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Association of individual and community factors with C-reactive protein and 25-hydroxyvitamin D: Evidence from the National Health and Nutrition Examination Survey (NHANES)



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ARTICLE INFO

Keywords:

Individual factors
Community/neighborhood factors
25-hydroxyvitamin D
C-reactive protein
Income-to-needs ratio
County crime rate

ABSTRACT

Many individual and community/neighborhood factors may contribute to inflammation and vitamin D deficiency leading to the development of chronic diseases. This study examined the associations of serum C-reactive protein (CRP) and 25-hydroxyvitamin D [25(OH)D] levels with individual and community/neighborhood (tract-level or county-level) factors using a nationally representative sample from 2001–2006 National Health and Nutrition Examination Survey (NHANES). Data from the 2001–2006 waves of the continuous NHANES was merged with the 2000 census and other neighborhood data sources constructed using geographic information system. Associations between multilevel factors and biomarker levels were assessed using multilevel random-intercept regression models. 6643 participants aged 19–65 (3402 men and 3241 women) were included in the analysis. Family income-to-needs ratio was inversely associated with CRP ($P=0.002$) and positively associated with 25(OH)D levels ($P=0.0003$). County crime rates were positively associated with CRP ($P=0.007$) and inversely associated with 25(OH)D levels ($P=0.0002$). The associations with income-to-needs ratio were significant in men [CRP, $P=0.005$; 25(OH)D, $P=0.005$] but not in women. For county crime rates, the association was only significant in women for CRP ($P=0.004$) and was significant in both men ($P=0.01$) and women ($P=0.001$) for 25(OH)D. Additionally, overall CRP was positively associated with age ($P < 0.0001$), female sex ($P < 0.0001$), Hispanic race/ethnicity ($P=0.0001$), current smokers ($P < 0.0001$), body mass index (BMI, $P < 0.0001$), and participants who were US-born ($P=0.02$). Non-Hispanic black ($P < 0.0001$) and Hispanic race/ethnicity ($P < 0.0001$), current smoker ($P=0.047$), and higher BMI ($P < 0.0001$) were associated with lower serum 25(OH)D levels. No significant associations were observed between other community/neighborhood variables and serum CRP and 25(OH)D levels. The current results suggest that family income-to-needs ratio and county crime rate may be important contributors to chronic inflammation and vitamin D status.

Introduction

Inflammation plays an important role in the development of chronic diseases such as cancer and cardiovascular diseases (Balkwill & Mantovani, 2001; Cesari et al., 2003; Danesh, Collins, Appleby, & Peto, 1998; Pollitt et al., 2007). The C-reactive protein (CRP) is a commonly used marker for low grade inflammation, and has been linked to increased risk of cancer, cardiovascular diseases and mortality (Balkwill & Mantovani, 2001; Cesari et al., 2003; Cooney et al., 2013; Danesh et al., 1998). The primary role of vitamin D is to maintain calcium homeostasis and bone health (Deeb, Trump, & Johnson, 2007). However, evidence suggest that vitamin D may have

anti-inflammatory properties with its involvement in the modulation of inflammatory pathways (Bikle, 2009). Deficiency in vitamin D has been linked to enhanced risk of chronic diseases such as cancer and cardiovascular diseases and all-cause mortality (Giovannucci, 2004; Michos & Melamed, 2008; Schottker et al., 2014).

There are many factors that contribute to the development of chronic diseases and health outcomes. Socioeconomic status (SES) can be considered as one of the main contributors. Lower SES, whether measured in terms of education, income, or other poverty associated variables, has been found to be associated with greater risk for disease development, poor prognosis and lower survival rates (Auluck et al., 2016; Baquet & Commiskey, 2000; Clark, DesMeules, Luo, Duncan,

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& Wielgosz, 2009; Pollitt, Rose, & Kaufman, 2005; Rawshani et al., 2016; Sacerdote et al., 2012). Previous studies have documented that individuals living in poverty tend to have elevated CRP levels even after the adjustment for potential confounders such as age, sex, and current health status (Alley et al., 2006; Nazmi & Victora, 2007), suggesting that chronic inflammation could be a mediator relating poverty-associated stress to health and disease outcomes. Relative to CRP, fewer studies have assessed the relations of SES to vitamin D levels. Hayden et al. measured serum levels of 25-hydroxyvitamin D [25(OH)D, an indicator for vitamin D status] among 11,291 patients living in the urban areas in the United Kingdom and reported that social deprivation, along with ethnicity contributed to the poor 25(OH)D levels observed in this patient population. Nevertheless a review suggests that inadequate vitamin D levels exist regardless of sex, age, ethnicity or health status (Collins, 2013).

