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Sex differences in the interaction of short-term particulate matter exposure and psychosocial stressors on C-reactive protein in a Puerto Rican cohort

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ABSTRACT

There is substantial evidence linking particulate matter air pollution with cardiovascular morbidity and mortality. However, health disparities between populations may exist due to imprecisely defined non-innate susceptibility factors. Psychosocial stressors are associated with cardiovascular disease and may increase non-innate susceptibility to air-pollution. We investigated whether the association between short-term changes in ambient particulate matter and cardiovascular health risk differed by psychosocial stressors in a Puerto Rican cohort, comparing women and men. We used data from the Boston Puerto Rican Health Study (BPRHS), a longitudinal study of cardiovascular health among adults, collected between 2004 and 2013. We used mixed effect models to estimate the association of current-day ambient particle number concentration (PNC) on C-reactive protein (CRP), a marker of systemic inflammation, and effect modification by psychosocial stressors (depression, acculturation, perceived stress, discrimination, negative life events and a composite score). Point estimates of percent difference in CRP per interquartile range change in PNC varied among women with contrasting levels of stressors: negative life events (15.7% high vs. 6.5% low), depression score (10.6% high vs. 4.6% low) and composite stress score (16.2% high vs. 7.0% low). There were minimal differences among men. For Puerto Rican adults, cardiovascular non-innate susceptibility to adverse effects of ambient particles may be greater for women under high stress. This work contributes to understanding health disparities among minority ethnic populations.

1. Introduction

There is substantial evidence linking particulate matter (PM) air pollution with both cardiovascular morbidity and mortality (Achilleos et al., 2017; Brook et al., 2010). Numerous studies have shown between group heterogeneity in air pollution-related health response. However, specific factors that increase susceptibility remain unclear (J.E. Clougherty, Shmool, & Kubzansky, 2014; Christina H. Fuller, Feeser, Sarnat, & O'Neill, 2017; Sacks et al., 2011). Psychosocial stressors, many of which are related to an individual's socioeconomic position (SEP), may increase non-innate susceptibility to cardiovascular disease (CVD) (B. E. Cohen, Edmondson, & Kronish, 2015). Psychosocial stress can be a function of adversity and occurs when external conditions overwhelm an individual's ability and resources to manage the negative effects of external stressors (S. Cohen, Janicki-Deverts, & Miller, 2007).

The pathophysiological impacts of psychosocial stress are thought to be mediated largely via activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (HPA-axis). This can result in adverse pathophysiological changes, such as endothelial dysfunction, inflammation and oxidative stress (B. E. Cohen et al., 2015; B.S. McEwen, 2005). In particular, a large body of research has shown that psychosocial stress and adversity can deleteriously impact cardiometabolic systems and contribute to the development of cardiovascular diseases (CVD) (An et al., 2016; B. E.; Cohen et al., 2015). Specifically, stress has been shown to result in compromised immune function, "wear-and-tear" on bodily systems and non-innate susceptibility to illness (S. Cohen et al., 2007; B. S. McEwen, 1998). It follows that psychosocial stress may also enhance non-innate susceptibility to

the potentially harmful effects of environmental exposures and act synergistically to increase CVD risk.

Few studies have examined non-innate susceptibility to air pollution health effects by psychosocial stress, with the majority focused on respiratory outcomes such as asthma (J. E. Clougherty & Kubzansky, 2009; J.E. Clougherty et al., 2014). Even fewer have examined CVD or cardiovascular health indicators, such as blood pressure, with mixed results (Christina H. Fuller et al., 2017). The interaction between air pollution concentrations and social conditions is difficult to quantify because they are often spatially correlated (Bullard, 2005). Additionally, many types of psychosocial stressors have the potential to modify associations between air pollution and CVD (J. E. Clougherty & Kubzansky, 2009; Christina H. Fuller et al., 2017). Some studies have focused on the modifying influence of stress as reflected by measures of SEP, like income, whereas others have examined overtly stressful experiences, such as exposure to violence (J. E. Clougherty et al., 2007). The inconsistency of measurements of stress makes comparison among the small number of studies difficult.

