers with >1 pack-year had elevated PSA. Statistically significant differences in continuous PSA increases were observed across categories of age ($P<0.001$) and other current tobacco use ($P<0.05$). Among other current tobacco users, mean PSA=1.98 (SD=3.62). A

statistical trend was observed between current marijuana use and decreased PSA elevation (P=0.073). Among current marijuana users, <5% had elevated PSA (**Table 14**).

Table 14: Participant characteristics and mean prostate-specific antigen (PSA) level among 928 African American (AA) men in Chicago.

Participant characteristic	PSA			
	n	Col %	Mean PSA	St. Dev.
Age§				
Age (years)				
40 to <45	108	11.6	0.99	0.94
45 to <50	176	19.0	0.97	1.06
50 to <55	213	23.0	1.42	2.31
55 to <60	196	21.1	1.69	2.44
60+	235	25.3	2.07	2.98
χ_2 P-value1				<0.001
One-way ANOVA P-value2				<0.001
Sociodemographic factors§				
Socioeconomic status (SES)				
Low	720	77.6	1.53	2.39
Middle	148	15.9	1.47	1.96
High	<10			~
Missing	53	5.7	1.34	1.63
χ_2 P-value1				0.82
One-way ANOVA P-value2				0.90
Marital Status				
Single, never Married	450	48.5	1.34	2.07
Married	158	17.0	1.57	2.21
Living with Partner	53	5.7	1.70	1.77
Separated	74	8.0	1.50	2.56
Divorced	156	16.8	1.93	2.99
Widowed	34	3.7	1.22	1.32
χ_2 P-value1				0.18
One-way ANOVA P-value2				0.18
Co-morbidities				
Overall health, 10-point score†				
Quintile 1 (Low)	185	19.9	1.86	2.98
Q2	71	7.7	1.45	1.64
Q3	168	18.1	1.36	2.05
Q4	286	30.8	1.47	2.09
Q5 (High)	218	23.5	1.37	2.17
χ_2 P-value1				0.53
One-way ANOVA P-value2				0.19

Table 14 continued.

Participant characteristic	PSA			
	n	Col %	Mean PSA	St. Dev.
Body mass index (BMI)				
Underweight	40	4.3	1.32	0.91
Normal weight	314	33.8	1.50	2.23
Overweight	294	31.7	1.69	2.50
Obese	240	25.9	1.25	1.89
Missing	40	4.3	1.81	3.58
χ_2 P-value[1]				0.24
One-way ANOVA P-value[2]				0.21
Hypertension medication				
No	608	65.5	1.53	2.46
Yes	320	34.5	1.45	1.89
χ_2 P-value[1]				0.91
One-way ANOVA P-value[2]				0.60
Healthcare utilization factors§				
Health insurance provider type				
Medicaid	306	33.0	1.37	1.75
Uninsured	223	24.0	1.32	1.98
Other govt supported	273	29.4	1.65	2.61
Private or single payer	119	12.8	1.85	3.06
Missing	<10			~
χ_2 P-value[1]				0.85
One-way ANOVA P-value[2]				0.17
Visits to doctor in last 12 months				
Quintile 1 (Low)	183	19.7	1.67	2.82
Q2	108	11.6	1.86	2.95
Q3	231	24.9	1.28	2.06
Q4	220	23.7	1.39	1.83
Q5 (High)	186	20.0	1.56	1.94
χ_2 P-value[1]				0.49
One-way ANOVA P-value[2]				0.16
Contextual factors				
Neighborhood socioeconomic status (SES), quintile◦				
Quintile 1 (Low)	313	33.7	1.52	2.20
Q2	326	35.1	1.58	2.41
Q3	197	21.2	1.41	2.31
Q4	87	9.4	1.36	2.06
Q5 (High)	<10			~
χ_2 P-value[1]				0.42
One-way ANOVA P-value[2]				0.85
Lifestyle factors§				
Cigarette smoking history				
Never	198	21.3	1.40	2.04
0 to 1 pack-year	605	65.2	1.47	2.27
>1 pack-year	125	13.5	1.86	2.64
χ_2 P-value[1]				0.01
One-way ANOVA P-value[2]				0.17

Table 14 continued.

Participant characteristic	PSA			
	n	Col %	Mean PSA	St. Dev.
Other current tobacco use●				
No	837	90.2	1.45	2.08
Yes	91	9.8	1.98	3.62
χ^2 P-value[1]				0.16
One-way ANOVA P-value[2]				0.04
Current marijuana use				
No	741	79.8	1.56	2.38
Yes	187	20.2	1.27	1.84
χ^2 P-value[1]				0.07
One-way ANOVA P-value[2]				0.12
Total	928		1.50	2.28

[1]χ^2 P-values use binary PSA <4 vs. 4+ ng/ mL as the outcome. Column frequencies not provided due to <10 case counts for PSA 4+ ng/ mL in a prohibitive number of table rows.
[2]One-way ANOVA (analysis of variance) provided for continuous PSA as the outcome.
§ based on self-report
†Presented as quintiles for descriptive purposes only. Analyzed continuously.
ǂ Presented as raw scores for descriptive purposes only. Analyzed ordinally.
◦ Quintiles of neighborhood-level contextual factors are modeled ordinally.
●Other tobacco use includes current regular use of E-cigarettes, cigars, pipes, snuff, chewing tobacco, and/ or hookah.

