



Effect of Poverty Level on the Relationship Between Hyperlipidemia and Cardiorenal Syndrome

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## Effect of Poverty Level on the Relationship Between Hyperlipidemia and Cardiorenal Syndrome

### Abstract

**Purpose.** Elevated cholesterol is known to be associated with chronic kidney disease (CKD) and cardiovascular disease (CVD) independently. Cardiorenal syndrome (CRS), a recently defined syndrome, is characterized by renal failure that is closely interrelated to cardiac dysfunction. The effect of socioeconomic status on cardiorenal syndrome has not been explored in a multi-ethnic population. In this retrospective secondary analysis, the hypothesis was tested if socioeconomic status modifies the effect of hyperlipidemia on CRS.

**Methods.** The National Health and Nutrition Examination Survey (NHANES) is a cross sectional survey done on the non-institutionalized population of the United States. All patients from the NHANES study, 20 years and older between the years 1999-2010 were included in the analysis. CRS was determined using a standard GFR equation and history of CVD. Analysis was performed using complex samples logistic regression to determine the relationship of hyperlipidemia on CRS.

**Results.** Data on CRS status was available for 24,625 individuals (48.9% males & 51.1% females) and was representative of 173,805,863 individuals. The overall unadjusted odds ratio of CRS for hyperlipidemia to no hyperlipidemia was 3.01 (95% confidence interval [CI], 2.62-3.47,  $p < 0.001$ ). The adjusted OR was elevated, 2.20 (CI 1.20-4.05,  $p < 0.01$ ), among individuals living below poverty threshold but close to 1.0 (1.63 CI 1.31-2.03,  $p < 0.001$ ) among patients above poverty threshold, after the results were controlled for medical risk factors and demographic risk factors.

**Conclusions.** Hyperlipidemia is strongly associated with CRS in a nationally representative multi-ethnic population and must be taken into special consideration when treating underprivileged patients. Longitudinal studies should further examine this association and demonstrate how socioeconomic status plays a role.

### Keywords

Hyperlipidemia; Socioeconomic Status; Cardiorenal Syndrome; NHANES

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## **Effect of Poverty Level on the Relationship between Hyperlipidemia and Cardiorenal Syndrome**

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### **ABSTRACT**

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## INTRODUCTION

Understanding chronic diseases through the lens of upstream factors like poverty and social disparities is an integral part of preventive medicine (Aikens & Piette, 2009; Overland, Hoskins, McGill, & Yue, 1993; Krishnaswami, Jaini, Howard, Ghaddar, 2018; Rutter et al., 2017). Managing and diagnosing hyperlipidemia is a standard of care to effectively prevent chronic kidney disease (CKD) and cardiovascular disease (CVD) (Althemery, Lai, & Alfaifi, 2015; Tarride, 2009). Hyperlipidemia refers to elevated cholesterol, elevated triglycerides, or both. Much of the work in chronic disease has focused on lifestyle changes; however, social determinants of health may provide a better understanding of why these lifestyle changes are not improving health outcomes (Althemery, Lai, & Alfaifi, 2015; Tarride, 2009). Rather than examining socioeconomic status individually, most researchers control for this variable. The lack of research on social determinants of health associated with cardiorenal syndrome demonstrates that there is a need for understanding whether these factors have direct or indirect effects and what the mechanism's underlying associations may be. The psychological demands of chronic diseases suggest that a pathway may exist, but more work is needed to overcome the current gaps in knowledge (Walker, Gebregziabher, Martin-Harris, & Egede, 2014).

Hyperlipidemia is a major cause of morbidity in the worldwide, causing cardiovascular and renal dysfunction simultaneously. Consequently, cardiorenal syndrome (CRS) is closely related complication of hyperlipidemia and is associated with increased mortality, growing complications, and increased cost of care (Flores, Chavez, Bolger, & Casad, 2018; Krishnaswami, Jaini, Howard, & Ghaddar, 2018; Liang et al., 2018; Taylor et al., 2017; Walker et al., 2014; Williams et al., 2018; Zeng et al., 2018). Cardiorenal syndrome can be defined as a bidirectional pathological impairment of either the heart or the kidney as a result of acute or chronic primary dysfunction in either organ (Banerjee & Panas, 2017; Lekawanvijit et al., 2012; Ronco, House, & Haapio, 2008; Stucker & Saudan, 2013; Virzi, Clementi, Battaglia, & Ronco, 2019). Depending on the primary organ affected and the acuteness of the condition, this syndrome constitutes five subtypes (Banerjee et al., 2017; Virzi et al., 2019). Hyperlipidemia is associated with CKD development due to renal artery sclerosis and nephroangiosclerosis and a faster rate of CKD progression. Additionally, dyslipidemia is associated with CVD and more mortality due to cardiovascular disease than end stage renal disease (ESRD) (Machado et al., 2018; Usui et al., 2017). More specifically low high-density lipoprotein (HDL) cholesterol and elevated non-HDL cholesterol are associated to a two-fold risk of renal insufficiency after adjustment for other risk factors (Usui et al., 2017). The risk of microvascular complications can be reduced by control of hyperlipidemia through statins, whereas benefit to CRS is less clear.