Some forms of stress may be more salient for certain populations than others and carry different implications for health impact, which complicates efforts to synthesize findings. Populations with a high prevalence of disease and cardiovascular risk factors may be especially susceptible to environmental exposures due to comorbidities. In addition, the modifying influence of stressors on air pollution and CVD associations may vary based on cultural norms of gender roles. Therefore, indicators of stress should reflect the sources of adversity experienced by a particular population (J. E. Clougherty, 2010). A potentially susceptible population is Puerto Ricans living in the mainland U.S., who make up the second largest Hispanic subgroup, after Mexican Americans. The Puerto Rican community is characterized by high cardiovascular risk and a high prevalence of disability and chronic diseases including type 2 diabetes, depression and hypertension compared to other Hispanic groups and non-Hispanic whites (Tucker et al., 2010). In the Multi-ethnic Study of Atherosclerosis (MESA), Puerto Rican participants had a high prevalence of subclinical cardiovascular disease markers (Allison et al., 2008). Puerto Rican women also had the highest prevalence of metabolic syndrome in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (Heiss et al., 2014). Moreover, Puerto Ricans report higher levels of depression and anxiety than other immigrant Hispanic/Latino groups (Sanchez et al., 2014), and experiences of discrimination and acculturation are prevalent and contribute to psychological distress (Held & Lee, 2017).

In this study, we explored the differential role of psychosocial stress indicators as modifiers of the relationship between short-term differences in air pollution and cardiovascular risk. We used data from the Boston Puerto Rican Health Study (BPRHS), a longitudinal cohort study designed to examine stress, social support and health outcomes among a cohort of Puerto Rican adults in the Boston area (Tucker et al., 2010). Previous work in this cohort identified an association between short-term differences in outdoor PM levels and C-reactive protein (CRP), a marker of inflammation and cardiovascular risk, among women (C. H. Fuller et al., 2018). In that study we examined exposure windows of current day; lags of 1 and 2 days; and moving averages of 3, 7 and 28 days. We observed similar associations between ambient PNC and CRP for all exposure windows of about 6.5%. Also, perceived discrimination was associated with a number of medical conditions, including diastolic blood pressure (Todorova, Falcon, Lincoln, & Price, 2010). Depression, psychological acculturation, and perceived stress have also been associated with respiratory disease among BPRHS participants (Henkin et al., 2011). Motivated by these findings, we examined the role of depression, psychological acculturation, perceived stress, perceived discrimination and negative life events as modifiers of the air pollution and CRP relationship, and whether that modified association differed between men and women.

2. Materials and methods

2.1. Framework

We utilize the Integrated Socio-Environmental Model of Health and Wellbeing (ISEM) as the conceptual model for this analysis (Olvera Alvarez, Appleton, Fuller, Belcourt, & Kubzansky, 2018). The ISEM describes how social and environmental factors combine and potentially interact, via multi-factorial pathways, to affect health and well-being over the life span. In this study, we explore the relationship between ambient air pollution (A) and non-innate susceptibility by individual psychosocial stressors (B) on C-reactive protein (C), as indicated in (Supplemental Fig. 1). We test associations between these elements while keeping in mind the larger upstream conditions that frame exposure and downstream adverse health effects.

2.2. Study design and population

The methods for recruitment and data collection are detailed elsewhere (C. H. Fuller et al., 2018; Tucker et al., 2010). Briefly, participants between the ages of 45 and 75 years were recruited from the Boston metropolitan area (primarily the cities of Boston, Chelsea and Lawrence) on an ongoing basis from 2004 to 2009 (baseline). Recruitment was conducted via door-to-door solicitation in census tracts identified in the 2000 Census as having 25 or more Puerto Rican adults. Additional participants were identified through referrals, calls to the study office, and community events. Follow up took place approximately 2 years (2006–2011) and 5 years (2011–2015) after initial recruitment. Baseline questionnaires and clinical measurements were completed in English or Spanish at the participant's home by trained bilingual staff. Demographic information on age, household income, education, employment history and family structure were collected at the baseline visit. Data on medications, health outcomes and behaviors were taken at all visits. The study was approved by the Institutional Review Boards at Tufts Medical Center, Northeastern University and the University of Massachusetts Lowell. All participants provided written informed consent.

