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Walden University

School of Health and Human Services

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Hassan Naji

has been found to be complete and satisfactory in all respects,
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Review Committee

Dr. Robert Marino, Committee Chairperson, Health Services Faculty

Dr. Xianbin Li, Committee Member, Health Services Faculty

Dr. Diana Naser, University Reviewer, Health Services Faculty

Chief Academic Officer

Eric Riedel, Ph.D.

Walden University

2015

Abstract

Association of Bisphenol A and C-Reactive Protein Concentrations with
Cardiovascular Diseases

by

Hassan S. Naji

MA, Everest University, 2009

BS, American University of Beirut, 1993

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

November 2015

Abstract

Bisphenol A (BPA), a widely used chemical in plastic, has drawn wide attention due to its presence in many consumer products and the environment. The purpose of this study was to examine the association between urinary BPA and the reporting of cardiovascular diseases (CVD), and then to examine the effect of C-reactive protein (CRP) as a moderating variable. The data used in this research were extracted from the National Health and Nutrition Examination Survey collected in 2009-2010. Guided by the advanced epidemiological triangle, analysis involved 2 stepwise binary logistic regressions. The first step suggested that the controls were significant in predicting CVD ($\chi^2 (5) = 83.72, p < .001, R^2 = .15$). The Nagelkerke R^2 coefficient of determination indicated that the controls explained approximately 15% of the variance in instances of CVD. The second step of the binary logistic regression included the controls and BPA level in the model together. The regression analysis suggested that the Nagelkerke coefficient of determination ($\chi^2 (6) = 83.76, p < .001, R^2 = .15$) did not increase from the 15% explained by the controls, and BPA level was found to be a nonsignificant predictor of CVD ($p = .853$). Due to lack of association between BPA and CVD, the analysis was shifted to examine the association between urinary BPA and serum CRP. The association between urinary BPA and serum CRP was also statistically nonsignificant (Spearman correlation coefficient, $r_s = .06, p = .015$). The results may have positive social change by contributing to the body of knowledge on BPA and by increasing scientific scrutiny for substances used in people's daily lives.

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Dedication

This work is dedicated for my two boys, Allen and Jad, for giving me the inspiration and support to pursue my education. Your “we will leave you daddy to work” was essential to write and research this dissertation. Thank you my two greatest boys of all time. You are part of this process and you are the most important achievement I have ever made.

This work is also dedicated to my mother, Zehriya, God rest her soul in peace, for never giving up on me. There was a time in my life where I decided to quit elementary school because of our poverty, but she insisted and negotiated with my beloved father to take part of the house budget for my education...Mom! Without you I could not be here!

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Chapter 1: Introduction to the Study

Introduction

Bisphenol A (BPA), 2, 2-bis-(4-hydroxyphenyl) propane, is a synthetic chemical found in polycarbonate plastic, in many household items including some water bottles and baby bottles, and in epoxy resins (Vogel, 2009). BPA is also used to line metal products including canned foods. Research suggested that when the BPA found in plastic containers was heated, it leaked into the contents, often consumable beverages and food (Vogel, 2009). Studies on BPA conducted by independent researchers (Bindhumol, Chitra, & Mathur, 2003; Melzer, Rice, Lewis, Henle, & Galloway, 2010; Newbold, Padilla-Banks, Jefferson, & Heindel, 2008; Repero, Alonso-Magdalena, Garcia-Garcia, Ripoll, & Fuentes, 2008) suggested an association between consumption of BPA and adverse health effects, such as breast and prostate cancers, cardiovascular diseases (CVD), obesity, reproductive anomalies, and neurological problems. Studies done by the Food and Drug Administration (FDA, 2009, 2010, 2013) deemed BPA safe on humans, but advised caution when dealing with plastic containing BPA, especially when heating food in plastic containers in a microwave oven.

Melzer, Rice, et al. (2010) assessed the association of urinary BPA and CVD, using data from the National Health and Nutrition Examination Survey (NHANES) collected in 2003/2004 and 2005/2006. The 2005/2006 concentrations of urinary BPA were lower than 2003/2004, yet there remained an association between BPA and CVD. Melzer, Rice, et al. recommended a replication of the study to establish and confirm the association between BPA and CVD. While CVD have been associated with unhealthy

lifestyle choices, socioeconomic factors, diabetes, and dyslipidemia, researchers know less about any association of CVD and environmental contaminants. Nash et al. (2003) and Weisskopf et al. (2009) reported an association of CVD with heavy metals (arsenic and lead), air pollutants, and other persistent organic pollutants. Only Melzer, Rice, et al. found an association between CVD risk and environmental phenols (such as BPA), providing support for this study.

In this research, I attempted to replicate and expand Melzer, Rice, et al.'s (2010) results by inspecting the association of BPA with CVD. In this cross-sectional study, I assessed the association of urinary BPA with CVD, using a different data set (NHANES 2009/2010) than that used by Melzer, Rice, et al. The addition of the C-reactive protein (CRP) to the analysis allowed me to explore the mechanism by which BPA might cause CVD. According to Melzer, Rice, et al., there seemed to be an association between BPA and CVD; however, Melzer, Rice, et al. did not pursue the mechanism by which BPA and CVD are associated. The researchers recommended replication of the study using a different set of data to confirm their findings. This study used multivariate analysis to assess the association between BPA and the presence of CVD. The study inspected the changes in reporting CVD after adjusting for CRP. According to Melzer, Rice, et al., BPA might induce oxidative stress to normal vascular endothelial cells, leading to inflammatory changes. I used this study to explore inflammation as measured by CRP and to assess its relevance to CVD.