Beyond individual-level factors, community/neighborhood as an important domain of one's immediate social environment is also relevant to health outcomes (Grafova, Freedman, Kumar, & Rogowski, 2008; Harrell & Gore, 1998). Evidence indicates that social inequalities relevant to chronic disease risk was not only captured by the SES at individual level but also extended to the communities where individuals reside (Borrell et al., 2004; Diez Roux et al., 2001, Jokela, 2014, Chichlowska et al. 2008), suggesting that communities/neighborhoods themselves are important to a person's health. Studies have shown that residents living in disadvantaged (a condition or circumstance unfavorable to success) neighborhoods characterized by socioeconomic disadvantage and social disorganization and disorder tend to have increased risk of obesity and chronic diseases and poorer health status than residents of other neighborhoods (Boardman, Saint Onge, Rogers, & Denney, 2005; Borrell et al., 2004; Burdette & Hill, 2008; Burdette, Wadden, & Whitaker, 2006; Cohen, Finch, Bower, & Sastry, 2006; Diez Roux, Borrell, Haan, Jackson, & Schultz, 2004; Jokela, 2014). Characteristics associated with disadvantaged communities/neighborhoods include physical, social and economic factors that may influence health behaviors, psychosocial health, access to healthy foods and opportunities for safe recreation. For example, in addition to poor economic status, communities/neighborhoods with high levels of social disorders such as crime, violence and other unfavorable conditions can become serious concerns for residents in these areas (Burdette & Hill, 2008; Latkin & Curry, 2003). Studies consistently show that chronic exposure to social disorders in one's neighborhood is associated with higher levels of depression and anxiety which could negatively affect a person's physical and mental health (Burdette & Hill, 2008; Latkin & Curry, 2003; Ross & Mirowsky, 2001). Community/neighborhood characteristics could also be relevant to an individual's vitamin D status. Since sunlight is the most important source of vitamin D in humans (Mehta & Mehta, 2002), unsafe environments could discourage outdoor recreational activities such as walking resulting in decreased vitamin D levels though reduced sunlight exposure. Additionally, residents living in disadvantaged communities/neighborhoods tended to be characterized as lower SES, which were less likely to take vitamin D supplements than those living in affluent communities since a positive association between dietary supplements use and SES has been reported (An, Chiu, & Andrade, 2015; Gahche et al., 2011; Wallace et al., 2014). In this regard, it is important to elucidate how community/neighborhood characteristics such as SES and place safety contribute to inflammation and a person's vitamin D status independent of key individual level factors.

Furthermore, beyond the biological differences between men and women it has been identified that gender differences in aspects such as social responsibility, behaviors, and stress management play a central role in the health of men and women. While women were more likely to have higher rates of morbidity and uses of health service compared to men, higher mortality rates were reported in men than in women (Arber & Cooper, 1999; Norris et al., 2016; Orfila et al., 2006). As an example of coronary artery disease (CAD), besides the widely recog-

nized pathophysiologic differences associated with sex (Sheps et al., 2001), previous work also suggested that women with CAD were more likely to have depressive symptom (Lesperance, Frasure-Smith, Juneau, & Theroux, 2000; Rutledge et al., 2001; Norris et al., 2008) and worse health related quality of life outcomes (Norris et al., 2008, 2004) compared to men. Thus, the biological, behavioral and psychosocial differences between men and women in relation to health may have great relevance when forming strategies for prevention programs. In the current study, we examined the associations of serum levels of CRP and 25(OH)D with individual and community/neighborhood-level factors (with an emphasis on SES factors) using a nationally representative sample from 2001–2006 National Health and Nutrition Examination Survey (NHANES). In addition, we sought to determine whether the associations of individual and community/neighborhood-level factors with CRP and 25(OH)D, if present, were consistent across sex subgroups. Community/neighborhood-level data in this investigation included data obtained at tract-level or county-level.

Material and methods

Sample

Individual-level data used in this study were from the 2001–2006 waves of the continuous National Health and Nutrition Examination Survey (NHANES) merged with the 2000 census data along with other neighborhood data sources constructed using the geographic information system (GIS) techniques. NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States. Since 1999, the survey has examined a nationally representative sample of about 5000 people each year. NHANES uses a complex, multistage, probability sampling design to select participants who are representative of the civilian, noninstitutionalized US population. The NHANES survey is unique in that it combines interviews and physical examinations (National Center for Health Statistics, 2016). The present study focused on 7268 adults aged 19 through 65 years who had data on serum CRP and 25(OH)D concentrations. Additional sequential exclusions included: pregnancy ($n=534$), missing BMI data ($n=86$), and missing linked tract information ($n=5$). Participants with and without BMI and tract data had similar age, gender, and race/ethnicity distributions. The final sample size was 6643, including 3402 men and 3241 women. Tract-level and county-level data were geo-linked to NHANES by staff at the Centers for Disease Control and Prevention (CDC) Research Data Center. The researchers had no access to information that could potentially identify the survey subjects.