Fully adjusted logistic regression and linear regression models are presented in **Table 15**. Each additional year of age was associated with an 8% increase in odds of elevated PSA (odds ratio [OR])=1.08; 95% confidence interval [CI])=1.04-1.13; P<0.001), and an incremental mean PSA increase of 0.06 ng/ mL (β=0.06; 95% CI=0.04-0.08; P<0.001), after full adjustment. Neither individual SES nor neighborhood SES were independently associated with odds of elevated PSA or mean PSA (continuous). Incremental increases in self-reported overall health were associated with statistically significant 15% decreases in elevated PSA (OR=0.85; 95% CI=0.73-0.99; P=0.031), after full adjustment. Upon further investigation, we identified that approximately 20% of AA men who reported overall health as 1 (worst) had elevated PSA,

whereas <5% of AA men who reported overall health as 10 (best) had elevated PSA). Hypertension medication was associated with a change in mean PSA= -0.35 (95% CI=-0.71 to -0.01; P-value=0.008), after full adjustment. Relative to private insurance, statistically significant changes in mean PSA were observed among AA men who reported Medicaid (β= -0.55; 95% CI= -1.06 to -0.05; P=0.033), uninsured (β= -0.62; 95% CI= -1.16 to -0.09; P=0.023), and other government supported (β= -0.52; 95% CI= -1.03 to -0.01; P=0.047), after full adjustment. Visits to doctor in the last 12 months were also associated with lower mean PSA, with -0.14 ng/ mL change in mean PSA for each increase in quintile of visits to doctor in the last 12 months (95% CI= -0.26 to -0.01; P=0.029), after full adjustment.

Table 15: Fully adjusted logistic regression and linear regression models with outcome of total PSA (≥4 ng/ mL [yes/ no] and continuous, respectively) among 928 African American (AA) men in Chicago

Participant characteristics	Model 1		Model 2	
	OR	(95% CI)	β	(95% CI)
Age (years)	1.08	(1.04-1.13)	0.06	(0.04 to 0.08)
Marital Status				
Married	1.00	(Reference)	0.00	(Reference)
Single, never Married	0.95	(0.42-2.13)	-0.05	(-0.48 to 0.37)
Divorced	1.85	(0.80-4.30)	0.37	(-0.13 to 0.87)
Living with Partner	1.52	(0.47-4.88)	0.22	(-0.48 to 0.93)
Separated	1.03	(0.34-3.06)	-0.03	(-0.65 to 0.59)
Widowed	0.49	(0.10-2.48)	-0.66	(-1.49 to 0.17)
Refused		~	-0.20	(-2.77 to 2.37)
Neighborhood socioeconomic status (SES)	1.30	(0.98-1.72)	0.07	(-0.07 to 0.22)
Individual SES				
Low	1.00	(Reference)	0.00	(Reference)
Middle or high	1.21	(0.63-2.34)	-0.19	(-0.56 to 0.18)
Overall health, 10-point score†	0.85	(0.73-0.99)	-0.07	(-0.15 to 0.02)
Hypertension medication				
No	1.00	(Reference)	0.00	(Reference)
Yes	0.63	(0.33-1.22)	-0.35	(-0.71 to 0.01)

Table 15 continued.

Participant characteristics	Model 1		Model 2	
	OR	(95% CI)	β	(95% CI)
Body mass index (BMI)				
Normal weight	1.00	(Reference)	0.00	(Reference)
Underweight	0.27	(0.03-2.09)	-0.33	(-1.06 to 0.41)
Overweight	1.64	(0.89-3.01)	0.29	(-0.07 to 0.64)
Obese	0.69	(0.32-1.49)	-0.16	(-0.55 to 0.23)
Missing	1.16	(0.12-11.1)	0.72	(-0.5 to 1.94)
Current marijuana use				
No	1.00	(Reference)	0.00	(Reference)
Yes	0.53	(0.24-1.18)	-0.21	(-0.57 to 0.16)
Other current tobacco use●				
No	1.00	(Reference)	0.00	(Reference)
Yes	1.98	(0.91-4.32)	0.65	(0.16 to 1.14)
Cigarette smoking history				
Never	1.00	(Reference)	0.00	(Reference)
0 to 1 pack-year	1.87	(0.85-4.11)	0.11	(-0.26 to 0.48)
>1 pack-year	4.22	(1.69-10.5)	0.50	(-0.01 to 1.02)
Health insurance provider type				
Private or single payer	1.00	(Reference)	0.00	(Reference)
Uninsured	0.77	(0.30-1.99)	-0.62	(-1.16 to -0.09)
Medicaid	0.87	(0.36-2.09)	-0.55	(-1.06 to -0.05)
Other govt supported	0.70	(0.29-1.67)	-0.52	(-1.03 to -0.01)
Missing	2.76	(0.27-28.8)	-0.34	(-2.05 to 1.37)
Visits to doctor in last 12 months, quintiles	0.82	(0.65-1.02)	-0.14	(-0.26 to -0.01)

●Other tobacco use includes current regular use of E-cigarettes, cigars, pipes, snuff, chewing tobacco, and/ or hookah.