2.3. Particulate matter air pollution measurement

We characterized the PM concentration (particle number concentration [PNC]) using a fixed monitor located within 45 km of all participants. The monitor was positioned on the rooftop (six floors above street level) of the Countway Library of Medicine at Harvard Medical School on Huntington Avenue in Boston. Measurements at this site have been found to provide good estimates of temporal variability in PNC at other locations in Boston, reflecting relative differences in population exposures from day to day (C. H. Fuller et al., 2012; Simon et al., 2017; Wu et al., 2014). Continuous hourly measurements of PNC (greater than 7 nm in aerodynamic diameter) were collected from January 1, 2004 through December 31, 2013 at the site using a butanol-based condensation particle counter (Model 3022A; TSI Inc., Shoreview, MN). Hourly measurements were averaged to calculate 24-h daily mean concentrations (C. H. Fuller et al., 2015). Ambient PNC on the day of CRP measurement was used as the estimate for exposure based on results from a previous study in this cohort (C. H. Fuller et al., 2018). Data on temperature were collected from a station located at Logan International Airport in Boston.

2.4. CRP measurement and other anthropometric markers

CRP was assessed at baseline and at up to two subsequent visits, resulting in repeated measures for the majority of participants (Tucker et al., 2010). A certified phlebotomist drew venous blood samples from each participant. We analyzed CRP, in mg/L, in blood serum using the Immulite 1000 High Sensitive CRP Kit (LKCRP1) on the Immulite 1000

(Seimens Medical Solutions Diagnostics, Los Angeles, CA). Standing height, weight, waist and hip circumference were measured in duplicate by trained study staff and the average of each measurement was used for the calculation of body mass index (BMI) and waist-hip ratio.

2.5. Measurement of demographic factors and psychosocial stress

Each participant completed a questionnaire at baseline and subsequent visits (details provided elsewhere) (Tucker et al., 2010). Information was collected on individual level education (5 categories), total household income (per year), type 2 diabetes (self-reported yes or no), hypertension (yes/no; according to medication use or measurement of systolic blood pressure >140 mmHg or diastolic > 90 mmHg), alcohol intake within the past year (none, moderate, heavy), physical activity score (that evaluates the level of activity over a 24-h period), marital status, and smoking. Information on medication use was also collected and categorized into the following groups for consideration in models: anti-lipid agents (i.e. statins), beta blockers, anti-diabetic agents, anti-hypotensive agents and anti-inflammatories for ear, nose and throat issues.

We explored several indicators of psychosocial stress in this analysis. The Spanish version of the perceived stress scale (PSS), a paper-based indicator of general perceived stress, was administered (Ramirez & Hernandez, 2007). Depressive symptoms were assessed using the Center for Epidemiology Studies Depression (CES-D) Scale (Miller, Markides, & Black, 1997). The Cronbach's alpha for the PSS and CES-D in the cohort are 0.85 and 0.91, respectively (Falcón, Todorova, & Tucker, 2009). Discrimination was evaluated using 4 questions of which we selected the first, 'Have you ever experienced discrimination as a result of your race, ethnicity or language?' due to the small number of responses to follow up questions (Henkin et al., 2011). Psychological acculturation was assessed based on the level of attachment to American or Puerto Rican culture using a 10-item scale previously created and validated in the Boston area (Tropp, Erkut, Coll, Alarcon, & Vazquez Garcia, 1999). Questions included, "With which group [either Puerto Ricans or Americans] do you feel you share most of your beliefs and values?" and "With which group of people do you feel most comfortable?" We compiled negative life events from responses to the Spanish version of the Life Events questionnaire. These indicators have shown consistency, reliability and validity in older adults as well as among Hispanics, including Puerto Ricans, and in this cohort (Falcón et al., 2009).

