Contributions of Social Determinants of Health to Susceptibility and Severity of COVID-19 across the U.S.

I. Introduction

A recent systematic review and meta-analysis documented clear evidence that individuals of Black and Asian race and Hispanic ethnicity are more likely to be infected with SARS-CoV-2, compared to those of White race *(Scz).* Suggested underlying mechanisms explaining these disparities include comorbidities, access to healthcare resources, social determinants of health (SDOH) and occupational risk. However, data regarding both SDOH and comorbidities are often not available for the general population. The Veteran population in the United States serves as a viable racially/ethnically diverse population to study with access to extensive SDOH and health related information. There are approximately 20.4 million veterans in the U.S., comprising 7.1% of the population and 73% are over the age of 50, 12% are Black and 7% Hispanic, and 9% are female *(Pew Research)*. As of November 23, 2020, the VA healthcare system had reported testing 813,727 Veterans, with 78,356 testing positive, 13,848 hospitalized, 5,533 needing care in an ICU, 1,730 requiring mechanical ventilation, and 4,226 deaths associated with COVID-19 *(US Department of Veterans Affairs).*

Two recent national VA studies have examined potential risk factors associated with higher rates of SARS-CoV-2 infection, hospitalization and mortality. One study of 88,747 Veterans, published in *JAMA Open*, found that Black race was strongly associated with testing positive; but among those testing positive, Black race was not associated with increased mortality; key risk factors for mortality among COVID-positive Veterans, included older age, fever, and shortness of breath, but not hypertension, smoking, COPD, obesity, Black race or Hispanic ethnicity (*Ioannou).* Another study *(Rentsch)* including 5,834,543 individuals receiving care in the VA, evaluated 254,595 tested for COVID-19, of whom 16,317 tested positive and 1,057 died within 30 days of diagnosis. Again, Black individuals were more likely to be tested than those with Hispanic and White ancestry, and minorities in general were more likely to test positive, but among those testing positive, there were no differences in 30 day mortality by race/ethnicity. Thus, both studies found that relative to the baseline cohort, Black individuals had increased mortality, consistent with observations in other populations *(Price-Haywood; Yancy; Owen)*. Noted limitations with all of these studies include the omission of detailed SDOH characteristics of the population. With SARS-CoV-2 infection rates escalating, additional research is needed to better understand the underlying SDOH mechanisms potentially contributing to disparities in the impact of COVID-19 among Veterans in the United States *(Burstrom and Tao; Rollston and Galea; Abrams and Szefler)*, which can assist with developing potential outreach and intervention strategies.

Social Determinants of Health are conditions in the places where people live, learn, work and play, that affect a wide range of health risks and outcomes *(CDC)*. Healthy People 2030 uses a place-based framework that focused on five key areas of SDOH: healthcare access and quality; education access and quality; social and community context; economic stability; and neighborhood and built environment *(Healthy People).* Despite the consistent evidence demonstrating that SDOH are critical factors in predicting health disparities, very little research has examined SDOH factors as related to health in a national population, and particularly among Veterans. In 2017, the Veterans Health Administration conducted an evidence review to examine social determinants of Veterans' health *(Duan-Porter)*. This review documented that the majority of research to date on SDOH and Veterans' health focused on classic socioeconomic factors (e.g., gender, race/ethnicity, income, employment), and indicated the need for more research exploring other SDOH characteristics of the Veteran population to better

understand the impact on health behaviors, health services utilization and health outcomes in this population *(Duan-Porter; National Healthcare Quality and Disparities Report Chartbook)*.