Fully adjusted logistic regression and linear regression models with outcome of elevated PSA and total PSA with a focus on lifestyle factors, stratified by age, are provided in **Table 16**. Cigarette smoking history was not associated with elevated PSA or mean PSA among 498 AA men aged 40-<55 years after full adjustment. However, among AA men aged 55+ years, those with >1 pack-year of smoking experienced a five-fold increase in odds of elevated PSA relative to non-smokers (OR=5.03; 95% CI=1.56-0.99; P=0.007), after full adjustment. This corresponded to a 0.80 increase in mean PSA (β=0.80; 95% CI= -0.05 to 1.66; P=0.064). After full adjustment for other factors examined, AA men aged 55+ years who were current users of other tobacco products had a statistically significant increase in mean PSA of 1.25 ng/ mL

(β=1.25; 95% CI= 0.27 to 2.24; P<0.05), which corresponded to an approximate 2.5-fold increase in odds of elevated PSA (OR=2.49; 95% CI=0.83-7.50; P=0.105). No difference in odds of elevated or mean PSA were observed among current marijuana users aged 40-55 years, after adjusting for other factors. However, among AA men aged 55+ years, current marijuana users experienced an approximate 72% reduction in the fully adjusted odds of elevated PSA relative to non-users (OR=0.28; 95% CI=0.08-0.99), which corresponded to an approximate change in mean PSA=-0.68 ng/ mL (95% CI= -1.41 to 0.04; P=0.065). Fewer than 5% of AA men who reported current marijuana use had a total PSA > 4 ng/ mL.

Table 16: Fully adjusted◦logistic regression and linear regression models with outcome of total PSA (≥4 ng/ mL [yes/ no] and continuous, respectively), stratified by age (y)

Participant characteristics	Age			
	40 to <55 years			
	Model 1		Model 2	
	OR	(95% CI)	β	(95% CI)
Cigarette smoking history				
Never	1.00	(Reference)	0.00	(Reference)
0 to 1 pack-year	0.99	(0.28-3.49)	-0.09	(-0.47 to 0.29)
>1 pack-year	1.60	(0.25-10.4)	-0.05	(-0.66 to 0.56)
Current marijuana use				
No	1.00	(Reference)	0.00	(Reference)
Yes	1.16	(0.36-3.71)	0.11	(-0.25 to 0.47)
Other current tobacco use●				
No	1.00	(Reference)	0.00	(Reference)
Yes	1.98	(0.54-7.23)	0.31	(-0.17 to 0.78)
Total	498			
Participant characteristics	55+ years			
	Model 1		Model 2	
	OR	(95% CI)	β	(95% CI)
Cigarette smoking history				
Never	1.00	(Reference)	0.00	(Reference)
0 to 1 pack-year	2.12	(0.73-6.21)	0.27	(-0.43 to 0.97)
>1 pack-year	5.03	(1.56-16.2)	0.80	(-0.05 to 1.66)
Current marijuana use				
No	1.00	(Reference)	0.00	(Reference)
Yes	0.28	(0.08-0.99)	-0.68	(-1.41 to 0.04)

Table 16 continued.

Participant characteristics	55+ years			
	Model 1		Model 2	
	OR	(95% CI)	β	(95% CI)
Other current tobacco use●				
No	1.00	(Reference)	0.00	(Reference)
Yes	2.49	(0.83-7.50)	1.25	(0.27 to 2.24)
Total	430			
Participant characteristics	All			
	Model 1		Model 2	
	OR	(95% CI)	β	(95% CI)
Cigarette smoking history				
Never	1.00	(Reference)	0.00	(Reference)
0 to 1 pack-year	1.87	(0.85-4.11)	0.11	(-0.26 to 0.48)
>1 pack-year	4.22	(1.69-10.5)	0.50	(-0.01 to 1.02)
Current marijuana use				
No	1.00	(Reference)	0.00	(Reference)
Yes	0.53	(0.24-1.18)	-0.21	(-0.57 to 0.16)
Other current tobacco use●				
No	1.00	(Reference)	0.00	(Reference)
Yes	1.98	(0.91-4.32)	0.65	(0.16 to 1.14)
Total	928			

◦Adjusted for age (continuous), marital status, socioeconomic status, self-reported health, body mass index (BMI), health insurance type, and visits to doctor in last 12 months (quintiles)

●Other tobacco use includes current regular use of E-cigarettes, cigars, pipes, snuff, chewing tobacco, and/ or hookah.

Robustness tests comparing the results from linear regression models with mean PSA outcome to those with natural-log transformed PSA outcome resulted in similar findings as reported here. Similarly, robustness tests with differing age cutoffs (<45 and 45+, <50 and 50+, and <55 and 55 to 69 years) resulted in similar findings as reported here.