Variables

Individual-level independent variables included in the analyses were age (continuous), gender (males vs. females), race-ethnicity [self-reported non-Hispanic white (reference group), non-Hispanic black, Hispanic, and other races], immigrant status (foreign-born vs. US-born), body mass index (BMI, continuous), education [less than high school, high school graduates (reference group), some college, and college graduate or more], income-to-needs ratio (continuous), and current smoking status (current smoker vs. current non-smoker). Income-to-needs ratio was computed by NHANES staff using annual family income divided by the federal poverty threshold for the appropriate family size, location, and year (United States Census Bureau, 2014).

Community/neighborhood-level independent variables included tract urban/rural status, tract socioeconomic status factor score (continuous), tract USDA food desert status (vs. non-food desert) and county crime rates (continuous). Literature has found that tract-level indicators are more consistently related to residents' health than indicators at other geographic levels (Fan et al., 2014; Krieger, Chen,

Waterman, Rehkopf, & Subramanian, 2003; Wan, Zhan, & Cai, 2011). As such, we used census tract as our main neighborhood geographic unit. Tract rural-urban status was defined using the U.S. Department of Agriculture (USDA) 2000 primary Rural-Urban Commuting Areas (RUCA) codes. The primary RUCA codes use a flexible scheme to classify sub-county components into ten detailed rural/urban categories (United States Department of Agriculture Economic Services, 2016). For this analysis, we followed the literature to define urban as all metro tracts (RUCA=1–3, areas with a population of at least 50,000 people) and rural as all non-metro tracts (RUCA=4–10, areas with a population of less than 50,000 people) (United States Department of Agriculture Economic Services, 2016). Tract SES factor score, a composite scale of neighborhood SES was derived from the 2000 census including percent households with annual income at \$75,000 or more (i.e., concentrated affluence), percent residents living in poverty (i.e., concentrated poverty), and percent college-educated residents (i.e., aggregate education). Tract SES factor score was constructed based on the above three SES indicators and has high reliability ($\alpha = 0.85$) (Wen and Kowaleski-Jones, 2012; Wen & Maloney, 2011). Tract USDA Food desert areas were determined using USDA Food Desert Locator, which defined food deserts as low income tracts with at least 500 people or 33 percent of residents in the tract living far away from a supermarket, super center, or a large grocery store (The United states Department of Agriculture, 2016). The community/neighborhood safety level was captured by county crime rates (due to the unavailability of tract-level crime data), namely the total number of crimes per 1000 persons in the county.

Data analyses

Associations between multilevel (individual and community/neighborhood-level) factors and serum biomarker levels [CRP and 25(OH)D] were assessed using weighted multilevel random-intercept regression models. We treated CRP and 25(OH)D (dependent/outcome variables) as continuous variables. CRP values were log-transformed for normality. Outliers of CRP and 25(OH) values were included in the analysis. Analyses were conducted remotely using SAS 9.2 on the secured server at the Research Data Center (RDC) at Center for Disease Control and Prevention (CDC). For descriptive statistics, Proc Survey means was used to account for NHANES's complex sample design. For multivariate analysis, because SAS 9.2 did not have a procedure that could account for both complex sample design of NHANES and multilevel modeling simultaneously, random intercept multilevel models were estimated using Proc Glimmix. For the survey models the NHANES MEC weights adjusting for 6 years of data were computed and used. Proc Glimmix models were not weighted as recommended by Carle (2009), because the SAS 9.2 Glimmix procedure was not designed to handle complex survey weights correctly. However, the use of unweighted multilevel regression was not likely to produce significant bias in our estimates because weights-related variables were controlled in the regressions, and the clustering nature of the survey was taken into consideration by the multilevel method. A two-sided p value of < 0.05 was considered statistically significant.

Results

A total of 6643 adults aged from 19–65 years (mean age: 40.1 ± 0.3 years) were involved in this analyses. Approximately 51.2% were males and 48.8% were females with 16.0% being immigrants (foreign-born). The race/ethnicity distributions for non-Hispanic White, non-Hispanic Black and Hispanics were 70.4%, 11.5% and 12.5%, respectively. Approximately 84.3% of the participants graduated from high school and 25.7% had a college degree or higher. The mean income-to-needs ratio was 3.11 ± 0.05 . In males, 39.3% were overweight, 32.2% were obese and 31.1% were current smokers. The corresponding distributions of the above variables in females were 25.5%, 34.9%, and 23.0%.

Table 1
Characteristics and biomarker levels of study participants.

