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Racial Disparities in COVID-19 Severity Are Partially Mediated by Chronic Stress—Evidence from a Large Integrated Healthcare System

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Abstract

Background Racial and ethnic minorities have experienced a disproportionate burden of severe COVID-19. Whether chronic stress, also disproportionately experienced by racial and ethnic minorities, explains this excess risk is unknown.

Methods We identified 9577 adults (≥ 18 years) diagnosed with COVID-19 from January 1, 2020, through September 30, 2021, enrolled in Kaiser Permanente Georgia (KPGA) with complete biomarker data. Self-reported race (Black or White) was defined from electronic medical records. Chronic stress, defined as allostatic load (AL), a composite score (scale 0–7) based on seven cardio-metabolic biomarkers, was categorized as below (low AL) or above (high AL) the median. Severe COVID-19 was defined as hospitalization or mortality within 30 days of COVID-19 diagnosis. The association between race, AL, and severe COVID-19 was assessed using multivariable Poisson regression. The mediating effect of AL was assessed using the Valeri and VanderWeele method. All results were expressed as risk ratios (RRs) with 95% confidence intervals.

Results Overall, Black (vs. White) KPGA members had an 18% excess risk of AL (RR: 1.18, 95%CI: 1.14–1.23) and a 24% excess risk of severe COVID-19 (RR: 1.24, 95%CI: 1.12, 1.37). AL explained 23% of the Black-White disparities in severe COVID-19.

Conclusions In our study, chronic stress, characterized by AL, partially mediated Black-White disparities in severe COVID-19 outcomes.

Keywords COVID-19 · Racial disparities · Mediation analysis · Chronic stress

Introduction

Racial disparities in health outcomes, including life expectancy and burden of chronic health conditions, have long been reported [1–3]. This was especially highlighted during the COVID-19 pandemic with racial and ethnic minority populations facing the greatest burden of new COVID-19 cases and the highest mortality rates [4–6]. While many acknowledge that structural racism plays a role in contributing to these health gaps, the exact mechanisms remain unclear.

Chronic stress, brought on by persistent and pervasive social and economic disadvantage, has previously been linked to poor health outcomes, and may contribute to existing racial and ethnic disparities in health [7–9]. Previous research has shown that stress is racially patterned with foreign-born Hispanic and Black individuals more likely to report more chronic stress exposure than White individuals [10, 11]. Chronic stress has also been consistently linked to increased risk of mortality [9, 12–14], depression [9, 15], metabolic and cardiovascular diseases [9, 15–17], and some infections [15, 18]. More specifically, numerous studies have found a link between stress and infection, such that many hypothesize that increased stress levels increase host susceptibility to infectious agents [19, 20]. While findings from the Common Cold Project have allowed

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researchers to identify stress and other risk factors for upper respiratory infection [21], whether chronic stress explains the excess risk of COVID-19 among racial and ethnic minorities remains unknown.

Therefore, using data from a large integrated healthcare system in the United States (US), we aimed to investigate whether chronic stress mediates the relationship between race and severe COVID-19.

Methods

Data Sources and Study Population

We identified all members of Kaiser Permanente of Georgia (KPGA) who were diagnosed with COVID-19 between January 1, 2020, and September 30, 2021 ($n=31,500$). COVID-19 was defined by a positive COVID-19 PCR test or an ICD-10 diagnosis (code U07.1, B97.29, B34.2, B97.21, or J12.81). We excluded anyone who was < 18 years at time of COVID-19 diagnosis ($n=2337$), did not identify as Black or White ($n=4650$), was missing data on sex ($n=1$), or any of the biomarkers of interest ($n=14,935$; 60.9%). Individuals with incomplete biomarker data were more likely to be men, younger, come from a neighborhood with moderately lower vulnerability and medium to higher income, have a high deductible premium, not report a history of smoking or alcohol overuse, and had fewer pre-existing comorbidities compared to those with complete biomarker data (Supplementary Table 1). Our final sample included 9577 Black or White adults with COVID-19 and complete measured biomarker data (Fig. 1).