DISCUSSION

Previously identified factors contributing to prostate cancer aggressiveness include sociodemographic factors such as race and SES, lifestyle-related factors such as smoking, history of diabetes and diet, and genetic factors [19, 36, 149, 150]. However, these associations have

largely been observed in predominantly white study populations. Little is known about factors that impact PSA levels, a marker of lethal prostate cancer, among AA men who experience the greatest risk of prostate cancer mortality. We examined the associations between cigarette smoking history, other current tobacco use including e-cigarettes, and current marijuana use on PSA levels within a sample of AA men of predominantly low SES in Chicago. Among AA men 55+ years in our sample, we found suggestive evidence that a history of smoking >1 pack-year was associated with increased odds of elevated PSA (4+ ng/ mL) relative to never smokers, other current tobacco use was associated with continuous increases in PSA levels relative to non-users of other tobacco products, and current marijuana smoking was associated with a decreased odds of elevated PSA relative to non-marijuana smokers. Future studies on whether these factors are associated with disparities in prostate cancer aggressiveness among AA men are warranted.

Cigarette smoking increases risk of lethal prostate cancer [144, 145] and may increase incident prostate cancer among those who smoke the most [145]. However, in a study that included 18.6% AA men in the National Health and Nutrition Examination Survey (NHANES), an inverse association was observed between current or former smokers and PSA levels. Our study was comprised of AA men with mean PSA level that exceeded each age-specific range reported in the NHANES study. Also, the NHANES study did not age-stratify findings, or examine pack-years of cigarette smoking to account for potential latency periods [151]. Future work may elucidate whether exposure to pack-years of cigarette smoking is associated with PSA levels, particularly in populations of men at high risk of aggressive prostate cancer, as well as longitudinal studies with cancer outcomes. Furthermore, future work examining tobacco products other than cigarettes are warranted.

To our knowledge, this is the first observational study to suggest a possible link between current marijuana use and changes in PSA levels among men 55+ years. Our findings are potentially consistent with basic science reports that marijuana reduces PSA levels *in vitro* [146]. A recent systematic review has found that exposure to cannabinoids is associated with reductions in mammalian testis size, spermatogenesis, fertilization rates, plasma concentrations of hypothalamic, pituitary, and gonadal hormones, and sexual behavior [152]. It is therefore possible that adverse effects of current marijuana use on plasma concentrations may be responsible for our findings. Separately, well-established evidence has identified that obesity contributes to decreases in PSA levels by increasing circulating plasma volumes (i.e., hemodilution of PSA), yet increases risk of aggressive prostate cancer [153, 154]. This suggests that serum PSA may not be an appropriate biomarker for aggressive prostate cancer among obese men. It is also possible that serum PSA may not be a useful biomarker for aggressive prostate cancer among marijuana users. A recent clinical case series of 4,305 men diagnosed with localized prostate cancer did not demonstrate reduced prostate cancer aggressiveness among previous marijuana users [147]. Future work should elucidate the impact of marijuana use on plasma concentrations in humans.

We are unaware of previous studies that have examined the association between the impact of visits to doctor's office/ clinics on PSA levels among men at high risk of advanced prostate cancer. In our study, we observed that AA men in higher quintiles of doctor's office or clinic visits had a relatively small (<-0.14 ng/ mL) but statistically significant decrease in PSA levels in our adjusted models, including adjustment for BMI, health insurance type and hypertension medication. Upon further investigation, we found that this finding persisted

independent of usual healthcare setting, health insurance provider type, timing of last PSA test, and timing of last digital rectal exam. It is possible that our findings may reflect differences in health-seeking behaviors, unaccounted medications, and/ or lifestyle factors not examined in our study.

Our study was strengthened by the relatively large sample of AA men of predominantly low SES – a group traditionally under-represented in research involving PSA measurements and more likely than other populations to experience prostate cancer disparities. Additionally, we tailored recruitment strategies to AA participants, including concordance of interviewer race/ ethnicity and provision of bio-specimen education to disadvantaged community residents.

Our study was subject to limitations common to observational studies. A previous COMPASS study determined an address-level response rate of 59.3% for the entire cohort, with evidence that households were more likely to enroll when they were of low neighborhood-level SES (chapter 3). Generalizability to men with different sociodemographic characteristics is unclear. Further, our findings relied on participant self-report, which may have been prone to recall bias. We minimized the threat of recall bias by study design features to maximize interviewer rapport – specifically training race-concordant interviewers with previous experience in low SES communities. Interestingly, 20.2% of our sample self-reported marijuana use, which is currently illegal in Chicago except for medical dispensaries. This improves our confidence in self-report for our sample. Nevertheless, specific measures with longer look back periods may have been particularly subject to recall bias, including healthcare utilization in the last 12 months, medical history, and medications/ treatments. Future linkage with electronic medical records (EMRs) in COMPASS will enable analyses to assess the validity of self-report for some

measures. We were further unable to account for unobserved characteristics such as plasma volume, sexual behavior and ejaculation patterns, sleep patterns, and genetic variants that may be associated with both PSA risk profile and the factors examined in our study [153, 155-158]. Our study suffered from limited statistical power to detect modest associations. Future work in Chicago may be warranted to examine the role of multi-level factors on PSA risk profile.

Conclusions

Generating knowledge about vulnerable populations is an important priority for reducing social inequities in cancer [108]. We found suggestive evidence that cigarette smoking history, other current tobacco use, and current marijuana use may impact serum PSA in AA men of predominantly low SES. Additional studies with data at individual and neighborhood levels may enable researchers to elucidate the extent to which individual and social stressors contribute to prostate cancer aggressiveness and AA health disparities. Future multi-level studies will be highly relevant for better understanding risk of lethal prostate cancer among AA men, as well as for targeting communities and individuals who may be more likely to experience benefit from PSA testing. Specifically, it is unclear whether PSA is an appropriate biomarker of prostate cancer risk among current marijuana users.