Variables	All Participants (N = 6643)	Males (N = 3402)	Females (N = 3241)
Individual characteristics			
Age (year)	41.10 \pm 0.33	40.59 \pm 0.41	41.61 \pm 0.35
Race/ethnicity (%)			
Black	11.52	10.79	12.24
Hispanic	12.48	12.96	12.00
White	70.32	70.72	69.91
Other	5.68	5.52	5.83
Foreign born (%)	15.98	17.21	14.73
Weight category (%) ^a			
Underweight	1.80	1.36	2.26
Normal weight	32.18	27.08	37.32
Overweight	32.45	39.33	25.52
Obese	33.57	32.24	34.90
Body mass index (kg/cm ²)	28.42 \pm 0.18	28.40 \pm 0.17	28.44 \pm 0.23
Current smokers (%)	27.53	31.09	23.93
High school graduates (%)	84.26	83.09	85.43
College degree or above (%)	25.66	25.10	26.21
Family income-to-needs ratio ^b	3.11 \pm 0.06	3.17 \pm 0.06	3.04 \pm 0.06
Serum biomarker levels			
C-reactive protein (mg/dL) ^c	0.41 \pm 0.01	0.33 \pm 0.02	0.48 \pm 0.02
25(OH)-vitamin D (ng/mL)	23.55 \pm 0.40	23.59 \pm 0.43	23.51 \pm 0.41
Community/neighborhood characteristics			
County crime rate (# of crime /1000 persons) ^d	4.17 \pm 0.26	4.12 \pm 0.27	4.22 \pm 0.26
Tract SES factor score ^e	0.10 \pm 0.06	0.10 \pm 0.06	0.10 \pm 0.06
Living in urban area (%)	73.88	73.83	73.92
Living in USDA food desert (%)	7.35	7.63	7.06

Note: Data are presented as mean \pm standard error (SE) or otherwise indicated.

^a Underweight: Body mass index (BMI) < 18.5 kg/cm²; Normal weight: BMI, 18.5–24.9 kg/cm²; Overweight, 25.0–29.9 kg/cm²; Obese: BMI > 30 kg/cm².

^b Family income-to-needs ratio: a ratio in which the numerator is a family's household annual income and the denominator is the federal poverty threshold given the appropriate family size, location and year.

^c C-reactive protein values were based on 6645 participants; 4 participants had missing data.

^d Total number of crimes per 1000 persons in the county.

^e Tract socioeconomic status (SES) factor score was constructed based on percent affluent households, percent residents in poverty and percent college educated residents.

For the community/neighborhood characteristics, the average county crime rate was 4.17 ± 0.26 crimes /1000 persons. Approximately 73.9% were living in the urban areas and 7.4% living in the areas defined as food desert. The mean levels of 25(OH)D were 23.5 ± 0.4 ng/mL for males and 23.5 ± 0.4 ng/mL for females; both were considered insufficient (sufficient ≥ 30 ng/mL; Holick et al., 2011). Females appeared to have higher serum CRP levels as compared to males (0.48 ± 0.02 mg/dL vs. 0.33 ± 0.02 mg/dL) (Table 1).

The average CRP value (0.42 mg/dL, 4.2 mg/L) in our study was comparable to those reported by previous studies using NHANES data (Batsis, Mackenzie, Jones, Lopez-Jimenez, & Bartels, 2016; Dabass et al., 2016). CRP is a nonspecific marker for inflammation. Since many conditions can cause an increased CRP production in our body, an elevated CRP level only supports the presence of inflammation and may

Table 2
Association of individual and community/neighborhood factors with serum C-reactive protein levels.

Variables	All Participants (N=6643)		Male (N=3402)		Female (N=3241)	
	β (SE)	P Value ^a	β (SE)	P Value ^a	β (SE)	P Value ^a
Individual factors						
Age (year)	0.014 (0.001)	< 0.0001	0.017 (0.001)	< 0.0001	0.010 (0.002)	< 0.0001
Male (vs. female)	-0.140 (0.020)	< 0.0001				
Black (vs. White)	-0.0004 (0.0395)	0.99	0.047 (0.053)	0.37	-0.068 (0.058)	0.25
Hispanic (vs. White)	0.172 (0.045)	0.0001	0.174 (0.062)	0.005	0.161 (0.064)	0.01
Foreign-born (vs. US-born)	-0.099 (0.042)	0.02	-0.111 (0.057)	0.05	-0.078 (0.062)	0.20
Body mass index (kg/m ²)	0.086 (0.002)	< 0.0001	0.079 (0.003)	< 0.0001	0.091 (0.003)	< 0.0001
Current smoker (vs. non-current smoker)	0.273 (0.033)	< 0.0001	0.299 (0.042)	< 0.0001	0.236 (0.051)	< 0.0001
Non-high school graduate (vs. high school graduate)	-0.029 (0.041)	0.48	-0.023 (0.055)	0.67	-0.086 (0.061)	0.16
College degree or above (vs. non-college graduate)	0.011 (0.037)	0.77	0.073 (0.062)	0.24	0.013 (0.066)	0.85
Income-to-needs ratio ^b	-0.033 (0.011)	0.002	-0.041 (0.014)	0.005	-0.021 (0.016)	0.18
Community/neighborhood factors						
Tract urban area (vs. rural area)	-0.058 (0.043)	0.17	-0.023 (0.055)	0.68	-0.091 (0.061)	0.14
County crime rate (# of crime/1000 persons) ^c	0.022 (0.008)	0.007	0.012 (0.011)	0.27	0.034 (0.012)	0.004
Tract SES factor score ^d	-0.003 (0.020)	0.88	-0.002 (0.027)	0.93	0.0005 (0.0294)	0.98
Tract USDA food desert (vs. non-food desert)	0.011 (0.052)	0.84	0.054 (0.067)	0.43	0.077 (0.075)	0.30