As an exploratory analysis we examined the possibility of a larger combined effect of multiple stressors by creating a composite score of psychosocial stress. Following methods used in recent psychosocial stress and cardiovascular research, we first dichotomized each continuous stress score into a value of 1 or 0 based on either an established cut point signifying high risk or according to extremes in the distributions (Appleton et al., 2013; Hicken, Dvonch, Schulz, Mentz, & Max, 2014). A CES-D score of 16 or above, which corresponds to high risk of depression, was given a score of 1 (Lewinsohn, Seeley, Roberts, & Allen, 1997). For perceived general stress, negative life events, and psychological acculturation scale, scores at or above the 75th percentile of the distribution were assigned a value of 1. As the discrimination variable was already dichotomous, a report of discrimination was assigned to 1. Next, a total score and a dichotomous variable representing higher and lower levels of overall stress were derived. The total score was a simple unweighted summary of each of the 5 stress scales, giving a possible composite score of 0–5. For the dichotomous variable, low stress included those with a composite score ranging from 0 to 2, and high stress included those with a score of 3 or more.

2.6. Statistical analysis

Standard descriptive statistics were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). We log-transformed CRP for regression models to accommodate its non-normal distribution. The

association between differences in ambient PNC and CRP was evaluated using mixed effects models with individual-specific random intercepts using the NLME package in R v 3.3.1 (Pinheiro J et al., 2016). We tested for statistically significant effect modification using interaction terms and calculated stratum-specific estimates using stratified models. We evaluated our results as percent difference in CRP per interquartile range (IQR) range increase in PNC and 95% confidence intervals as the measure of precision. Age was included in the models *a priori,* given its strong association with the outcomes. Other covariates were included based on their strength of an independent association with the outcome (p-value < 0.05) in univariate models and/or difference in effect estimates of 10% or more. We considered for inclusion the following participant-level covariates: BMI, waist-hip ratio, household income, education, type 2 diabetes, hypertension, alcohol intake, physical activity, marital status, smoking and medication use.

After specifying a model for estimating associations between ambient PNC and CRP (C. H. Fuller et al., 2018) we built two models for women and two for men testing each psychosocial stress effect modification hypothesis. We categorized continuous stress indicators dichotomized by the median for each sex, except for depression score, which was dichotomized at a score of 16 (Lewinsohn et al., 1997). Model 1 used baseline data, which was available for all six stress indicators, to evaluate effect modification: depression, perceived stress, psychological acculturation, negative life events, discrimination and an exploratory composite stress score. Model 2 utilized repeated measures, which increased the data provided by each participant for four stress indicators. This model used repeated data that was available for depression, perceived stress, psychological acculturation and negative life events.

3. Results

The cohort was comprised of 70% women and 30% men with a mean age at baseline of 57.3 years (SD: 7.5) and 56.6 years (SD: 7.9), respectively (Table 1). Men had completed more education then women, and reported higher mean household income ($20,410 [SD: $20,606] vs. $16,733 [SD: $18,469]). A higher percentage of men than women reported working outside of the home (25% vs. 16%). Men were more

Table 1
Baseline characteristics of participants in the Boston Puerto Rican Health Study (BPRHS) (n = 1499).

Characteristic		
Number (%) except where indicated	Women (n = 1056)	Men (n = 443)
Age (years) (Mean ± SD)	57.3 (7.5)	56.6 (7.9)
Education *		
Less than 5th grade	248 (23)	73 (16)
5th – 8th grade	255 (24)	118 (27)
9–12th or high school equivalent	386 (36)	187 (41)
Some college or bachelor's degree	145 (14)	55 (12)
Some graduate school	20 (2)	8 (2)
Household income (Mean ± SD) *	$16,733 ($18,469)	$20,410 ($20,606)
Employment *		
Currently working	170 (16)	110 (25)
Not working outside the home	883 (84)	333 (75)
Smoking *		
Current	218 (20)	149 (34)
Past	296 (28)	153 (34)
Never	540 (51)	137 (31)
BMI (kg/m^2) (Mean ± SD) *	32.8 (6.9)	29.6 (5.3)
Waist-hip ratio (Mean ± SD) *	0.92 (0.08)	0.97 (0.06)
Physical Activity Score (Mean ± SD) *	31.1 (4.1)	32.6 (5.9)
Place of Birth		
Puerto Rico	1010 (96)	427 (96)
US or elsewhere	43 (4)	14 (3)
Years in the U.S. (Mean ± SD)*	34.0 (12.3)	36.2 (11.9)