The precise connection between socioeconomic status and lipid status is unknown. Specifically, the effect of hyperlipidemia on CRS has not been explored in a nationally representative multi-ethnic population previously, especially in the context of social disparities. In this retrospective secondary analysis, the hypothesis was tested if poverty level has an effect on lipid status and if poverty level modifies the effect of hyperlipidemia on CRS.

## METHODS

The National Health and Nutrition Examination Survey (NHANES) is a cross sectional survey done on the non-institutionalized population of the United States by the Center for Disease

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Control and Prevention and National Center for Health Statistics. All patients from the nationally representative NHANES study, 20 years and older between the years 1999-2010 were included in the analysis.

Presence of cardiorenal syndrome was designated by determining the presence of CKD and CVD. Glomerular filtration rate (GFR) was derived from the Cockcroft-Gault equation. For the purposes of this study, a GFR of less than 60 mL/min per 1.73 m<sup>2</sup> was considered to be CKD as previously validated. Even though, technically, a GFR less than 90 mL/min per 1.73 m<sup>2</sup> is considered CKD, the high number from advanced age places most people with a high age in either Stage I or Stage II CKD. CVD was determined by the self-reported diagnosis of coronary heart disease, angina, stroke, Congestive Heart Failure (CHF), and heart attack.

All respondents over the age of 20 were asked “Other than during pregnancy, have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?”. For the purposes of this study, the participants who answered “borderline” or “yes” was considered as having diabetes. However, those participants who answered “no” was considered as non-diabetic.

Below poverty threshold was considered when poverty-income ratio less than one. This is equivalent to less than 100% of the Federal Poverty Level. Poverty-income Ratio (PIR) greater than or equal to 1 was considered above poverty threshold.

Each respondent was asked about their cholesterol status. Hyperlipidemia was defined by the respondent answering “yes” to being told of having high cholesterol, was taking cholesterol-lowering drugs, or had a cholesterol level of 240 mg/dL or higher. The rest of the subjects were ascertained as not having high cholesterol.

The smoking data was subdivided into a two-variable indicator as a smoker versus never smoker. The subject was considered a “smoker” if s/he reports “yes” to the question, “Have you smoked at least 100 cigarettes in your entire life?” and did not answer “not at all” to the question, “Do you now smoke cigarettes...” in the NHANES 1999–2010. Any answers by the participants such as “don’t know”, “refuse”, or “not sure” was recorded as missing data and was not be included in the data analyses. In order to ascertain the race/ethnicity of the subject, the interviewer asked “What race do you consider yourself to be?” Within the NHANES questionnaire, respondents were allowed to select one out of five categories. The different categories were coded as follows: Non-Hispanic White, Non-Hispanic Black, Hispanic, and Other.

Hs-CRP was quantified by using latex-enhanced nephelometry, and a high-sensitivity assay was performed on a Behring (Deerfield, IL) nephelometer. The lower limit of detection for this test was 0.2 mg/L. For continuous analyses, all values of 0.2 mg/L were coded as equal to 0.1. Research in adults has indicated increased risk of cardiovascular disease beginning at values of > 2.0 mg/L, so this value was used as a cut point for analysis (Ridker, 2003; Ridker et al., 2005). Values of hs-CRP < 1.0 mg/L was considered as cardiovascular risk, and the rest was not.

Before data collection for NHANES, the NCHS received approval from the NCHS Research Ethics Review Board (changed from the Institute Review Board), continuance of the protocol #2011-17. The NCHS complies strictly with the different laws and regulations which are written with the intent of protecting the specific participant’s confidentiality and safety.

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### Study Population

All non-institutionalized patients from the nationally representative NHANES study, 20 years and older between the years 1999-2010 were included in the analysis. This study is especially needed in a national population as broad policy guidelines are needed at a national level.

### Statistical analysis

Continuous variables were described as both mean  $\pm$  standard deviation (SD). Normal distributions of values were assessed by using the Shapiro-Wilk test. Categorical variables were expressed as percentage values and analyzed using chi-square testing. Analysis was performed using complex samples logistic regression to determine relationship of hypercholesterolemia on CRS. Complex samples multiple logistic regression models were used to examine below-above poverty line patient differences after adjusting for sociodemographic and health factors, estimating variances using the Taylor series linearization method. All missing variables were excluded. All statistical analysis was performed in SAS 9.2 and SPSS 21.0.