Note: β = β coefficient; SE = standard error.

^a P values were estimated using multilevel random-intercept regression model. Log-transformed values of C-reactive protein were used for β Coefficient and P value estimation.

^b A ratio in which the numerator is a family's household annual income and the denominator is the federal poverty threshold given the appropriate family size, location and year.

^c Total number of crimes per 1000 persons in the county.

^d Tract socioeconomic status (SES) factor score was constructed based on percent affluent households, percent residents in poverty and percent college educated residents.

not be used as a specific prognostic indicator (Seo, 2012). Nevertheless, a CRP level above 2.4 mg/L (0.24 mg/dL) has been associated with a twofold increase in risk of a coronary event compared to a CRP level less than 1.0 mg/L (0.1 mg/dL) (Hirschfield & Pepys, 2003; Seo, 2012). Research also reported that chronic lymphocytic leukemia patients with CRP levels ≥0.4 mg/dL (4.0 mg/L) were significantly associated with an increased risk of mortality (≈4-fold risk) and development of second solid cancer (≈3-fold risk) relative to patients with CRP levels < 0.4 mg/dL (4.0 mg/L) (Herishanu et al., 2016). The cut off points for CRP in the above studies (2.4 mg/L for risk of coronary event and 4.0 mg/L for mortality risk in leukemia patients) appeared to be lower than the mean value of CRP (0.42 mg/dL, 4.2 mg/L) observed in our study.

Associations of multilevel variables with serum CRP levels are

shown in Table 2. Serum CRP levels were positively associated with age (P < 0.0001), female sex (P < 0.0001), Hispanic race/ethnicity (P = 0.0001), current smokers (P < 0.0001), and body mass index (BMI, P < 0.0001), and inversely associated with family income-to-needs ratio (P = 0.002) and participants who were foreign-born (P = 0.02). Overall, the results were consistent after stratification by sex. However, the association with family income-to-needs ratio was only significant in men (P = 0.005) and the association with foreign-born was not significant in both men and women. As for community/neighborhood variables, significant and positive association between serum CRP levels and county crime rate was observed among all the participants (P = 0.007) as well as among females (P = 0.004). The relation was not significant among males in the study. In addition, CRP was not significantly associated with tract urban/rural status, tract

Table 3
Association of individual and community/neighborhood factors with serum 25(OH)-vitamin D levels.

Variables	All Participants (N=6643)		Male (N=3402)		Female (N=3241)	
	β (SE)	P Value ^a	β (SE)	P Value ^a	β (SE)	P Value ^a
Individual factors						
Age (year)	-0.004 (0.007)	0.59	0.019 (0.009)	0.04	-0.019 (0.011)	0.08
Male (vs. female)	0.260 (0.187)	0.16				
Black (vs. White)	-9.371 (0.290)	< 0.0001	-9.380 (0.361)	< 0.0001	-9.676 (0.430)	< 0.0001
Hispanic/Latino (vs. White)	-5.119 (0.325)	< 0.0001	-4.674 (0.425)	< 0.0001	-5.884 (0.473)	< 0.0001
Foreign-born (vs. US-born)	-0.086 (0.295)	0.77	-0.178 (0.381)	0.64	-0.609 (0.443)	0.17
Body mass index (kg/m ²)	-0.255 (0.014)	< 0.0001	-0.255 (0.014)	< 0.0001	-0.291 (0.020)	< 0.0001
Current smoker (vs. non-current smoker)	-0.446 (0.224)	0.047	-0.368 (0.278)	0.19	-0.628 (0.366)	0.09
Non-high school graduate (vs. high school graduate)	-0.157 (0.281)	0.58	0.014 (0.361)	0.97	-0.486 (0.437)	0.27
College degree or above (vs. non-college graduate)	0.113 (0.312)	0.72	-0.733 (0.409)	0.07	0.820 (0.471)	0.08
Family income-to-needs ratio ^b	0.268 (0.074)	0.0003	0.269 (0.095)	0.005	0.206 (0.112)	0.07
Community/neighborhood factors						
Tract urban area (vs. rural area)	-0.446 (0.390)	0.25	-0.312 (0.446)	0.48	-0.204 (0.499)	0.68
County crime rate (# of crime /1000 persons) ^c	-0.255 (0.069)	0.0002	-0.212 (0.082)	0.01	-0.292 (0.091)	0.001
Tract SES factor score ^d	0.202 (0.162)	0.21	0.208 (0.162)	0.20	0.007 (0.196)	0.97
Tract USDA food desert (vs. non-food desert)	0.340 (0.434)	0.43	0.342 (0.434)	0.43	0.187 (0.516)	0.72

Note: β = β Coefficient; SE = Standard error.