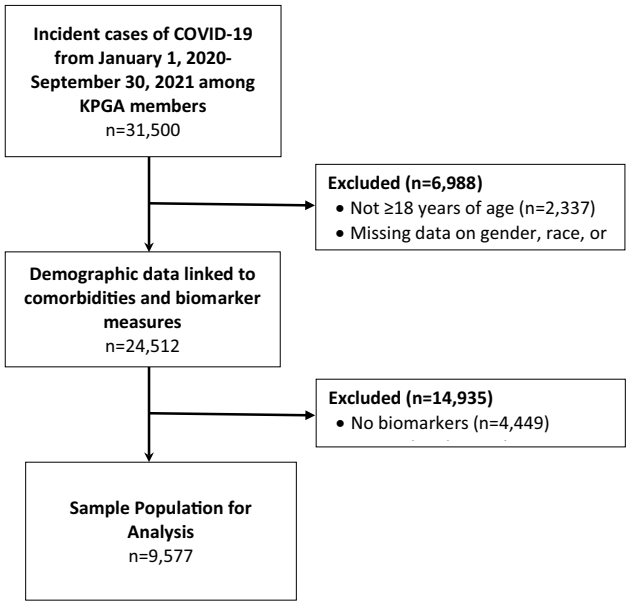

Fig. 1 CONSORT diagram – Kaiser Permanente of Georgia (KPGA) study population

Definition of Race

We characterized individuals as Black or White based on self-reported race in electronic medical record (EMR) data. Over 80% of KPGA members identify as Black or White, thus other races including Asian, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native, Multiple races, and others (defined as those who did not identify as any of the race options) were not included in the sample due to small sample sizes. For individuals with missing race, $n=316$ (3.3%), we imputed race using a probability distribution using patient zip code and surname [22]. This method of imputation has shown to have a predictive accuracy of 93% for both Black and White individuals [23]. In this study, we consider race a social construct [4, 24] and a proxy for structural racism experienced to those historically marginalized [25].

Chronic Stress: Allostatic Load

Chronic stress was measured using allostatic load (AL) and calculated based on seven cardio-metabolite biomarkers: total cholesterol, HDL cholesterol, blood pressure (BP), glycated hemoglobin (HbA1C), body mass index (BMI), albumin, and creatinine [26–29]. These biomarkers were measured within 45 days and up to 5 years before the first COVID-19 diagnosis. For individuals with multiple measurements, the most recent was used. Each biomarker was given a score: 1 for high risk, 0.5 for moderate risk, and 0 for low risk, based on current clinical guidelines (Table 1). Anti-hypertensive medication was used as a proxy for high BP. Scores were then summed to determine a total AL score, on a scale of 0–7, and categorized as below (low AL) or above (high AL) median based on the total AL score median of 2.5.

Severe COVID-19

COVID-19 severity was defined as hospitalization or mortality within 30 days of COVID-19 diagnosis. Hospitalization data was extracted from KPGA claims and billings data. Death data was extracted from a variety of sources including enrollment data, encounter data, and registry data.

Covariates

Using KPGA EMRs, we included individual-level data on age, sex, high deductible insurance plan (yes/no), smoking status, and comorbidities, including history of alcohol

Table 1 Clinically relevant biomarker cutoffs to develop AL score, a proxy for chronic stress

System	Measures	AL risk categorization	Clinical cut-off	Source
Cardiovascular	Total cholesterol	High (score 1)	≥240 mg/dL	National Cholesterol Education Program (45)
		Medium (score 0.5)	200—<240 mg/dL	
		Low (score 0)	<200 mg/dL	
	HDL cholesterol	High (score 1)	<40 mg/dL	National Cholesterol Education Program (45)
		Medium (score 0.5)	40–<60 mg/dL	
		Low (score 0)	≥60 mg/dL	
	Blood pressure [a]	High (score 1)	Taking blood pressure meds	Prescriber's Digital Reference (46)
		Low (score 0)	No reported meds	
Metabolic	Glycated hemoglobin	High (score 1)	≥6.5%	American Diabetes Association (47)
		Medium (score 0.5)	5.7–<6.5%	
		Low (score 0)	<5.7%	
	Body mass index	High (score 1)	<18 kg/m^2; ≥30 kg/m^2	Center for Disease Control (48)
		Medium (score 0.5)	25—<30 kg/m^2	
		Low (score 0)	18—<25 kg/m^2	
	Albumin [a]	High (score 1)	Outside normal range	Clinical Key (49)
		Low (score 0)	Normal range: 3.5–5.5 g/dL	
	Creatinine [a]	High (score 1)	Outside normal range	Medline Plus Medical Text (50)
		Low (score 0)	Normal range: 0.65–1.2 mg/dL	

[a]Denotes the absence of a moderate risk categorization according to current health guidelines

overuse, depression, chronic obstructive pulmonary disease (COPD), liver disease, renal disease, and coronary heart disease (CHD), at time of COVID-19 diagnoses. Comorbidities were ascertained using ICD-10-CM and ICD-9-CM codes [30–33] (Supplementary Table 2) and chosen based on a priori knowledge. Comorbidities did not include those related to the key biomarkers of interest (e.g., diabetes and HbA1c). Neighborhood-level social vulnerability index (SVI) [34] and median household income was extracted from the American Community Survey (ACS) and geocoded to patient zip codes. For all covariates, there was < 0.1% of data missing and thus we conducted a complete case analysis.

Statistical Analysis

Baseline characteristics of the study population, by race and AL status, were compared using *t*-tests for continuous variables and chi-square for categorical variables. All continuous variables were normally distributed.