Abbreviations: SD, standard deviation; BMI, body mass index.
* Statistically significant difference between women and men (p < 0.05).

likely to be current or past smokers (64%) than women (48%). Women had significantly higher BMI, 32.8 (SD: 6.9) than men 29.6 (5.3), while men had higher waist-to-hip ratio (0.97 [SD: 0.06]) than women (0.92 [SD: 0.08]). Men also reported being more physically active. Ninety-six percent of the cohort were born in Puerto Rico; however, men lived a mean of 36.2 years (SD: 11.9) on the mainland U.S. and women 34.0 years (SD: 12.3).

CRP and stress indicators were not normally distributed, so we report median values and the interquartile range (IQR) (Table 2). Median CRP among women was significantly higher than for men (4.2 mg/L [IQR: 6.7 mg/L] and 2.5 mg/L [IQR: 3.8 mg/L]). CRP values greater than 3.0 mg/L indicate a clinically elevated risk for cardiovascular disease (Ridker, 2003). There were statistically significant differences between women and men for depressive symptoms, perceived stress, discrimination and negative life events at each time point (with the exception of PSS in year 5). For example, median CES-D at baseline was higher for women (21 [IQR: 20]) than for men (15 [IQR: 17]). The median CES-D score among women was greater than the threshold of 16, indicating an elevated risk for depression. Men reported significantly higher experience with discrimination (42.3% vs. 35.4% at baseline). Mean PNC measured at the fixed site has been previously reported; in brief, PNC was 26,000 particles/cm^3 (SD: 8000) over the entire study period (2004–2013) with an IQR range 11,650 particles/cm^3 for the current-day lag and 10,000 particles/cm^3 for the 28-day moving average (C. H. Fuller et al., 2018).

At baseline, we examined potential effect modification by all stressors on the relationship between PNC and CRP (Table 3 and Fig. 1). We conducted several tests for association in our analyses and therefore, emphasize effect estimates in lieu of statistical tests for significance. Our results among women show differences in effect size comparing sub-groups of sex and stressor level. Effect estimates were higher for women with CES-D score ≥16 (10.6% [95% CI: 1.5%, 19.7%]) compared to those with lower scores (4.6% [95%CI: −8.2%, 17.5%]). In addition, for women reporting negative life events above, compared to below, the median there was a difference of 15.7% (95% CI: 2.9%, 24.5%) compared to 6.5% (95% CI: −2.6%, 15.5%). A comparable difference was seen for women with high composite stress score 16.2% (95% CI: 2.8%, 29.6%) compared to low composite stress score (7.0% (95% CI: −1.82%, 15.87%). An effect opposite to that hypothesized was found for women with low PSS (10.7% [95% CI: 2.0%, 19.4%]) vs. high PSS (4.5% [95% CI: −9.5%, 18.5%]). For men, all sub-group estimates included the null. However, effect estimates were greater for higher perceived stress (8.3% [95% CI: −13.1%, 29.8%]) compared to lower perceived stress (1.5% [95% CI: −12.1%, 15.1%]) and for those with higher composite stress scores (14.4% [95% CI: −9.0%, 37.7%]), compared to those with lower scores (−1.7% [95% CI: −14.8, 11.4%]).

Results for repeated measures models were similar to baseline models for depressive symptoms, PSS and negative life events (Fig. 1). Notably, the difference in effect between women comparing lower and higher negative life events was wider, (22.9% [95% CI: 13.3%, 32.5%]

vs. 2.8% [95% CI: −3.43%, 9.11%]) and confidence intervals did not overlap. An inverse association for PSS was also noted, specifically a larger effect for women with low PSS (9.2% [95% CI: 3.1%, 15.3%]) vs. high PSS (5.6% [95% CI: −7.2%, 18.3%]), which was opposite the hypothesized direction.