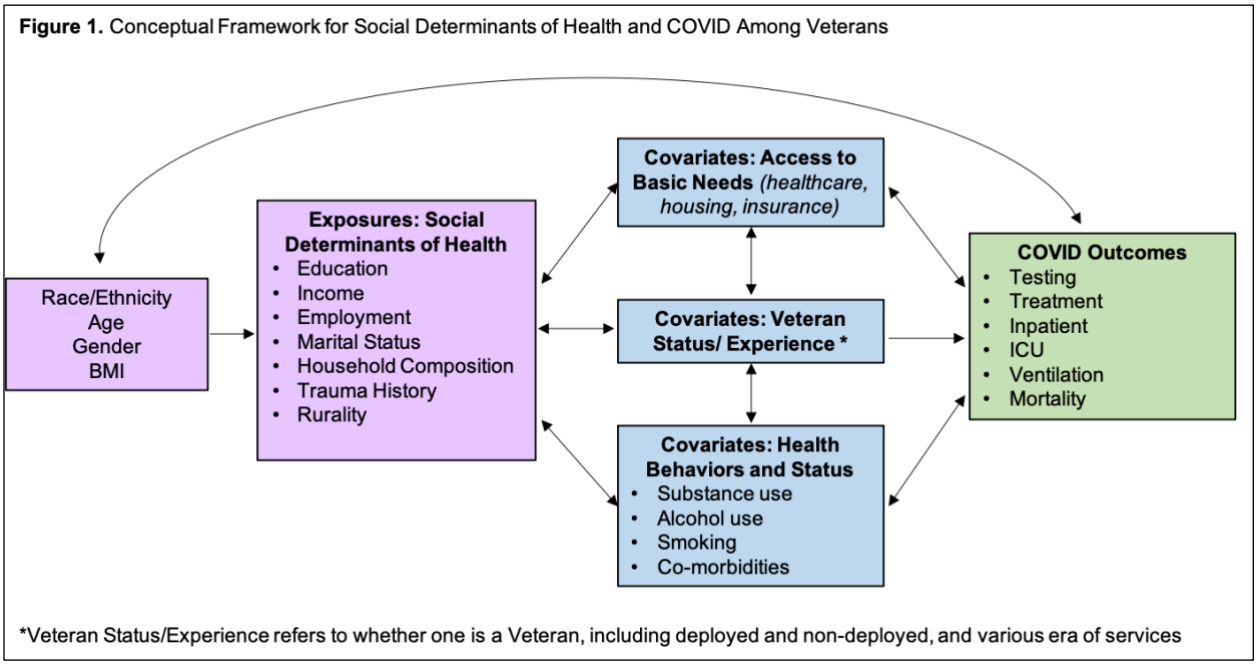
II. Specific Aims

The long term goal is to create policies and practices that mitigate the adverse impact of SDOH on health outcomes among Veterans – and the US population in general.

Specific objectives of this pilot project are to:

1) identify key SDOH constructs that influence Veterans' health;
2) examine SDOH factors influencing COVID-19 testing, treatment and outcomes in the national VA population; and
3) compare the Atlanta VA population to national data, to assist with development of pilot interventions.

Our conceptual framework is shown in Figure 1, which is adapted from the evidence-based review of SDOH factors for Veterans *(Duan-Porter)*



III. Study Methodology

A. Study Setting

The Veterans Health Administration (VHA) is one of the largest health systems in the United States and provides Veterans with a broad range of inpatient, outpatient, mental health, rehabilitation, and long-term care services, which are all linked by an electronic health record system (*Fihn*). Over 9 million Veterans each year receive care from 1,255 health care facilities, including 170 medical centers and 1,074 outpatient clinics *(Veterans Health Administration).*

Within days of the first confirmed COVID-19 cases, the VHA developed a comprehensive response and operations plan to protect Veterans and their families. Early in the COVID-19 pandemic, the VA developed a detailed "COVID-19 Response Plan". This plan included details about the necessary activities to protect Veterans and

staff from COVID-19 and ensure continuity of access to and delivery of healthcare services to Veterans. *(Veterans Health Administration – Office of Emergency Management).* Because of this planning, the VHA has not been "overwhelmed" by COVID-19, ensuring the validity of evaluation of SDOH in relation to this health problem.