To assess the association between race, AL, and severe COVID-19 (visually depicted in Supplementary Fig. 1), we employed a Poisson regression with robust error variance [35, 36]. All results were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). In a first step, we estimated the association between race and severe COVID-19 adjusting for potential confounders in a stepwise manner. Model 1 was unadjusted, Model 2 adjusted for age and sex, and Model 3 adjusted for age, sex, SVI, median household income, insurance status, smoking status, alcohol use, depression, COPD, liver disease, renal disease, and CHD. Variables were chosen for inclusion based on significant associations with the outcome in bivariable analysis, a priori knowledge, and appropriately low collinearity measures with all other covariates. All variables were retained in the model as they did not violate our cut-off of a variance inflation factor of 2.5. In a second step, we examined the association between race and AL using the same approach as above. In a third and final step, we assessed if AL mediates the association between race and severe COVID-19, using the Valeri and VanderWeele method of mediation [37] across the same three multivariable models. The percent of the race disparity attenuated by AL was derived by calculating the percent change in RR estimations from the unadjusted association of race and severe COVID-19 to the AL-adjusted race and severe COVID-19 relationship, as a fraction of the change in RR estimation over the unadjusted estimation [38].

Sensitivity Analyses

In our first sensitivity analysis, we examined the impact of AL on race and severe COVID-19 when AL was defined on a continuous scale (from 0–7). Second, we restricted our sample to those with more recent biomarker data available recorded within 2 years prior to the COVID-19 diagnosis ($n = 4987$). Third, to assess potential effect modification by sex, we stratified our models by sex to obtain sex-specific estimates. Lastly, preliminary studies have found differences

in COVID-19 severity by year of infection; thus, we stratified our models by COVID-19 pandemic era (2020 vs 2021) to obtain year-specific estimates.

All analyses were conducted via SAS v 9.4 (SAS Institute Inc.). Study ethics and research dissemination were reviewed and approved by The KPGA Institutional Review Board (IRB# 00000406) and Emory University Institutional Review Board (IRB#: STUDY00001631). This study adheres to STROBE guidelines (Supplementary Table 3).

Results

Baseline Characteristics

Among KPGA members with COVID-19 and measured biomarkers, 41.8% self-identified as White and 58.2% as Black. Black KPGA members were more likely to be women, younger, live in low-income and high social vulnerability neighborhoods, and be diagnosed with COPD, CHD, and renal disease, but less likely to report a history of smoking or alcohol overuse as compared to White members (Table 2).

Overall, 60.8% of KPGA members had a high AL risk level (i.e., above the median). KPGA members with high (vs. low) AL were more likely to Black, men, older, live in low-income and high social vulnerability neighborhoods, report a history of smoking, and be diagnosed with depression, COPD, liver disease, renal disease, and CHD (Supplementary Table 4).

Race and Severe COVID-19

Overall, 15.3% ($n=1463$) of KPGA members developed severe COVID-19, of which 87.9% ($n=1286$) were hospitalized and 12.1% ($n=177$) died within 30 days of diagnosis. Overall, 15.61% ($n=871$) and 14.8% ($n=592$) of Black and White members, respectively, had severe COVID-19. In fully adjusted models, Black KPGA members had a 24% higher risk of severe COVID-19, when compared to White members (RR: 1.24, 95%CI: 1.12, 1.37) (Table 3).

Race and Chronic Stress

Overall, 64.3% ($n=3585$) and 56.0% ($n=2238$) of Black and White KGPA members, respectively, had high AL (Supplementary Table 4). In fully adjusted models, Black members had an 18% higher risk of high AL when compared to White KPGA members (RR: 1.18, 95%CI: 1.14, 1.23) (Table 3).

Chronic Stress as a Mediator of Race and Severe COVID-19

After adjustment for AL, the relative risk of severe COVID-19 in Black vs. White KPGA members decreased from 1.25 to 1.19 (1.06, 1.34), but an excess risk remained (Table 4). Partial mediation by AL risk level explained 23% of the disparity in severe COVID-19 among Black vs. White KPGA members.

Sensitivity Analyses

The percent of Black-White disparities in COVID-19 attenuated by chronic stress was relatively similar across various AL calculation methods, populations with more recent biomarker data, sexes, and COVID-19 pandemic eras, with some exceptions (Supplementary Table 5–8). When using a continuous measure of AL risk (vs a binary measure), chronic stress explained a greater magnitude of the Black-White disparity, such that continuous AL risk explained 28% of the excess severe COVID risk in Black vs. White KPGA members vs. 23% when using binary AL (Supplementary Table 5). Similarly, when restricting our study sample to KGPA members with biomarker data recorded within 2 years of their COVID-19 diagnosis ($n=4987$), fully adjusted models yielded an overall 28% mediating effect of AL in Black vs. White members (Supplementary Table 6). Sex-stratified models showed that AL risk mediated a greater proportion of the Black-White disparity in men, such that 25% and 18% of the Black-White disparity in COVID-19 disparity was explained by AL in men and women, respectively (Supplementary Table 7). Lastly, the mediating effect of chronic stress differed throughout the COVID-19 pandemic depending on the time of infection (2020 vs 2021), such that 14% of the Black-White disparities in COVID-19 severity was explained by chronic stress in 2020, while there was no evidence of chronic stress mediation in 2021 (Supplementary Table 8).