4. Discussion

We observed differences in effect estimates for associations between PNC and CRP among Puerto Rican women by differing levels of stress indicators, including negative life events, perceived stress, psychological acculturation, depression, and an exploratory composite stress score. However, none of the tests for effect modification reached statistical significance. As in previous analyses in the BPRHS, women had higher levels for each stress marker than men (Falcón et al., 2009; Tucker, 2005). This study is the first, to our knowledge, to examine how psychosocial stressors may modify the effect of PNC on CRP, and few studies have sought to characterize differential non-innate susceptibility to health effects of PNC.

Our results provide some evidence that differences in non-innate susceptibility to air pollution based on psychosocial stress may be a gendered response, with women at higher risk than men. Clougherty et al. summarized the literature on sex-specific differences in air pollution epidemiology. Despite variation between studies, there was a suggestion of a greater main effect of air pollution on respiratory outcomes for women, compared to men (J. E. Clougherty, 2010). There is also evidence that the main effect of psychosocial stress and adversity affect cardiometabolic health more strongly for women than men (O'Neil, Scovelle, Milner, & Kavanagh, 2018). Therefore, it appears possible that modification of air pollution effects by psychosocial stress would be larger among women. The absence of effect modification among men in the present analysis may be due to the lack of association of CRP with PNC, along with a smaller sample size. Previous analysis in this cohort identified statistically significant associations between short-term differences in ambient PNC and CRP among women, but not men (C. H. Fuller et al., 2018).

Because the literature is small we compare our results to studies with a range of outcomes. Rammah et al. identified main effects of O_3 and psychosocial stressors (i.e. racial discrimination and worries about health or money) on prevalent hypertension, but did not find an interaction between O_3 and stressors in a cohort of participants of Mexican origin in the Houston, TX area (Rammah et al., 2018). Hazlehurst et al. identified interactions between PM_{10} and adverse childhood experiences on diabetes; $PM_{2.5}$ and neighborhood deprivation index (NDI) on stroke; and NO_2 and NDI on both diabetes and stroke (Hazlehurst, Nurius, & Hajat, 2018). The Detroit Healthy Environment Partnership study identified significant interactions between an index of stress and $PM_{2.5}$ on blood pressure in one of the three neighborhoods (Hicken et al., 2014). In the Southwest neighborhood, participants with higher stress had a greater effect of $PM_{2.5}$ on both pulse pressure and systolic blood

Table 2
C-reactive protein and measures of psychosocial stress in the Boston Puerto Rican Health Study (BPRHS).

Characteristic	Baseline		2 year		5 year	
	Median (IQR)		Median (IQR)		Median (IQR)	
	Women (n = 1056)	Men (n = 443)	Women (n = 905)	Men (n = 353)	Women (n = 644)	Men (n = 247)
C-reactive protein (mg/L)*	4.2 (6.7)	2.5 (3.8)	3.8 (7.3)	2.3 (4.0)	4.4 (6.6)	2.6 (3.6)
Depression score*	21 (20)	15 (17)	19 (19)	11 (18)	16 (16)	12 (15)
Psychological acculturation scale	18 (10)	18 (12)	18 (12)	19 (14)	N/A	N/A
Perceived stress scale *	25 (12)	23 (14)	24 (12)	22 (12)	27 (10)	27 (9)
Discrimination [Number (%)]*	317 (35.4%)	158 (42.3%)	NA	NA	NA	NA
Negative life events*	6 (9)	4 (8)	5 (7)	3 (6)	NA	NA
Composite stress score	3 (2)	2 (2)	NA	NA	NA	NA

* Statistically significant difference between women and men.
NA, not applicable, represents no measurements taken for the time period.

Table 3

Association between an interquartile range change in current-day particle number concentration (PNC) and C-reactive protein (CRP) and effect modification by dichotomized stress measures in the Boston Puerto Rican Health Study (BPRHS).