CHAPTER 5

Summary, future directions, and further considerations

This project had three primary aims: 1) to elucidate primary contributors to racial/ ethnic disparities in prostate cancer aggressiveness among 17,787 African American (AA) men and 112,591 non-Hispanic white (NHW) men diagnosed with prostate cancer in the California Cancer Registry (CCR) (chapter 2); 2) to identify whether bio-specimen research participation differed according to neighborhood-level socioeconomic status (SES) among 5,108 addresses in the ChicagO Multethnic Prevention And Surveillance Study (COMPASS) (chapter 3); and 3) to examine the impact of cigarette smoking history, current use of other tobacco products, and current marijuana use on prostate-specific antigen (PSA) risk profile in a non-screening sample of 928 AA men of predominantly low SES in COMPASS (chapter 4).

In chapter 2, we observed that racial/ ethnic disparities in prostate cancer aggressiveness in California for AA men relative to NHW men were driven by high PSA prostate cancer rather than by high gleason score grade (GS) and/ or TNM stage (stage) disease. We further characterized age at diagnosis and neighborhood SES to be primary contributors to these racial/ ethnic disparities in high PSA prostate cancer. Our finding that neighborhood SES was a primary contributor to racial/ ethnic disparities in prostate cancer aggressiveness may be particularly compelling given findings from others that the long term adverse social and health outcomes of residence in disadvantaged neighborhoods has a more pronounced effect on males than females [10, 11]. However, our findings in chapter 2 may have been driven by racial/ ethnic differences in PSA-based screening. Among men 50 years and older in a recent nationally representative

study, routine PSA testing in the past year was reported among 27.4% of AA men and 35.4% of NHW men [159]. Delayed diagnosis among AA men relative to NHW men resulting from differential screening may have had a stronger impact on high PSA prostate cancer at diagnosis than on high GS prostate cancer, which is generally considered to be less susceptible to early detection. Our binomial logistic regression findings would be more prone to exaggerated risk estimates as a result of differential early detection than our stratified IRR-based analyses for which we considered high PSA disease only (20+ ng/ mL). Our binomial logistic regression findings were also robust to a three-level categorization in a multinomial logistic regression analysis, which strengthened our confidence in the binomial logistic regression findings. Furthermore, it is not readily apparent that racial/ ethnic differences in early detection would disproportionately impact high PSA prostate cancer at diagnosis over and independent of high stage disease. Our definition of high PSA 20+ ng/ mL is much higher than the traditional 4 ng/ mL cutoff used to perform a biopsy following PSA testing. Future work is necessary to inform whether differences in PSA-based screening across AA and NHW populations result in racial/ ethnic disparities in prostate cancer aggressiveness characteristics observed at diagnosis.

Differences in the clinical course of prostate cancer have also been reported for AA men relative to NHW men. In a case series of autopsy data among Detroit men who died of causes other than prostate cancer, sub-clinical prostate cancer in AA men was observed to occur at an earlier age and with higher stage and GS. In a supplemental analysis in the Detroit SEER registry, metastatic prostate cancer occured at a 4:1 ratio among AA men relative to NHW men [160]. Some have speculated that the higher PSA levels among AA men than NHW men at diagnosis of non-metastic prostate cancer may be due to higher tumor cell burden [161]. It is

therefore uncertain whether racial/ ethnic disparities in prostate cancer aggressiveness at diagnosis are due to biological differences in clinical course and/ or non-biological contributors including screening for the early detection of prostate cancer. Importantly, our SEER study lacked individual-level data on SES and exposures including lifestyle factors. We were therefore unable to tease apart what factors were related to such racial/ ethnic disparities in prostate cancer aggressiveness among AA men and NHW men (chapter 2). Unpacking multi-level contextual factors and their sole and joint impacts on cancer outcomes requires increasingly rich datasets, analytical methods, and care in interpretation. The present projects laid the groundwork for future RESPOND studies that will elucidate multi-level factors that contribute to enduring racial/ ethnic disparities in prostate cancer aggressiveness and survival among AA men relative to NHW men using a multi-state sample. Given findings from chapter 2, we suggest that special care be given to understanding racial and ethnic disparities in high PSA prostate cancer specifically. Future RESPOND studies will focus on whether neighborhood-level factors, including racial bias and redlining in mortgage lending and a racial and ethnic typology of neighborhood composition, contribute to racial and ethnic disparities in prostate cancer aggressiveness and prostate cancer survival. Importantly, California has less variability in these measures of neighborhood-level racial residential segregation and social environment and relatively few census tracts with high levels of redlining and racial bias in mortgage lending compared to other RESPOND regions such as Louisiana and Texas. In the larger RESPOND study, we will be particularly interested in understanding what features of the racial residential segregation and social environments contribute to differences in tumor biology and survivorship for AA men and NHW men, after adjusting for neighborhood level SES. We conceptualize that

more exposure to institutional discrimination for AA men residing in neighborhoods identified as high in redlining may impact individual beliefs about medical providers, which in turn may contribute to racial/ ethnic disparities in utilization and/ or effectiveness of cancer care.