B. Study Population

The study population will be based on the retrospective cohort of 4,547,853 Veterans who received primary care at the VA in 2019. This will be defined operationally as having had ≥1 primary care provider visit and ≥1 outpatient drug prescription, with known race and ethnicity, and detailed information about both important comorbidities such as hypertension, diabetes, and cardiovascular disease. These will be identified by ICD-10 and CPT codes, using the VA Phenomics Library. We will also have accurate measures of control of risk factors such as blood pressure, hemoglobin A1c, LDL cholesterol, and renal function – ideal for a rigorous retrospective cohort study. We will examine both the full cohort, and the subset included in the VA COVID-19 Shared Data Resource (SDR), which includes information about testing, hospitalization, use of the ICU, mechanical ventilation, and mortality. The SDR subset includes approximately 860,000 Veterans across the country who were "active" patients in the VA healthcare system – with at least one primary care visit in the preceding 18 months (n=710,553). Preliminary data analysis indicates that of this population, 93,021 tested positive, 15,771 of those testing positive were hospitalized, 6,190 were in the ICU, 1,845 received mechanical ventilation, and 4,615 died. This is a "live" dataset, updated daily, and we anticipate that we will be able to study SDOH in a subset of close to a million Veterans who have been tested. Baseline health and SDOH related factors in 2019 will be obtained for this cohort and we will track COVID testing and related outcomes from February 1, 2020 through December 31, 2020.

C. Data Sources

Two data sources that are both extensive and unique worldwide will be utilized for this proposed project: 1) The Corporate Data Warehouse (CDW) which is hosted in the VA Informatics and Computer Infrastructure (VINCI) will be accessed for key outcomes and covariate information. VINCI provides access to both deidentified data and statistical tools behind firewalls, and allows the export of summary statistics but not the data itself. The CDW is a repository for patient-level data aggregated from across the VHA's national health delivery system, within a business-driven logic structure that enforces higher data quality and interoperability. The CDW consolidates over sixty domains of key clinical and operational data (such as demographics, laboratory results, medications dispensed from outpatient pharmacies, immunizations, and vital signs). The CDW is one of the most formidable data aggregation efforts undertaken by a health care system. The CDW features 4,000 central processing units (CPUs), 1.5 petabytes of storage, with over twenty million unique patient records, 1,000 separate data tables, 20,000 columns, eighty billion rows, and a range of data elements. The CDW is refreshed nightly with new data, and the refresh frequency is being upgraded to every four hours, permitting "near real-time" analysis and reporting"; and 2) United States Veterans Eligibility Trends and Statistics (USVETS), a data source on all Veterans, containing 250+ variables from 35+ data sources (e.g., Department of Defense, Veterans Health Administration, National Cemetery Administration, Veterans Benefits Administration, Social Security Administration), including Veteran military history, socioeconomic status (e.g., where they live, household income, education, employment, health insurance, etc.), and utilization of VA benefits and services *(see "Additional Information" document with details regarding specific data)*. USVETS will be accessed for all of our SDOH related

constructs (exposure variables). Both of these sources are accessed by request protocols specific to each data source and our research team is experienced in using them and has been approved by the Office of Enterprise Integration to access these databases. The VA has a “Data Access Request Tracker” (DART) process for assuring that the study has IRB and VA Research & Development (R&D) Committee approval, and that all involved have VA research credentialing and human subjects protection training, and we are familiar with this.

D. Data Measures

Outcomes: We will examine five outcomes available from the CDW: 1) likelihood of being tested; 2) testing results (index date); 3) Hospitalization at the index date (positive test) or within 15 and 30 days of the index date; 4) Treatment in an Intensive Care Unit (ICU); 5) Mechanical ventilation at the index date or within 30 and 60 days; and 6) all - cause mortality within 30 days after the index date. These outcome measures are standard in the SDR and have been utilized in recent studies conducted in the VA population *(Ioannou; Rentsch).*

Exposures: The following SDOH factors will be examined as primary exposures: 1) race/ethnicity; 2) age; 3) marital status; 4) education; 5) income; 6) occupation; 7) household characteristics; 8) geography (urban/rural); 9) benefits/insurance; and 10) benefits (e.g., health insurance in addition to VA coverage; and history of estimated health care expenditures, both within and outside the VA).