Characteristic	Women				Men			
	Dichotomized psychosocial stress marker							
	Low		High		Low		High	
	% Difference	95% CI	% Difference	95% CI	% Difference	95% CI	% Difference	95% CI
Baseline data model								
Depression score ($\geq$ 16)	4.6%	(-8.2%, 17.5%)	**10.6%**	**(1.5%, 19.7%)**	2.3%	(-13.2%, 17.8%)	0.8%	(-16.4%, 18.0%)
Psychological acculturation scale	7.0%	(-1.4%, 15.5%)	11.6%	(-3.5%, 26.8%)	1.8%	(-11.0%, 14.6%)	−2.4%	(-26.5%, 21.8%)
Perceived stress scale	**10.7%**	**(2.0%, 19.4%)**	4.5%	(-9.5%, 18.5%)	1.5%	(-12.1%, 15.1%)	8.3%	(-13.1%, 29.8%)
Discrimination (Yes/No)	4.0%	(-6.7%, 14.7%)	10.9%	(-2.1%, 23.9%)	−0.1%	(-15.5%, 15.3%)	−1.4%	(-22.4%, 19.7%)
Negative life events	6.5%	(-2.6%, 15.5%)	**15.7%**	**(2.9%, 28.5%)**	2.4%	(-10.7%, 15.5%)	−7.2%	(-29.6%, 15.2%)
Composite stress score[a]	7.0%	(-1.8%, 15.9%)	**16.2%**	**(2.8%, 29.6%)**	−1.7%	(-14.8%, 11.4%)	14.4%	(-9.0%, 37.7%)
Repeated measures model								
Depression score ($\geq$ 16)	2.5%	(-6.3%, 11.4%)	**9.9%**	**(2.6%, 17.1%)**	3.0%	(-8.3%, 14.4%)	−1.0%	(-15.7%, 13.7%)
Psychological acculturation scale	**7.1%**	**(0.9%, 13.4%)**	6.2%	(-5.2%, 17.5%)	2.0%	(-8.4%, 12.4%)	0.3%	(-18.1%, 18.7%)
Perceived stress scale	**9.2%**	**(3.1%, 15.3%)**	5.6%	(-7.2%, 18.3%)	1.7%	(-8.5%, 11.9%)	3.1%	(-14.0%, 20.1%)
Negative life events	2.8%	(-3.4%, 9.1%)	**22.9%**	**(13.3%, 32.5%)**	0.9%	(-9.1%, 10.9%)	13.9%	(-4.1%, 31.9%)

Effect Estimates in bold are statistically significant (p < 0.05).

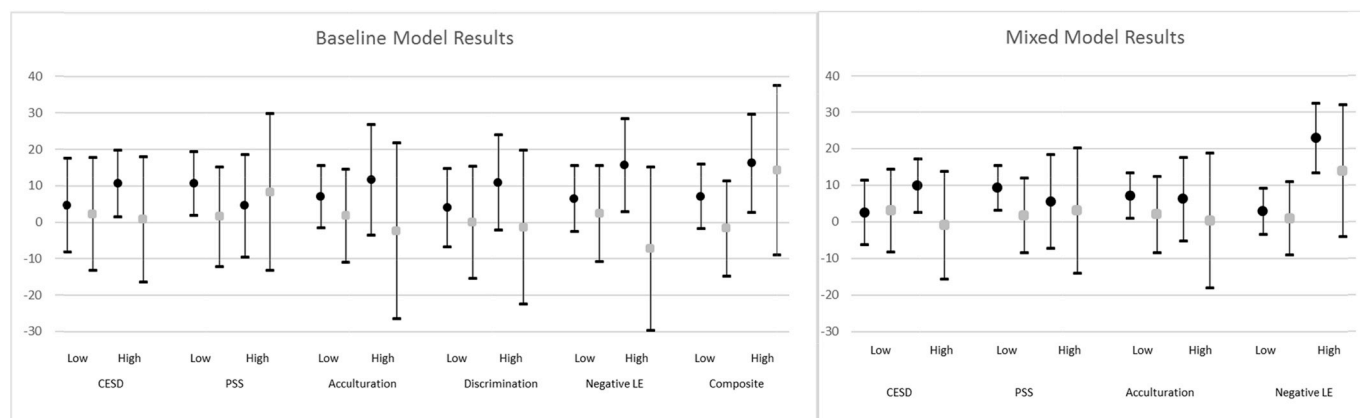[a] Composite score has been categorized into 0–2 and 3+.