RESPOND is well-positioned to elucidate how racial/ ethnic differences in first course of prostate cancer treatment are associated with racial/ ethnic disparities in prostate cancer mortality. RESPOND will include a diverse sampling of states and will include data on approximately 149,358 AA men and 667,590 NHW men. A recent study in California identified that contributors to racial and ethnic disparities in prostate cancer mortality include first course of treatment and marital status (possibly as a surrogate for adherence to prostate cancer treatment and social stress) [23]. However, cancer registry studies without linkage to a claims database only include data on first course of treatment and are therefore unable to evaluate potentially relevant patterns of care, including inadequate screening and delayed presentation. A recent multiple cohort study of 306,100 patients with prostate cancer found no racial disparities in stage-for-stage prostate cancer-specific mortality in healthcare systems with similar access to care [74]. Presumably, the differences in quality of care contribute to a mortality gap [74,6-7].

In chapter 3, we observed that our design of door-to-door recruitment and $50 compensation for research participation including bio-specimen collection was particularly successful among AA addresses (80.3% participation among AA addresses located in low SES neighborhoods). After controlling for design, interviewer, and household factors, we observed an approximate 3-fold increase in the odds of research participation for AA addresses in low SES neighborhoods relative to AA addresses in average SES neighborhoods. The mechanism for these findings is unclear, but may have been due to increased motivation by the $50

compensation for potential participants in low SES vs. average SES neighborhoods, and/ or increased at-home availability of potential participants who were unemployed. Future work on the bioethical implications of financial compensation for bio-specimen research participation may be appropriate. Previous work has suggested that patient perspectives on whether or not they should be paid for participation in bio-banks reflect mixed opinions about the role of compensation in bio-specimen research [162]. A recent online experiment of willingness to participate in a blood draw study with compensation amount as an experimental condition ($25, $100, and $1,000), found that higher payments increased interest in participation as well as information searching and vigilance [163]. These studies suggest that compensation for bio-specimen research involves a complex set of issues that is ethically complex. On the one hand, it would be unethical to provide different compensation amounts to different individuals for the same involvement, yet on the other hand it is unclear if modest compensation for bio-specimen research may be coercive for individuals in financial need. Our study was performed consistent with guidance from the IRB, including community engagement with a focus on bio-specimen education for individuals and communities. The $50 compensation was deemed by the IRB to be consistent with studies that have required similar and substantive time input and bio-specimen collection from participants in the University's catchment area. Although our team is not comprised of bio-ethicists, findings from this study may fuel subsequent work to improve minority participation in academic research, including supporting communities to become well-informed about bio-specimen research. We also observed an unexpected interviewer gender effect, with improvements in research participation by female interviewers who recruited non-AA addresses but improvements in research participation for male interviewers who recruited

AA addresses. We were unsure whether this finding reflected potential interviewer bias in data collection for a handful of interviewers in our study. However, we found that these findings were robust to removing the most over- and under-performing interviewers. Future work may elucidate whether male interviewers may experience improvements in recruiting AA addresses located in low SES neighborhoods for bio-specimen research. Importantly, our main findings for chapter 3 are potentially promising for improving minority representation in academic research, as they suggest the potential opportunity to improve bio-specimen research in traditionally under-represented communities with appropriate design features in place; including compensation for participants and community engagement with bio-specimen research education.

Finally, in chapter 4, we observed suggestive evidence in a sample of AA men of predominantly low SES that cigarette smoking history, current use of other tobacco products, and current marijuana use were related to changes in serum PSA levels. It is unclear whether these findings have clinical relevance for prostate cancer risk profiles, since PSA 4+ ng/ mL has a relatively low sensitivity and specificity. Findings from a trial of 18,882 healthy men 55 years of age or older reported that only 20% of men who tested positive actually had the disease, and 6% of men who do not have prostate cancer falsely tested positive at this threshold [164]. Other clinical correlates of serum PSA include larger prostate volume, inflammation, infection, trauma, and medical procedures involving the prostate gland [61-66]. Future work in prospective cohort studies with information on prostate cancer outcomes are therefore critical to assess whether the factors examined in our study may contribute to an adverse prostate cancer risk profile in AA men of predominantly low SES. Our findings in chapter 4 that current marijuana use decreases

serum PSA requires further consideration in terms of clinical implications. In particular, it is unclear how this finding may help to inform individual patient-physician decision-making about, and interpretation of, PSA testing. It is possible that a lower PSA cut-off for biopsy should be considered for current marijuana users, and also that magnetic resonance imaging (MRI) may be a useful diagnostic tool for this current marijuana users. Similar strategies have been suggested for clinical populations with low PSA levels that are not necessarily indicative of a low prostate cancer risk profile [165].