Discussion

In our study among members of an integrated healthcare system, Black members had a 24% higher risk of severe COVID-19, and an 18% higher risk of having higher chronic stress levels at the time of COVID diagnosis, as compared to White members. Overall, 23% of the excess severe COVID-19 risk in Black adults can be explained by higher chronic stress levels. While relatively small, this proportion when translated nationally is likely to impact a significantly large number of Black individuals in the US disproportionately experiencing both chronic stress and severe COVID-19. Results from this study suggest that targeting chronic stress, and its upstream causes, may alleviate some of the excess risk of severe COVID-19 outcomes experienced by some underrepresented populations.

Our study is the first to examine chronic stress as a mediator of the relationship between race and severe COVID-19.

Table 2 Baseline characteristics of adult KGPA members with an incident COVID-19 diagnosis between 2020 and 2021, by race

Baseline characteristics	Total study population $n=9577$	Black $n=5578$ (58.2%)	White $n=3999$ (41.8%)
Sex	5,944 (62.1)	3,721 (66.7)	2,223 (55.6)
Women	3,633 (37.9)	1,857 (33.3)	1,776 (44.4)
Men			
Age, mean (SD)	52.5 (14.4)	50.6 (13.6)	55.2 (15.1)
Median household income, mean (SD)	67,165 (25,150)	59,549 (20,447)	77,780 (27,167)
Median household income	2,486 (26.0)	1,989 (35.7)	497 (12.4)
50 k or less	6,261 (65.4)	3,395 (60.9)	2,866 (71.7)
> 50 k to 100 k	706 (7.4)	168 (3.0)	538 (13.4)
> 100 k to 150 k	119 (1.2)	21 (0.4)	98 (2.5)
> 150 k			
Social vulnerability index [a]*,* mean (SD)	0.47 (0.27)	0.56 (0.25)	0.35 (0.25)
Social vulnerability index [a]	2,319 (24.2)	714 (12.8)	1,605 (40.2)
Quartile 1 (low vulnerability)	2,884 (30.1)	1,488 (26.7)	1,396 (34.9)
Quartile 2	2,473 (25.9)	1,830 (32.8)	643 (16.1)
Quartile 3	1,895 (19.8)	1,541 (27.7)	354 (8.9)
Quartile 4 (high vulnerability)			
High deductible insurance (yes)	370 (3.9)	228 (4.1)	142 (3.6)
Comorbidities			
Smoking	1,920 (20.1)	916 (16.4)	1,004 (25.1)
Alcohol overuse	492 (5.1)	255 (4.5)	237 (5.9)
Depression	3,031 (31.7)	1,556 (27.9)	1,475 (36.9)
COPD	3,384 (35.3)	1,864 (33.4)	1,520 (38.0)
Liver disease	155 (1.6)	74 (1.3)	81 (2.0)
Coronary heart disease	807 (8.4)	451 (8.1)	356 (8.9)
Renal disease	1,286 (13.4)	800 (14.3)	486 (12.2)
Chronic stress level [b]*,* mean (SD)	2.6 (1.2)	2.7 (1.1)	2.4 (1.2)
Chronic stress level [b]	3,754 (39.2)	1,993 (36)	1,761 (44)
Low AL (below median) [c]	5,823 (60.8)	3,585 (64)	2,238 (56)
High AL (above median) [c]			
Biomarkers [d]	180.8 (40.9)	179.3 (39.7)	182.8 (42.4)
Total cholesterol, mean (SD)	51.8 (15.2)	52.4 (14.8)	51.1 (15.7)
HDL cholesterol, mean (SD)	5,697 (59.5)	3,419 (61.3)	2,278 (60.0)
Blood pressure	6.0 (1.3)	6.2 (1.5)	5.9 (1.1)
Glycated hemoglobin, mean (SD)	33.2 (8.1)	34.1 (8.1)	31.8 (7.9)
BMI, mean (SD)	4.1 (0.3)	4.1 (0.4)	4.2 (0.4)
Albumin, mean (SD)	1.0 (0.7)	1.1 (0.8)	0.9 (0.4)
Creatinine, mean (SD)			