^a P values were estimated using multilevel random-intercept regression model.

^b A ratio in which the numerator is a family's household annual income and the denominator is the federal poverty threshold given the appropriate family size, location and year.

^c Total number of crimes per 1000 persons in the county.

^d Tract socioeconomic status (SES) factor score as constructed based on percent affluent households, percent residents in poverty and percent college educated residents.

SES factor score, and tract USDA food desert status.

Table 3 demonstrates the associations of multilevel factors with serum levels of 25(OH)D. Non-Hispanic black ($P < 0.0001$) and Hispanic race/ethnicity ($P < 0.0001$), lower family income-to-needs ratio ($P = 0.0002$), current smoker ($P = 0.047$), and higher BMI ($P < 0.0001$) were associated with lower circulating 25(OH)D levels. However, when stratified by sex, the association between 25(OH)D and income-to-needs ratio was significant in men ($P = 0.005$) but not in women ($P = 0.07$). Association between 25(OH)D and current smokers were not significant in both men ($P = 0.19$) and women ($P = 0.09$). With respect to community/neighborhood-level factors, county crime rate was significantly and inversely associated with circulating 25(OH)D levels overall ($P = 0.0002$) and in both males ($P = 0.01$) and females ($P = 0.001$). No significant associations were observed between other community/neighborhood variables (tract SES factor scores, tract urban/rural, tract USDA food desert areas) and serum 25(OH)D levels.

Discussion

Results from our multilevel regression model suggest that serum CRP levels were significantly and inversely associated with family income-to-needs ratio. Our results were consistent with previous studies which demonstrated inverse associations between serum inflammatory markers such as CRP and income levels (Aiello & Kaplan, 2009; Alley et al., 2006; Brummett et al., 2013; Friedman & Herd, 2010; Nazmi & Victora, 2007). However, we did not observe a significant association between CRP and participants' education background while several previous studies reported that serum CRP levels were significantly and inversely associated with both income and education levels (Brummett et al., 2013; Gruenewald, Cohen, Matthews, Tracy, & Seeman, 2009). Our results was in agreement with the study by Friedman et al. who reported that CRP, interleukin 6 (IL-6) and fibrinogen were inversely associated only with income levels but not education background in a multivariate regression model (Friedman & Herd, 2010). Likewise, our analyses also took into account of various factors such as age, sex, race/ethnicity, immigrant status, BMI, current smoking status, and some community/neighborhood characteristics since these factors could potentially confound the association of CRP with income-to-needs ratio and education levels.

The association of low income-to-needs ratio with higher CRP levels may be partially explained by the poor health related behaviors and their outcomes since research suggests that lower SES was associated with lower levels of physical activity, poorer diets, smoking and obesity, consequently leading to increased risk of metabolic symptoms and systematic inflammation (Baltrus, Lynch, Everson-Rose, Raghunathan, & Kaplan, 2005; Pollitt et al. 2007). Several theories have been proposed to understand how health behaviors and psychosocial factors contribute to the relation between lower SES and poorer health. One model is based on the assumption that health behaviors mainly reflect individual's free choices. This approach suggests that many poor health outcomes are associated with the daily conduct of people's lives since unhealthy behaviors are viewed as the consequence of poor lifestyle management. The other model suggests while individuals makes choices about how they act, those choices are situated within economic, family, cultural and political contexts. Therefore, SES can influence an individual's choices of health behaviors (Lynch et al., 1997).

The inverse association of family income-to-needs ratio with CRP could also be mediated by various psychosocial stress due to the fact that chronic stress was correlated to increases in circulating inflammatory makers such as CRP, IL-6, and tumor necrosis factor- α (Aiello & Kaplan, 2009). Brydon et al. reported that low SES participants were less able to adapt to stress with prolonged stress-induced increases in IL-6 compared to their high SES counterparts (Brydon, Edwards, Mohamed-Ali, & Steptoe, 2004). Therefore, one underlying mechanism that has been suggested for the inverse association between SES

and cardiovascular disease risk is through sustained activation of stress-related biological pathways to promote inflammatory response and subsequently atherosclerosis (Bryant et al., 2008; Pollitt et al., 2007). This mechanism coincided with our finding that participants with higher CRP levels was associated with lower individual economic status (as indicated by lower income-to-needs ratio).