Fig. 1. Box plots of effect modification according to dichotomized psychosocial stress indicator in the BPRHS. Results are given as a percent difference in CRP per 10,000 particles/cm^3 increase in ambient PNC. (Women are represented by black circles and men by grey squares.)

pressure (SBP). This effect was not found in the other two neighborhoods, possibly due to differences in sex composition. In the Multi-Ethnic Study of Atherosclerosis (MESA), Hicken et al. did not identify statistically significant interaction between PM$_{2.5}$ and stressors (as individual indicators or a composite score) on hypertension (Hicken et al., 2013). Contrary to the hypothesis, participants below the 10th percentile of depressive symptoms showed a higher effect of PM$_{2.5}$ on SBP compared to participants above the 90th percentile of depressive symptoms, although confidence intervals overlapped. In our study, most differences in effect estimates among women were in the expected direction, with the exception of perceived stress. In that case, effect estimates showed higher effect of PNC on CRP with low perceived stress than for high perceived stress. This result may be due to precision of the perceived stress instrument, which might not accurately measure a stressful state with as much specificity as other measures such as depressive symptoms or negative life events. In addition, the PSS instrument is designed to represent the prior month, which is a longer timescale than the PNC exposure measured in this study; thus opening up the possibility of reverse causation.

We note several advantages and limitations in the study design and analysis. A beneficial aspect of the study is that we focused on the Puerto Rican community, a population that has received little attention in this area of research. Conducting analyses in multiple populations is key to

understanding health disparities. Although all participants are of Puerto Rican origin, this cohort is diverse with regards to several genetic and demographic measures (Lai et al., 2009). Our study utilizes a stationary monitor as a measure of population PNC exposure. Our group has analyzed spatial and temporal variation in PNC collected using three approaches: central site, residential site and mobile on-road monitoring (Simon et al., 2017). The analysis found that on average concentrations were highest on-road compared to central site and the residences had the lowest concentrations. The analysis also noted that temporal correlations between central site and residential daily averages of PNC were fairly high (r ~ 0.7). Variation in the correlations was linked to factors such as wind direction. Based on these results we find it appropriate to use stationary measurements in the current analysis. A particular strength of the design is that repeated measures data allow us to examine information collected at multiple time points so that each participant contributes more data to the study. We've added value to the analyses by including a composite score that includes multiple distinct, but related stressors. We elected to provide equal weighting for each stressor and acknowledge that this decision may over emphasize certain stressors. For consistency, we chose to dichotomize the measures in the same way as when they were used individually, which does reduce variation in each stressor. As a limitation, we have not utilized physiological based indicators of stress; however, the questionnaire-based indicators we

used have been validated as good indicators of chronic stress (Tucker et al., 2010). Our analysis examined the impact of chronic stress on associations between short-term differences in PNC and CRP, an indicator of cardiovascular disease risk. These analyses could be expanded to examine questions outside this scope such as short-term measures of stress or discrete cardiovascular events such as myocardial infarction and stroke.

5. Conclusion

We identified potential non-innate susceptibility of Puerto Rican women under high psychosocial stress to adverse cardiovascular disease risk with exposure to high ambient particle concentrations. Differences in effect were minimal among men. Our results suggest that additional investigation is warranted to evaluate this relationship using physiological stress measures as well as linkages with clinical outcomes in similar and diverse cohorts.

Author contributions

CH Fuller conceived the analytical design, obtained the data, conducted analyses, wrote and edited the manuscript. AA Appleton, MS O'Neill and JA Sarnat provided feedback on analyses and contributed to the manuscript. PJ Bulsara ran statistical analyses. HH Chang provided guidance on statistical modeling and contributed to the manuscript. LM Falcon provided input into data interpretation and contributed to the manuscript. KL Tucker provided access to data, background study information, contributed to the manuscript and was the PI on the project. D Brugge was Project Leader for the study, provided input on model building, data interpretation and contributed to the manuscript.

Ethical approval

The study was approved by the Institutional Review Boards at Tufts Medical Center, Northeastern University and the University of Massachusetts Lowell. All participants provided written informed consent.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2019.100500.

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