## **RESULTS**

Data was available for 12,332 individuals (53% females vs. 47% males). Table 1 provides data on the distribution of demographic characteristics of the participants by socioeconomic status using bivariate analysis. The prevalence of CRS in US population in the age group between 20-85 was 5.1%. The average age of participants with CRS was  $73.4 \pm 0.28$ . There was statistically significant ( $p < 0.05$ ) association between poverty level and obesity, cholesterol, diabetes, gender, age, race/ethnicity, and CRP status. There were significantly more females (61.7%) with  $PIR < 1$  than females (51.6%) with  $PIR \geq 1$ , as seen in Table 1. Among Non-Hispanic Blacks, the percentage with  $PIR < 1$  (17.3%) was higher than  $PIR \geq 1$  (9.0%). A similar pattern was observed among the Hispanic population.

In addition to the basic demographic descriptive statistics, the following variables that may be associated with socioeconomic status are presented in Table 1. Based on bivariate analyses, more individuals with  $PIR < 1$  (14.1%) had diabetes than individuals with  $PIR \geq 1$  (9.9%). Also, among smokers, more individuals had  $PIR < 1$  (52.5%) than individuals with  $PIR \geq 1$  (44.9%). Finally, when assessing C-reactive protein, individuals with  $PIR < 1$  (5.0%) had higher rates of high CRP than those in  $PIR \geq 1$  (2.5%).

Table 1. Baseline Clinical Characteristics of Study Participants stratified by Poverty-to-Income Ratio

<b>Variable</b>	<b>Total population (n=12,332)</b>	<b>PIR ≥ 1 (n=9,565)</b>	<b>PIR &lt; 1 (n=1,740)</b>
<b>Demographic Risk Factors</b>			
<b>Female**</b>	52.7%	51.6%	61.7%
<b>Mean age (SE)</b>	48.5 (0.21)	48.6 (0.19)	45.4 (0.28)
<b>Ethnicity**</b>			
<b>Non-Hisp. White</b>	74.1%	77.3%	50.6%
<b>Non-Hisp. Black</b>	9.9%	9.0%	17.3%
<b>Hispanic</b>	10.8%	8.8%	25.2%
<b>Other</b>	5.2%	4.9%	6.9%
<b>CRS Risk Factors</b>			
<b>CRP Levels (µg/ml)**</b>			
<b>Low (&lt;1)</b>	90.3%	90.7%	84.9%
<b>Intermediate (1-2)</b>	6.9%	6.8%	10.1%
<b>High (&gt;2)</b>	2.7%	2.5%	5.0%
<b>Diabetes**</b>	10.4%	9.9%	14.1%
<b>Smoking Status</b>			
<b>Smoker</b>	45.9%	44.9%	52.5%
<b>Non-Smoker</b>	54.1%	55.1%	47.5%
<b>Obesity Status**</b>			
<b>Non-obese</b>	62.5%	63.0%	52.3%
<b>Obese</b>	37.5%	37.0%	13.4%

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<b>Hyperlipidemia**</b>	37.8%	37.0%	41.4%
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\*\*p < 0.05

As seen in Table 2, significant predictors to CRS among patients above poverty threshold (PIR  $\geq$  1) were patients: with diabetes (OR= 2.71; CI= 1.55-4.73), with hyperlipidemia (OR= 1.63; CI=1.31-2.01), without obesity (OR= 0.61; CI=0.48-0.77), high CRP (OR=2.14; CI=1.28-2.58), Non-Hispanic Black race (OR=1.58; CI=1.17-2.13, male sex (OR= 1.30; CI=1.01-1.68) and increased age (OR= 1.19; CI= 1.17-1.21). As seen in Table 3, significant predictors to CRS among patients below poverty threshold (PIR < 1) were patients: with diabetes (OR= 3.92; CI= 2.95-5.22), with hyperlipidemia (OR= 2.20; CI=1.20-4.05), Non-Hispanic Black race (OR=2.71; CI=1.43-5.16), and increased age (OR= 1.11; CI= 1.08-1.14).