Interestingly, the association of CRP with family income-to-needs ratio was significant only in men not in women. There are some possible biological and socio-behavioral explanations. As mentioned above, people with lower SES had greater and more sustained IL-6 response to acute psychological stress relative to people with higher SES (Bryant et al., 2008). However, the association between stress induced IL-6 responses and CRP levels differed by sex. In males, larger stressor-evoked IL-6 responses were associated with higher CRP concentrations, whereas in females, stressor-evoked IL-6 responses showed a non-significant negative association with CRP possibly due to the potential anti-inflammatory effect of estrogen (Lockwood, Marsland, Cohen, & Gianaros, 2016). It is further suggested that cardiovascular disease incidence occurred approximately ten years behind in females than that in males and this lag maybe attributable to the hormonal changes during and after menopause (Lockwood et al., 2016; Roger et al., 2012). On the other hand, research suggests that differences in health outcomes between men and women maybe better explained by characteristics such as gender roles, gender identity, gender relationships and gender associated behaviors than biological attributes associated with sex (Norris et al., 2016). A study conducted in college students reported that female students had healthier health related behaviors such as alcohol consumption, nutrition and physical activity compared to male students (von Bothmer & Fridlund, 2005), which may also in part explained why no significant association between CRP and individual income-to-needs ratio was observed for women in the current study. In addition, it could also be that men might be more vulnerable to low income than women due to the traditional bread earner pressure. Thus, a more complex model is needed to examine how sex differences contribute to inflammation and health outcomes by including various biological, psychological, social and behavioral factors and their interactions.

The current study also observed that lower serum CRP levels were associated with foreign-born individuals relative to participants who were U.S.-born. This may suggest that immigrants generally tend to be healthier than their native counterparts which was supported by previous work. For instance, research suggests that Caribbean and African immigrants had more favorable physical and mental health indicators compared to native-born blacks (Doamekpor & Dinwiddie, 2015; Singh & Siahpush, 2002; Williams et al., 2007). This could be partially due to the healthy immigrant effect, that is, immigrants have healthier lifestyles in their home countries, are among the healthiest from their home country, and are those most willing and able to endure the stressors associated with immigration, thereby placing them at a health advantage (Doamekpor & Dinwiddie, 2015). However, research also suggest that the health advantage declines with increasing length of U.S. residence when immigrants adapt to the US sociocultural environment (Doamekpor & Dinwiddie, 2015; Read & Gorman, 2006).

In our study, there were no associations of CRP with neighborhood SES (as indicated by the tract SES factor score). Petersen et al. examined the associations of both individual and community SES with inflammatory markers of CRP and IL-6 in 851 men and women, 30 to 54 years of age and found that community SES was associated with both IL-6 and CRP after the adjustment for age, sex and race; but this link attenuated when adjusting for other lifestyle factors such as smoking, alcohol consumption, sleep, exercise, and BMI (Petersen et al., 2008). This finding was largely in agreement with the current finding that serum CRP was not associated with SES at neighborhood level after the adjustment for various covariates in this national representative sample. However, county crime rate was positively

associated with serum CRP levels, which brought up a serious issue regarding social disorders of disadvantaged communities/neighborhoods. There are many signs of community/neighborhood social disorders and place safety can be one of the main components. Living in an environment that one constantly perceives to be dangerous can cause psychological distress, leading to the potential of triggering physiological stress response (Burdette et al., 2006; Ross & Mirowsky, 2001) and in turn, chronic inflammation and unfavorable health outcomes. We also observed that the association between county crime rates and CRP was only significant in women not in men after adjustment for other individual and community/neighborhood factors. This further suggests that psychological distress associated with the concern of place safety appeared to be more persistent and overwhelming for women than for men, thereby making women more susceptible to stress associated inflammation.

With respect to the associations of vitamin D with individual SES and community/neighborhood qualities, the current results suggest that levels of serum 25(OH)D (indicator of vitamin D status) were positively associated with family income-to-needs ratio and inversely associated with county crime rates. The positive association between serum vitamin D levels and family income-to-needs ratio observed in the current study could be in part due to the fact that individuals with higher income were more likely to have access to primary care and test their vitamin D levels as compared to those with lower income individuals, thereby more aware of vitamin D deficiency they might have. De Koning et al. examined 1436 census dissemination areas within the city of Calgary, Canada to determine age and sex-specific 25(OH)D testing rates over a one year period and reported that median household income was associated with increased testing utilization of vitamin D (de Koning, Henne, Woods, Hemmelgarn, & Naugler, 2014). In addition, previous studies also reported that individuals with higher SES (e.g., education attainment, income, and health insurance status) are more likely to use dietary supplements than their lower SES counterparts (Bailey, Gahche, Miller, Thomas, & Dwyer, 2013; Wallace, McBurney, & Fulgoni, 2014). Similar to CRP results, we also observed that the association of 25(OH)D with family income-to-needs ratio was significant in men not in women, suggesting women in general might be more conscious about their health regardless of SES. In support, it has been reported that women were more likely to use dietary supplements compared to men among U.S. adults with disabilities and in the general U.S. population (An, Chiu, & Andrade, 2015; Gahche et al., 2011; Wallace et al., 2014). Previous research also shows that females tended to have better health related behaviors such as nutrition compared to males (von Bothmer & Fridlund, 2005).