Data are *N* (%) unless otherwise stated

[a]Social vulnerability index is reported on a scale of 0–1. Categories are classified using quartiles: 0 to .2500 (lowest), .2501 to .5000 (moderately low), .5001 to .7500 (moderately high), and .7501 to 1.0 (highest)

[b]Chronic stress, as defined by AL

[c]Median allostatic load is 2.5 (range 0–7)

[d]Total cholesterol and HDL cholesterol are reported in units of mg/dL. Glycated hemoglobin is reported as a percent. BMI is reported in units of kg/m^2. Albumin is reported in units of g/dL. Creatinine is reported in units of mg/dL

Abbreviations: *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *HDL* high density lipoprotein, *KGPA* Kaiser Permanente Georgia, *SD* standard deviation, *SVI* social vulnerability index

However, several non-COVID studies have examined the effects of stress mediation on other health outcomes with similar findings. For example, in a US population, Duru et al. [13] found that AL mediated Black-White disparities in cardiovascular disease (CVD) and diabetes-related mortality among women by 71.4%, but did not explain

Table 3 Risk ratio estimations [a] of the relationship between race, COVID-19 severity, and chronic stress [b]

	Model 1 [c]	Model 2 [d]	Model 3 [e]
Relationship 1: Race and risk of COVID-19 severity			
White ($n=3999$)	Reference	Reference	Reference
Black ($n=5578$)	1.05 (0.96, 1.16)	1.37 (1.25, 1.51)	1.24 (1.12, 1.37)
Relationship 2: Race and risk of high chronic stress [b]			
White ($n=3999$)	Reference	Reference	Reference
Black ($n=5578$)	1.15 (1.11, 1.19)	1.25 (1.21, 1.29)	1.18 (1.14, 1.23)

[a]All reported measures are risk ratio (95% confidence intervals), using White as the reference group

[b]Chronic stress, as defined by AL

[c]Model 1: Crude Model

[d]Model 2: adjusts for sex and age

[e]Model 3: adjusted for sex, age, SVI, income, high deductible insurance plan, smoking status, alcohol use, depression, COPD, liver disease, renal disease, and CHD

Abbreviations: *AL* allostatic load, *CHD* coronary heart disease, *COPD* chronic obstructive pulmonary disease, *SVI* social vulnerability index

Black-White disparities among men. The sex-specific findings here are interesting and the authors suggest that these might be partially explained by a combination of genetic differences and psychological stressors, such as racism, healthcare accessibility, and adverse financial incentives that may impact men and women differently [13]. In our study, men were more likely to have high AL compared with women, but AL mediated a similar proportion of the excess risk of severe COVID-19 in Black vs. White members (18% and 21% in women and men, respectively). Furthermore, the magnitude of the percent disparity attenuated is lower in our study than in Duru et al. [13]; this may be explained by the more causal relationship between each biomarker and diabetes and CVD (e.g., cholesterol and HbA1c), which is less well established for COVID-19 [39, 40]. It is also possible that for outcomes of diabetes and CVD, which take years to develop, chronic stress may play a more important role than in something like severe COVID-19 with relatively acute onset.

Other studies have used other indices of socioeconomic status (SES), rather than race, to examine the role of AL on difference in cognitive function in the elderly. One study found that 4.5% of the relationship between low SES and cognitive function in the elderly was explained by AL, but it was not a significant mediator [41]. In another study assessing the relationship between adverse childhood experiences (ACEs) and multimorbidity [defined as an index of 21 prevalent and high impact/burden conditions], researchers found that social engagement and AL acted as partial mediators

Table 4 Risk ratio estimations [a] describing the proportion of the relationship between race and severe COVID-19 that is mediated by chronic stress [b]

	Direct effect RR [c] (95% CI), adjusted for AL	Total effect RR (95% CI), not adjusted for AL	Percent mediated by AL [d]
Model 1: Crude model [e]			
White ($n=3999$)	Reference	Reference	Reference
Black ($n=5578$)	0.99 (0.89, 1.10)	1.06 (0.96, 1.18)	NR [d]
Model 2: Demographic adjusted model [f]			
White ($n=3999$)	Reference	Reference	Reference
Black ($n=5578$)	1.28 (1.15, 1.43)	1.40 (1.25, 1.55)	25%
Model 3: Fully adjusted model [g]			
White ($n=3999$)	Reference	Reference	Reference
Black ($n=5578$)	1.19 (1.06, 1.34)	1.25 (1.11, 1.41)	23%

[a]All reported measures are risk ratio (95% confidence intervals), using White as the reference group

[b]Chronic stress, as defined by AL

[c]The direct effect RR gives the estimated association between race and COVID-19 severity, when the AL mediator is held constant at 0

[d]Percent mediated was not reported (NR) for results that showed no evidence of a significant association in the total effect

[e]Model 1 only contains exposure of interest and the mediator, when applicable

[f]Model 2 adjusts for sex and age

[g]Model 3 adjusted for age, sex, SVI, income, high deductible insurance plan, smoking status, alcohol use, depression, COPD, liver disease, renal disease, and coronary heart disease

Abbreviations: *AL* allostatic load, *CHD* coronary heart disease, *COPD* chronic obstructive pulmonary disease, *NR* not reported, *RR* risk ratio, *SVI* social vulnerability index

[14]. More specifically, they found that increases in ACEs were associated with an increased risk of multimorbidity later in life, of which 28% and 23% of the association in women and men, respectively, was partially explained by the combined effects of AL and social engagement.