Differential effect of poverty level on CRS

Specifically, there is a differential effect observed of poverty level on hyperlipidemia and ethnicity. The overall unadjusted odds ratio of CRS for hyperlipidemia to no hyperlipidemia was 3.01 (95% confidence interval [CI], 2.62-3.47, p < 0.001). As seen on Table 2 and Table 3, the adjusted OR was elevated, 2.20 (CI 1.20-4.05, p < 0.01), among individuals living below poverty (PIR < 1) threshold but close to 1.0 (1.63 CI 1.31-2.03, p < 0.001) among patients above poverty threshold (PIR  $\geq$  1), after the results were controlled for medical (obesity, smoking status, diabetes, and C-reactive protein) risk factors and demographic (ethnicity, gender, and age) risk factors. Additionally, the adjusted OR of CRS to no CRS among Non-Hispanic Blacks was elevated, 2.71 (CI 1.43-5.16, p < 0.001), among individuals living below poverty (PIR < 1) threshold but close to 1.0 (1.58 CI 1.17-2.13, p < 0.05) among patients above poverty threshold (PIR  $\geq$  1), after the results were controlled for medical (obesity, smoking status, diabetes, and C-reactive protein) risk factors and demographic (ethnicity, gender, and age) risk factors.



Table 2: Multiple regression analysis between Hyperlipidemia and CRS in those individuals with Poverty-Income-Ratio  $\geq 1$ .

Variable	B	95% Confidence Interval		P
		Lower	Upper	
<b>Diabetes</b>	2.71	1.55	4.73	<0.001
<b>Hyperlipidemia (mg/dL)</b> (Reference: LDL<240)	1.63	1.31	2.03	<0.001
<b>Obesity</b> (Reference: BMI<30)	0.61	0.48	0.77	<0.001
<b>Smoking Status</b> (Reference: Never Smoker)	0.86	0.68	1.08	0.198
<b>C-reactive protein</b>				
<b>(<math>\mu\text{g/ml}</math>)</b>				
<b>Low (&lt;1)</b>	Reference	Reference	Reference	Reference
<b>Intermediate (1-2)</b>	1.57	1.03	2.38	0.005
<b>High (&gt;2)</b>	2.14	1.28	2.58	0.005
<b>Ethnicity</b>				
<b>Non-Hisp. White</b>	Reference	Reference	Reference	Reference
<b>Non-Hisp. Black</b>	1.58	1.17	2.13	0.017
<b>Hispanic</b>	0.94	0.606	1.45	0.017
<b>Other</b>	1.41	0.60	3.28	0.017
<b>Gender</b> (Reference:Female)	1.30	1.01	1.68	0.042
<b>Age</b>	1.19	1.17	1.21	<0.001

Table 3: Multiple regression analysis between Hyperlipidemia and CRS in those individuals with Poverty-Income-Ratio < 1.

Variable	B	95% Confidence Interval		P
		Lower	Upper	
<b>Diabetes</b>	3.92	2.95	5.22	<0.001
<b>Hyperlipidemia (mg/dL)</b> (Reference: LDL<240)	2.20	1.20	4.05	0.010
<b>Obesity</b> (Reference: BMI<30)	0.66	0.40	1.09	0.106
<b>Smoking Status</b> (Reference: Never Smoker)	0.73	0.40	1.36	0.319
<b>C-reactive protein (µg/ml)</b>				
<b>Low (&lt;1)</b>	Reference	Reference	Reference	Reference
<b>Intermediate (1-2)</b>	0.77	0.37	1.62	0.283
<b>High (&gt;2)</b>	1.82	0.81	4.08	0.283
<b>Ethnicity</b>				
<b>Non-Hisp. White</b>	Reference	Reference	Reference	Reference
<b>Non-Hisp. Black</b>	2.71	1.43	5.16	<0.001
<b>Hispanic</b>	0.86	0.45	1.64	0.001
<b>Other</b>	0.15	0.03	0.85	0.001
<b>Gender (Reference:Female)</b>	1.10	0.56	2.17	0.777
<b>Age</b>	1.11	1.08	1.14	<0.001

## DISCUSSION

Hyperlipidemia is a significant comorbidity which brings significant complications to the prognosis of CKD and CHF simultaneously (Althemery et al., 2015). The novel finding in this study was that lipid status is associated with socioeconomic status in a nationally representative population. This finding has been corroborated in other studies conducted from the National Cardiovascular Data Registry's Practice Innovation and Clinical Excellence (PINNACLE) Registry. The reason may be due to differential medication access or access to lipid-lowering diet depending on the level of income (Tanguturi et al., 2019)