Covariates: Conditions that have been associated with increased risk of severe illness from the virus that causes COVID-19 will be included as covariates and include: 1) chronic health conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, cardiovascular disease, immunocompromised state, hypertension, and diabetes, along with relevant risk factor control [blood pressure, blood glucose and hemoglobin A1c, and lipid profile]); 2) Body Mass Index; 3) health behaviors (substance abuse, alcohol use, smoking) *(CDC).*

E. Analysis

Relative risks will be calculated to measure the degree of association between each risk factor and outcome by fitting a modified Poisson regression model. The modified Poisson regression model is appropriate for a binary outcome when the error for the estimated relative risk is estimated using a robust error variance known as a sandwich estimator. We will use the SAS GENMOD procedure (SAS Institute, Version 9.4, Cary, North Carolina) to implement the regression model as previously described *(Zou)*. Risk factor selection will be driven by available knowledge from previous COVID-19 reports, biological plausibility of potential confounders and the reliability of the covariates as predictors of the outcome evaluated, using 1000 bootstrap samples *(Brieman).* Univariable analysis will include SDOH exposure factors, covariates (underlying chronic health conditions, health behaviors and laboratory measurements). Multivariable Poisson regression models for each outcome will include adjustment for demographics (model 1) to identify individual and neighborhood sociodemographic risk factors, additional adjustment for comorbid conditions (model 2) and further adjustment for SDOH (Model 3, final model). For each outcome, the relative risk and its 95% confidence interval will be calculated for each factor in the presence of the others in the final model and summarized with a forest plot. Additionally we will evaluate racial/ethnic

disparities in testing positive for COVID-19 by stratifying the final adjusted model by calendar time, geographic region (South, West, Northeast, Midwest; Region based on US census groupings) and site-level outbreak patterns (early, late, resurgent, steady, other; *Rentsch*).

Rates of COVID-19 per 1000 patients for the Atlanta VA population and national results will be estimated and compared using exact methods based on the Poisson distribution. If x is the observed number of patients with COVID-19, and P*t* the number of patients at risk (number of patients tested), the incidence rate (IR) is given by IR = x/P*t*. The 95 percent confidence interval for the incidence rate will be calculated using the methods described by Bailar and Ederer (1964). The incidence rates will be compared between 'subgroups' using the methods described by Brownlee. Specifically, an exact (significance) test will be used to compare the equality of two Poisson rates by testing whether the ratio of two Poisson rates was different from one.

Standardized incidence ratios (SIRs) for SARS-CoV-2 infection will be calculated and mapped by county. Using a Getis-Ord Gi* statistic, hotspot and coldspot analyses will be performed to indicate census tracts with significantly greater SARS-CoV-2 positive and negative patients than expected. Further stratification by racial or income distribution will be calculated.

We propose to use geographic information system tools (GIS) and geo-spatial statistical modeling to identify specific socio -environmental and -economic conditions, which may be associated with incidence of testing and clinical outcomes of SARS-CoV-2 infection. We will apply an eco-social model combined with principles of spatial diffusion to analyze our dataset. Specifically, we will focus on income, housing conditions and household crowding, and built environments. By using GIS, we will be able to link individual patient profiles, based on their specific place of residence and patient health information records, to US Census data variables related to income, crowding and housing conditions to get a better sense of a patient's community area. Combining both individual and community area variables will allow us to better understand the role a patient's socio environmental conditions play in his/her risk for infection.

IV. Anticipated Results

We hypothesize that once we account for covariates and SDOH related factors, many of the disparities that have been documented in the literature (particularly race/ethnicity) will be less significantly associated with COVID-19 morbidity and mortality.

V. Significance of Project

Results from this pilot study will provide a foundation to better understand SDOH related factors influencing COVID-19 testing, treatment and outcomes in the national VA population, a vulnerable and underexamined population. Results from this study will be of immediate interest to the VA, and will also serve as valuable pilot data for outreach and intervention studies (e.g., an R01 proposal). Specifically, future research could include conducting both quantitative (surveys) and qualitative (focus groups) research with Veterans to better understand barriers to testing and treatment, and developing and testing strategies aimed to mitigate susceptibility to and severity of the disease. This information could then be used to pilot intervention projects in the Atlanta Veterans population. Moreover, the SDOH framework developed from this project can be utilized to examine other important health care conditions prevalent in the Veteran population.

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