Taken together, our results enhance and inform one another. Our findings from chapters 2 and 4 suggest that PSA is an important biomarker for understanding aggressive prostate cancer occurrence among AA men of predominantly low SES. Furthermore, our findings from chapter 3 suggest that AA households in low SES neighborhoods provide a potentially promising opportunity to improve population health through academic research, disease prevention, and community engagement. Although provocative, our findings beg the question of whether PSA is a biomarker of male health generally, or prostate cancer aggressiveness specifically. While future work to better understand PSA as a biomarker is critical, the findings revealed in this dissertation point to a broader set of implications on health equity. In this regard, we emphasize the elegant work from Dess et. al. that demonstrated racial/ ethnic disparities for AA men in health systems with unequal access to treatment but no such racial/ ethnic disparities for AA men in health systems with equal access [74,75]. The author of this dissertation suggests that these findings provide a compelling case for ameliorating health disparities by improving equitable access to quality cancer care and academic research. Furthermore, long-term trajectories of neighborhoods that have been disadvantaged by redlining in mortgage lending provide important insights into

how the social and built environments of neighborhoods have developed, and how individuals within disadvantaged neighborhood environments have experienced adverse health outcomes. The author considers historical racism and institutional discrimination to be at least partially responsible for persistent racial/ ethnic disparities in prostate cancer aggressiveness currently experienced by AA men; particularly those who reside in low SES neighborhoods. Our conceptual framework emphasizes that multi-level social stressors are embodied across the life-course to impact prostate cancer aggressiveness; and hence, effective amelioration of racial/ ethnic disparities will likely require multi-level approaches to take the whole person into account – his ancestry, social environment, lifestyle factors, and life-course. For example, the well-established findings that marital status impacts cancer aggressiveness and mortality, possibly through social support mechanisms that impact inflammation and adherence to treatment, suggest that strengthening family systems may be an important component of multi-level strategies to improve equity in individual and population health. In conclusion, the author of this work suggests that evidence-based, multi-level health promotion and disease prevention strategies, including evidence-based multi-level health policy reforms, are necessary to address disparities in prostate cancer aggressiveness and mortality.

Some have argued for PSA screening guidelines that are specific to AA men [161, 166]. In average risk populations, a single serum PSA test measured at age 60 years is associated with a man's lifetime risk of death from prostate cancer (area under the curve=0.90). Although only a minority of men with PSA >2 ng/ mL will develop lethal prostate cancer, about 90% of prostate cancer deaths occur among men with PSA in this range [167, 168]. At a cutoff of 4 ng/ mL in average risk populations, the positive predictive value (PPV) for prostate malignancies is 30%.

Given that few studies have evaluated PSA test performance in AA populations, the American Cancer Society (ACS) suggested that the corresponding PPV of 59% among AA men of advanced age be interpreted with caution [169]. In average risk populations, approximately 1.3 deaths from prostate cancer per 1000 men screened at ages 55 to 69 years may be prevented over 13 years. However, PSA-based screening exposes male populations to potential harms in follow up to frequent false-positive results such as harms from diagnostic biopsies and from over-treatment. These harms include erectile dysfunction, urinary incontinence, bowel symptoms and psychological harms. In light of the lack of available evidence on the clinical utility of PSA-based screening in AA populations, the recent USPSTF recommendations did not provide specific recommendations for this high risk group but called for such additional research [68]. Future work is necessary to characterize whether screening in AA populations may have a more beneficial impact on preventing prostate cancer mortality than in average risk populations.

Our results from chapter 2 contribute to the literature by suggesting that AA men experience racial/ ethnic disparities at presentation in high PSA prostate cancer for all ages including ages <50 years relative to NHW men. Despite higher risks of disease, AA men are less likely than NHW men to be informed about the option of having a PSA test and are also less likely to have reported having had a PSA test in the past year [170]. Previously reported barriers to screening for prostate cancer among AA men include lack of access to healthcare, SES, inadequate knowledge, fear, patient-provider communication, distrust of the medical profession, and aversion to digital rectal exam [171]. Future work is necessary to characterize strategies to overcome barriers to prostate cancer screening among AA men.

The USPSTF interprets its role as focusing on evaluating the science of preventive services, yet recognizes that insurance coverage decisions involve other important considerations, including preferences of patients, clinicians, consumers, communities, special populations, purchasers, and others. Payers therefore have discretion regarding coverage for preventive services that are not grade A or grade B recommendations [172]. Therefore, AA men currently experience both a lack of scientific evidence to support their preventive needs related to prostate cancer detection as well as a concomitant lack of understanding among physicians, payers and communities about how to support their preventive care needs. These implications suggest a need for future study to examine bioethical and economic considerations for PSA-based screening guidelines that are specific to AA men, as well as strategies to increase education about PSA testing among AA men.

Our chapter 3 provides some hope that AA persons may be willing to participate in epidemiological research with certain design features in place, including bio-specimen education and community engagement. These findings help to clarify previous findings that AA persons are cautious about contributing bio-specimens to academic research [173, 99], by suggesting the possibility that distrust of the medical profession may be ameliorated by culturally competent health care professionals. The observation in chapter 2 that residence in low SES neighborhoods was associated with increased incidence of high PSA prostate cancer suggests that COMPASS represents a potentially useful resource to examine participant characteristics associated with racial/ ethnic disparities in prostate cancer aggressiveness. COMPASS is a prospective longitudinal study with ongoing recruitment and routine linkage to the population-based Illinois State Cancer Registry to ascertain invasive prostate cancer occurrence among participants.