COVID-19 is entering into an endemic phase with seasonal outbreaks, similar to the flu [42, 43] and thus our findings will likely have several long-term public health implications. For instance, our data suggest that reducing AL may reduce the excess risk of severe COVID-19 in Black individuals, at least in the Southeast US. Individualized care plans to reduce the cumulative effects of AL among individuals at high risk for severe COVID-19 may include any combination of improved nutrition, regular exercise, adequate sleep, blood pressure and glucose management, and mental health assessments, as well as increased social support as appropriate [44]. However, we acknowledge that causes of high AL and subsequent severe COVID-19 among minority populations are likely upstream and require longer term system-wide solutions that include addressing housing standards, healthcare accessibility via affordable insurance, and racial discrimination [1, 3, 4, 7, 45]. For example, in one study among Puerto Rican adults living in Boston, access to the Supplemental Nutrition Assistance Program (SNAP) minimized the impact of food insecurity on AL [46].

The key strength of this study is the use of KPGA's expansive EMR data repository that allowed for a large sample size and clinically measured lab results, provider diagnosed comorbidities, and verified hospitalization and mortality information with minimal missing data. However, there are some limitations. First, AL is a proxy for chronic stress, and there is no validated method to calculate AL despite some consistency across studies. Additionally, prescribed medications that can alter AL biomarkers were not considered. Second, our results may not be generalizable to non-insured settings, or to individuals not accessing healthcare frequently to have biomedical measurements taken. In our study, it is most likely that those without biomedical measurements taken were, on average, healthier than those who did have measurements taken and thus our results may be more generalizable to a less healthy population. Interestingly, our population all have relatively uniform access to healthcare via private insurance and thus we can conclude that healthcare access is an unlikely contributor to our observed findings. Third, our population has a higher proportion of Black individuals and thus may not be extrapolated to other populations or regions in the US. Fourth, other races were excluded due to limited sample size in this population. Future research should examine the impact of AL on severe COVID-19 in other ethnic and racial minorities. Fifth, AL is measured at baseline and is not updated over time and thus cannot be considered a "true" mediator. Longitudinal studies with time-varying data are needed in the future to address this. Finally, our study is limited to data captured in KPGA's EMR and thus likely has residual confounding as a result of missing data, in particular individual level SES variables.

Conclusion

In conclusion, we report that Black members within an integrated healthcare system in the Southeast US are at increased risk for developing severe COVID-19, and this excess risk is, in part, explained by an unequal distribution of chronic stress among Black (vs. White) members. Identification of individuals at high risk for both chronic stress and severe COVID-19, and management of the effects and number of stressors may alleviate some of excess burden of severe COVID-19 in underrepresented racial and ethnic populations.

Abbreviations PCR: Polymerase chain reaction; ICD: International Classification of Disease; KPGA: Kaiser Permanente Georgia; AL: Allostatic load; RR: Risk ratio; CI: Confidence interval; US: United States; EMR: Electronic medical record; STROBE: STtrengthening the Reporting of OBservational studies in Epidemiology; COPD: Chronic obstructive pulmonary disease; CHD: Coronary heart disease; SVI: Social vulnerability index; ACS: American Community Survey; OR: Odds ratio; CVD: Cardiovascular disease; NR: Not reported; SES: Socioeconomic status; CKD: Chronic kidney disease

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Author Contribution MMM conceptualized this study, conducted statistical analysis, and wrote the manuscript. SS contributed to the creation of the allostatic load measure and reviewed/edited the manuscript. SP, TD, and JCG contributed to conceptualization, study design, and reviewed/edited the manuscript. REP, RJ, and LT contributed to study design and reviewed/edits the manuscript. BM contributed to data management and reviewed/edited the manuscript. JLH contributed to conceptualization, study design, oversaw statistical analyses, and reviewed/edited the manuscript, and is the corresponding author. All authors have read and approved the manuscript. JLH is the guarantor of this work and take responsibility for the decision to submit this work.

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Data Availability The data that support the findings of this study are available from Kaiser Permanente Georgia, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available

from the authors upon reasonable request and with permission of Kaiser Permanente Georgia.

Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by KPGA Institutional Review Board (IRB# 00000406) and Emory University Institutional Review Board (IRB#: MOD004-STUDY00001631).