Also, in this study, we found that there was a strong association between hyperlipidemia and CRS. According to our findings, individuals who have hyperlipidemia and low socioeconomic status (less than 100% of Federal Poverty Guidelines) have 320% higher likelihood of developing CRS than those that do not have hyperlipidemia in our nationally representative sample. Previous researchers have found hyperlipidemia and socioeconomic status individually have an impact on cardiovascular disease (Ahmed et al., 2018; Cain, Glover, Young, & Sims, 2018; Heidenreich et al., 2011; Ma, Wang, Liu, & Cao, 2016; Xu, 2018). Additionally, hyperlipidemia and socioeconomic status has an effect on CKD. According to researchers analyzing the Jackson Heart Study, Cain et al. (2018) found that stress was related to the development of CKD. Due to acute and chronic stress through allostatic load affecting the hypothalamic-pituitary-adrenal axis,

socioeconomic status has repeatedly been tied to chronic disease (Christensen, Flensburg-Madsen, Garde, Hansen, Pedersen, Mortensen, 2018; Xu, 2018). More specifically cortisol has been connected with psychoneuroendocrine dysfunction which is a by-product of chronic stress from living in poverty (Christensen et al., 2018). Low socioeconomic status has been associated with many other diseases as well (Walker, Williams, & Egede, 2016; Hannibal & Bishop, 2014).

Additionally, other CRS risk factors affect individuals living below poverty level status differently than those living at or above poverty level. Specifically, when assessing known differences in CRS risk factors, we found that there was a statistically significant association observed between C-reactive protein among individuals below poverty level.

Similarly, ethnicity had a differential effect in the hyperlipidemia versus CRS model among individuals in low socioeconomic status versus individuals in high socioeconomic status. More specifically, according to our study, Non-Hispanic Blacks living below poverty had higher odds of CRS among those with hyperlipidemia than those without. This is alarming because African Americans require dialysis or transplant at younger ages and have greater incidence rates of end stage renal disease (ESRD) at each decade of life as compared to any other racial/ethnic group (Cain et al., 2018; De Moraes, Carvalho, McClelland, Diez-Roux, Szklo, 2018; Inman et al., 2016; Marmot & Allen, 2014; Vart et al., 2018). Health care practitioners need to be made aware of how social determinants of health affects CRS (Cockerham, Hamby, & Oates, 2017; Joshi, John, & Jha, 2017; Kang et al., 2018; Norris, Nicholas, García-García, Agodoa, 2017; Phillips et al., 2018). According to our study, individuals who have CVD and diabetes have a 125% higher likelihood of developing CKD than those that do not have CVD, after controlling for CVD related risk factors in a multi-ethnic population.

There were multiple limitations in this study. First of all, this is a cross-sectional study, making it difficult to establish causation without reasonable doubt (Lê-Scherban et al., 2018). More longitudinal studies need to be done to understand the precise role of diabetes in the context of CRS. Additionally, many times self-reported data may suffer from recall bias or social desirability bias. However, wherever possible, we cross-checked self-reported data with laboratory tests.

The study has several strengths. This study is the first to demonstrate on a national level that hyperlipidemia is more strongly associated with cardiorenal syndrome in individuals with low socioeconomic status than in a high socioeconomic status. Due to the study design, the association can be generalized to the national level. Additionally, there are differential risk factors between low and normal socioeconomic status as is pertain cardiorenal syndrome. Demonstrating risk factors of cardiorenal syndrome is important as this is a typical endpoint for several chronic diseases like cardiovascular disease, diabetes, and congestive heart failure.

#### Future Research and Practical Recommendations

In light of cyclical economic downturns, it is increasingly important to understand the health effects of varying poverty levels. Recently, with the global impact of COVID-19, many individuals are experiencing poverty and limited access to preventative care. Future policy should be tailored to address economic disparities in the population so that modifiable risk factors can be mitigated. Potential disparities in access to care should be addressed by identifying important barriers experienced by the poor.

In our study, it is unclear why income level modifies the impact that lipid status has on the development of CRS. One possibility is that hyperlipidemia may have an interaction with

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adrenergic overactivity and corticoadrenal activity especially among those with chronic emotional stress (Lopez-Cepero et al., 2020). Chronic stress has been shown to be experienced by those who are poor. These potential connections can be assessed through further physiological or fMRI studies. Additionally, the precise longitudinal connections should be explored using interaction studies between income status and lipid status. This will help establish causation more strongly.

### CONCLUSION

Chronic diseases risk factors are different according to the socioeconomic disparities of the population. Specifically, lipid metabolism is important as it pertains to chronic diseases like cardiorenal syndrome. However, when considering poverty and low socioeconomic status, hyperlipidemia has a differential effect on the group. More studies need to explore which risk factors are important as it pertains to specific socioeconomic status. Policies from the governmental level need to address health inequity and provide resources and education for individuals in different socioeconomic status. Self-management and better coordination of care needs to take place in this subpopulation as well.

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