COMPASS may therefore be useful to address evidence gaps for AA men and racial/ ethnic disparities in prostate cancer aggressiveness, in risk factor knowledge, screening, and cancer outcomes. In particular, it would be useful to examine whether routine PSA screening in COMPASS participants is associated with early detection of prostate cancer, with a focus on whether utilization of PSA screening tests has a differential impact on stage migration for AA men relative to NHW men. As mentioned above, AA men experience unique social and economic barriers to PSA screening including poor health seeking behaviors which can delay a prostate cancer diagnosis [174]. In a preliminary analysis of COMPASS participants accrued to date, we observed relatively low PSA screening rates for AA men. Specifically, among men aged 50+ years, never having a PSA test performed was self-reported among 47.7% of 1,039 AA men and 24.7% of 93 NHW men. Future work may elucidate whether racial/ ethnic in never having a PSA test performed among men aged 50+ years may be due to individual factors or other factors related to the healthcare setting.

Future COMPASS studies with data on prostate cancer occurrence among participants may be used to elucidate other non-biological contributors to racial/ ethnic differences in prostate cancer risk, including individual- and neighborhood-level social stressors. Interestingly, in a multivariable exploratory data analysis related to chapter 4, we observed a possible signal for neighborhood-level factors and their impact on free-to-total PSA ratio. However, the effect size was not large enough to be statistically significant in our relatively small sample of 135 men with elevated PSA levels. Specifically, we observed that self-reported perceived stress at home and perceived anxious/ depressed (as well as history of anxiety disorder) were associated with decreased free-to-total PSA ratio among men with elevated total PSA as a combined marker of

an adverse prostate cancer risk profile. We also observed a statistically significant inverse association between years at current residence (as a surrogate for residential stress) and total PSA in multivariable models among all 928 AA men included in the study. However, our sample was composed of AA participants residing in predominantly low SES neighborhoods and hence lacked data variability to inform a possibly informative difference in neighborhood SES. Importantly, people residing in lower SES neighborhoods are exposed to fewer smoking prevention education programs, experience poorer physical functioning, less social integration, less perceived control, greater financial strain, and poorer quality of care [12-16]. Previous research has demonstrated a cause-effect relationship between behavioral stress and prostate cancer tumor development in mice [175], as well as evidence in humans that stress-related signaling pathways at the transcription level are associated with lethal prostate cancer development [176]. At the neighborhood-level, recent evidence suggests temporal improvements from 1980 to 2010 in ameliorating the AA disadvantage due to a narrowing of the gap in neighborhood poverty between AA and other American populations [45]. Furthermore, recent evidence suggests that neighborhood characteristics influence DNA methylation of genes involved in stress response and inflammation [177]. AA men in COMPASS with more years at their current residence may be subject to lower residential stress, and fewer changes in their current life cycle, which may be related to total PSA. Future COMPASS research with prostate cancer outcomes may be used to elucidate whether perceived health and stressors and neighborhood level stressors help to inform racial/ ethnic disparities in PSA risk profile. COMPASS can take advantage of prospective study design, which minimizes the threat that self-report on measures of perceived stress and anxiety disorder would be impacted by subsequent

cancer diagnoses (i.e. recall bias). Importantly, however, the large sample size in excess of 100,00 subjects, and decades of follow up time, necessary to power the anticipated modest effect size are potentially prohibitive limitations.

Other evidence gaps that a population-based sample like COMPASS and RESPOND may help to address include biological contributors to racial/ ethnic disparities in prostate cancer risk experienced by AA men. Importantly, COMPASS has bio-specimen data that enable sequencing on an over-sample of AA men. Our future work in RESPOND will be the largest coordinated research effort of its kind and will use a multi-level framework to examine genetic contributions to racial disparities in prostate cancer aggressiveness and survival for AA men relative to NHW men. Emerging evidence suggests that African ancestry-specific germline variations may contribute to population differences in prostate cancer risk [178-182]. For example, risk variants of chromosome 8 are highly differentiated in frequency between West African and European American populations and span a fivefold range in prostate cancer susceptibility [181, 182]. Studies among men of African ancestry also support the hypothesis that genetic differences contribute to racial/ ethnic disparities in prostate cancer risk. A genome-wide association study among 3,425 AA men with prostate cancer and 3,290 AA men without prostate cancer identified 17 novel single nucleotide polymorphism (SNP) markers, including a novel risk variant on chromosome 17q21. This risk variant is associated with an OR per allele of 1.51 ($p=3.4x10^{-13}$) and is more frequent in men of African descent (~5%) than those in other populations (<1%) [178,179]. Other studies have shown a higher rate of variants among AA men in cell apoptosis genes such as *BCL2*, tumor-suppressor genes such as *EphB2*, and other genes involved in androgen biosynthesis and metabolism [183].

Findings from these projects point to potentially promising new research opportunities using multi-level data from COMPASS and RESPOND to clarify non-biological and biological contributors to racial/ ethnic disparities in prostate cancer aggressiveness and mortality experienced by AA men relative to NHW men. The observations from future work in these cohorts may fuel new interventional studies to ameliorate racial/ ethnic disparities in prostate cancer. These interventional studies may include patient navigation. Patient navigation is a novel approach to reduce racial/ ethnic and socio-demographic disparities that has not been widely applied to prostate cancer patients [184].

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