Consent to Participate A waiver of consent was obtained for the use of this de-identified dataset.

Consent for Publication A waiver of consent for publication was obtained to publish aggregate results from this de-identified dataset.

Conflict of Interest The authors declare no competing interests.

References

1. Montoya MM. Re-examination of health disparities in the United States: a 3-pronged health intervention proposal. 2020 Dec [cited 2022 Dec 16]; Available from: https://rrpress.utsa.edu/handle/20.500.12588/234
2. National Center for Health Statistics (US). Health, United States, 2015: with special feature on racial and ethnic health disparities [Internet]. Hyattsville (MD): National Center for Health Statistics (US); 2016 [cited 2023 Sep 23]. (Health, United States). Available from: http://www.ncbi.nlm.nih.gov/books/NBK367640/
3. A systematic review of allostatic load, health, and health disparities - Theresa M. Beckie, 2012 [Internet]. [cited 2023 Mar 17]. Available from: https://doi.org/10.1177/1099800412455688?journalCode=brna
4. Webb Hooper M, Marshall V, Pérez-Stable EJ. COVID-19 health disparities and adverse social determinants of health. Behav Med. 2022;48(2):133–40.
5. CDC. Cases, Data, and Surveillance [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2022 Dec 16]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html
6. Hill L, Artiga S. COVID-19 cases and deaths by race/ethnicity: current data and changes over time. In: Henry J (ed) Kaiser Family Foundation. 2022. https://www.kff.org/coronavirus-covid-19/issue-brief/covid-19-cases-and-deaths-by-race-ethnicity-current-data-and-changes-over-time
7. Forde AT, Crookes DM, Suglia SF, Demmer RT. The weathering hypothesis as an explanation for racial disparities in health: a systematic review. Ann Epidemiol. 2019;33:1-18.e3.
8. Geronimus AT. The weathering hypothesis and the health of African-American women and infants: evidence and speculations. Emory Univ Lib. 1992;2(3):207–21.
9. Epel ES, Crosswell AD, Mayer SE, Prather AA, Slavich GM, Puterman E, et al. More than a feeling: a unified view of stress measurement for population science. Front Neuroendocrinol. 2018;49:146–69.
10. Crosswell AD, Lockwood KG. Best practices for stress measurement: how to measure psychological stress in health research. Health Psychol Open. 2020;7(2):205510292093307.
11 Brown LL, Mitchell UA, Ailshire JA. Disentangling the stress process: race/ethnic differences in the exposure and appraisal of chronic stressors among older adults. Carr D, editor. J Gerontol Ser B. 2020;75(3):650–60.
12 Robertson T, Beveridge G, Bromley C. Allostatic load as a predictor of all-cause and cause-specific mortality in the general population: evidence from the Scottish Health Survey. Abe T, editor. PLOS ONE. 2017;12(8):e0183297.
13. Duru OK, Harawa NT, Kermah D, Norris KC. Allostatic load burden and racial disparities in mortality. J Natl Med Assoc. 2012;104(1–2):89–95.
14. Atkinson L, Joshi D, Raina P, Griffith LE, MacMillan H, Gonzalez A. Social engagement and allostatic load mediate between adverse childhood experiences and multimorbidity in mid to late adulthood: the Canadian Longitudinal Study on Aging. Psychol Med. 2021;23:1–11.
15. Cohen S, Murphy MLM, Prather AA. Ten surprising facts about stressful life events and disease risk. Annu Rev Psychol. 2019;70(1):577–97.
16. Liu YZ, Wang YX, Jiang CL. Inflammation: the common pathway of stress-related diseases. Front Hum Neurosci. 2017;20(11):316.
17. Cundiff JM, Bennett A, Carson AP, Judd SE, Howard VJ. Socioeconomic status and psychological stress: examining intersection with race, sex and US geographic region in the REasons for Geographic and Racial Differences in Stroke study. Stress Health. 2022;38(2):340–9.
18. Lamontagne SJ, Pizzagalli DA, Olmstead MC. Does inflammation link stress to poor COVID-19 outcome? Stress Health. 2021;37(3):401–14.
19. Cohen S, Frank E, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM. Types of stressors that increase susceptibility to the common cold in healthy adults. Health Psychol Off J Div Health Psychol Am Psychol Assoc. 1998;17(3):214–23.
20. Cohen S, Tyrrell DA, Smith AP. Negative life events, perceived stress, negative affect, and susceptibility to the common cold. J Pers Soc Psychol. 1993;64(1):131–40.
21. Cohen S. Psychosocial vulnerabilities to upper respiratory infectious illness: implications for susceptibility to coronavirus disease 2019 (COVID-19). Perspect Psychol Sci. 2021;16(1):161–74.
22. Bayesian Indirect Surname Geocoding (BISG) [Internet]. RAND Corporation. [cited 2022 Dec 20]. Available from: https://www.rand.org/health-care/tools-methods/bisg.html
23. Elliott MN, Morrison PA, Fremont A, McCaffrey DF, Pantoja P, Lurie N. Using the Census Bureau's surname list to improve estimates of race/ethnicity and associated disparities. 2009 Jan 1 [cited 2023 Mar 17]; Available from: https://www.rand.org/pubs/external_publications/EP20090611.html
24. Krieger N. Discrimination and health inequities. Int J Health Serv Plan Adm Eval. 2014;44(4):643–710.
25. Advancing health equity: a guide to language, narrative and concepts | AMA [Internet]. [cited 2023 Mar 17]. Available from: https://www.ama-assn.org/about/ama-center-health-equity/advancing-health-equity-guide-language-narrative-and-concepts-0
26. Rodriquez EJ, Kim EN, Sumner AE, Nápoles AM, Pérez-Stable EJ. Allostatic load: importance, markers, and score determination in minority and disparity populations. J Urban Health Bull N Y Acad Med. 2019;96(Suppl 1):3–11.
27. Liu SH, Juster RP, Dams-O'Connor K, Spicer J. Allostatic load scoring using item response theory. Compr Psychoneuroendocrinol. 2021;5:100025.
28. Kezios KL, Suglia SF, Doyle DM, Susser E, Bradwin G, Cirillo P, et al. Comparing different operationalizations of allostatic load measured in mid-life and their patterning by race and cumulative life course socioeconomic status. Psychoneuroendocrinology. 2022;1(139):105689.
29. Read S, Grundy E. Allostatic load and health in the older population of England: a crossed-lagged analysis. Psychosom Med. 2014;76(7):490–6.
30. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130.

31. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson comorbidity index: ICD-9 update and ICD-10 translation. Am Health Drug Benefits. 2019;12(4):188–97.
32. 2023 ICD-10-CM Codes F17*: Nicotine dependence [Internet]. [cited 2023 Mar 16]. Available from: https://www.icd10data.com/ICD10CM/Codes/F01-F99/F10-F19/F17-#F17.21
33. ICD-10 | CMS [Internet]. [cited 2023 Apr 25]. Available from: https://www.cms.gov/medicare/coding/icd10?redirect=/icd10
34. CDC/ATSDR SVI Fact Sheet | Place and Health | ATSDR [Internet]. 2022 [cited 2023 Jan 25]. Available from: https://www.atsdr.cdc.gov/placeandhealth/svi/fact_sheet/fact_sheet.html
35. Lindquist K. How can I estimate relative risk in SAS using proc genmod for common outcomes in cohort studies? | SAS FAQ [Internet]. Advances Research Computing. [cited 2023 Sep 23]. Available from: https://stats.oarc.ucla.edu/sas/faq/how-can-i-estimate-relative-risk-in-sas-using-proc-genmod-for-common-outcomes-in-cohort-studies/
36. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol. 2003;157(10):940–3.
37. Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods. 2013;18(2):137–50.
38. Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. Int J Epidemiol. 2013;42(5):1511–9.
39. Al-Sabah S, Al-Haddad M, Al-Youha S, Jamal M, Almazeedi S. COVID-19: impact of obesity and diabetes on disease severity. Clin Obes. 2020;10(6):e12414.
40. Why it's important to manage obesity and diabetes right now [Internet]. Cleveland Clinic. 2022 [cited 2023 Apr 13]. Available from: https://health.clevelandclinic.org/why-having-obesity-can-put-you-at-greater-risk-for-covid-19-complications/
41. Akrivos J, Zhu CW, Haroutunian V. Role of cumulative biological risk in mediating socioeconomic disparities in cognitive function in the elderly: a mediation analysis. BMJ Open. 2020;10(9):e035847.
42. Will COVID-19 become seasonal like the flu? - Covid Clinic [Internet]. [cited 2023 Apr 6]. Available from: https://covidclinic.org/blog/will-covid-19-become-seasonal-like-the-flu/
43. Respiratory Disease Season Outlook [Internet]. 2023 [cited 2023 Oct 26]. Available from: https://www.cdc.gov/forecast-outbreak-analytics/about/season-outlook.html
44. Rosemberg MAS, Granner J, Li Y, Seng JS. A scoping review of interventions targeting allostatic load. Stress. 2020;23(5):519–28.
45. Szanton SL, Gill JM, Allen JK. Allostatic load: a mechanism of socioeconomic health disparities? Biol Res Nurs. 2005;7(1):7–15.
46. McClain AC, Xiao RS, Gao X, Tucker KL, Falcon LM, Mattei J. Food insecurity and odds of high allostatic load in Puerto Rican adults: the role of participation in the Supplemental Nutrition Assistance Program during 5 years of follow-up. Psycosom Med. 2018;80(8):733–41.