With regard to the inverse association between serum vitamin D levels and county crime rate, it could be partially attributable to the fact that high area crime rate discouraged residents from actively participating in outdoor activities and thus lowered their vitamin D levels since vitamin D in our body is mainly synthesized through skin exposure to ultraviolet radiation such as sunlight (Mehta & Mehta, 2002). It is possible that some participants living in disadvantaged communities/neighborhoods were likely to be outdoor workers which had increased chances of sunlight exposure, thereby potentially confounding the currently observed association. However, this confounding effect would be minimal since the inverse associations of circulating vitamin D levels with county crime rates were significant in both men and women. Nevertheless, further studies examining the relations between occupation and serum vitamin D levels are necessary. Another explanation could be that residents living in disadvantaged communities/neighborhoods such as areas with high crime rates tended to be characterized as those with lower SES, which were less likely to take supplements than their higher SES counterparts (An, Chiu, & Andrade, 2015; Gahche et al., 2011; Wallace et al., 2014). However, the inverse association between SES and serum 25(OH)D levels was captured only at the individual level (income-to-needs ratio) not at the community/neighborhood level in our study. Indeed, the fact

that county crime rates were the sole community/neighborhood factor that was significantly linked to both biomarkers (CRP and vitamin D) further suggests that place safety may be an overwhelming contextual determinant that outran other tract-level factors in terms of the explanatory power even though we did not have the precise measure of neighborhood tract-level crime rate.

Our study was one of the few studies to assess the associations of both individual and community/neighborhood-level factors with serum CRP levels and was the first study to examine multi-level factors (individual and community/neighborhood-level) with serum vitamin D levels in a large-scale, nationally representative sample (NHANES) which strengthened the generalizability of study results. There were several limitations of the current study. First and foremost, due to the cross-sectional design, no causality should be assumed from the results. Second, to keep the analyses focused, only main effects were examined while complex within-level or cross-level interaction effects as well as mediation or moderation effects by other relevant factors are left for future research. For example, it would be interesting to test how community/neighborhood characteristics vary by individual SES such as in-come-to needs and education levels in relation to serum CRP and vitamin D concentrations. It would also be interesting to examine if vitamin D status moderates or mediates the associations of individual or community/neighborhood factors with CRP since research suggests that vitamin D may have anti-inflammatory properties (Bikle, 2009). Third, in the present study the neighborhood was defined by census tract, an administrative unit used in the US census. Although this approach takes advantage of easily accessible census data and is often adopted in the literature, the drawback of using artificially defined spatial boundaries to circumscribe socio-culturally meaningful neighborhoods is an inevitable exposure misspecification, a conservative bias commonly shared in studies of neighborhood effects on health. Also, because of the unavailability of tract-level data, the county-level crime rates were used in the analyses. However, since we found significant correlations of both serum CRP and 25(OH)D concentrations with area crime rates at more distant county level, it is more likely we would observe significant associations between these biomarkers and crime rates at tract level if the data were available. Future research focusing on tract-level crime data is warranted. Lastly, we did not include individual's lifestyle habits (such as dietary and physical activity behaviors) except for smoking status in the analyses. However, it is more likely that lifestyle factors mediate the association between SES and CRP and vitamin D levels instead of confounding, therefore, including lifestyle factors as covariates in the model may not be relevant to the associations observed in the current study.

In conclusion, the results from this multilevel nationwide study provide evidence that lower income-to-needs ratio was associated with increased serum CRP and decreased serum vitamin D levels, suggesting individual socioeconomic status may contribute to the disparity in health and chronic disease outcomes through inflammation and/or reduced vitamin D levels. Thus, increasing need and action to address socioeconomic differentials is necessary for reducing health disparity and preventing chronic diseases. The inverse association of neighborhood crime rate with serum vitamin D levels and positive association with CRP concentrations also suggest that building a safe community is important to prevent vitamin D deficiency, reduce chronic inflammation, and improve overall health of residents in the area.

Acknowledgment

This research was supported by the National Institute of General Medical Sciences of the National Institutes of Health (NIH) Grant R01CA140319–01A1.

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