In the introduction in Chapter 1, I briefly describe the need for the study and the implications for social change. I present a brief literature review in the background of the

study, which demonstrates the importance of this study and the need to conduct the study. In the problem statement, I summarize the evidence related to BPA and its effects on health, provided by studies conducted in the last 5 years. The purpose section of this chapter describes the intention of the study. The research questions, along with the associated null and research hypotheses, are listed, and in the theoretical framework section, I identify the theory supporting this study and detail its relevance to research. The Nature of the Study section identifies the design of the study and includes a brief description of the key variables. In this chapter, terms are defined, along with the limitations and delimiters of the study. The chapter concludes with a brief summary of the information presented in Chapter 1 and an overview of the material presented in the following chapters.

Background of the Problem

Studies on BPA are of two types: independents and studies supported by the FDA. The Office of Food Additive Safety (OFAS) of the FDA reviewed studies concerning BPA and found no evidence of toxicity, especially at the low level people exposed (FDA, 2013). OFAS ascertained that the level of BPA in adults and children is less than the toxicity level of these chemicals. While OFAS has been assuring the public that BPA is safe at typical exposure levels from food and drink, they encourage consumers to limit the exposure of infants and children to BPA, especially through baby bottles and "Sippy" cups. Consumers have been encouraged to read the bottoms of these products to assess the presence of BPA. The norm for the plastic industry is to label polycarbonate plastic containing BPA with the recycle triangle containing the number 3 or 7 (FDA, 2013).

The National Toxicology Program (NTP), along with National Institute of Environmental Health Science (NIEHS) and the National Center for Toxicology Research (NCTR) are involved in evaluating the safety of BPA. Both, NTP and NCTR concluded that the level of BPA might pose some toxicity for children and infants, but there has to date been no confirmation of these conclusions (FDA, 2013). Their findings confirmed the passage of BPA from mother to fetus, though in very low amounts. Researchers from NCTR injected pregnant rodents with 100 to 1,000 times more BPA, but found minimal amounts in fetal blood up to 8 hours after exposure. The human fetal exposure was 84% to 92% lower than calculated in studies not supported by the FDA (2013).

Although the FDA never confirmed the toxicity of BPA, the FDA (2013) has continued to warn consumers when dealing with plastic containing BPA. These warnings advise users to avoid boiling liquid in BPA containers, because these containers release higher levels of BPA, due to the melting of plastic in hot liquid. The FDA has advised consumers to discard plastic containers with scratches as they harbor bacteria and they promote the release of BPA. The FDA makes every effort to spread awareness of products containing BPA by encouraging consumers to watch for recycle codes 3 or 7, as those markings indicate the presence of BPA.

In the United States, studies on BPA are extracted from the NHANES (2009/2010). In a meta-analysis of several studies on humans and animals, Vandenberg, Hauser, Marcus, Olea, and Welshons (2007) listed the harmful effect of BPA on the development of the human fetus by acting as an estrogen disruptor. According to

Vandenberg et al., high concentration of BPA stimulated the inflammatory response similar to acute and chronic diseases. Vandenberg et al. assessed the effect of BPA on the body through inflammation. This assessment paved the way for this study, which included CVD, in a multivariate model, to assess the effect of urinary BPA and serum concentrations of CRP on reporting CVD.

Lang, Galloway, Scarlett, Henley, and Depledge (2008) associated higher concentration of urinary BPA with CVD, liver diseases, inflammation, and glucose homeostasis. Okada, Tokunaga, Liu, Takayanagi, and Matsushima (2008) provided direct evidence of the high binding ability of BPA to estrogen receptors in the body in the conclusion of a study in Japan. Okada et al. ascertained that even with such low concentrations of BPA in the body, BPA was able to bind to estrogen-related receptors (ERR), leading to the disruption of the endocrine system and inflammation.

Using NHANES data collected in 2003/2004 and 2005/2006, Melzer, Rice, et al. (2010) correlated BPA and CVD, using the same data source as this study but collected in 2009/2010. Melzer, Rice, et al. researched 1,455 participants from 2003/2004 NHANES and 1,493 participants from 2005/2006 NHANES and found levels of urinary BPA to be higher in individuals reporting CVD. The geometric mean of BPA in the data collected in 2003/2004 was 2.49 nanograms per milliliter (ng/ml), and that of the data collected in 2005/2006 was 1.79 ng/ml. Melzer, Rice, et al. found a 30% fall in the concentration of urinary BPA in the data collected in 2005/2006 but still found higher reports of CVD in both data sets. Melzer, Rice, et al. noticed the inconsistency in their data analysis and recommended the replication of the analysis to fully explore this inconsistency. Melzer,

Rice, et al. reflected that a higher urinary BPA associated with CVD was a significant finding that needed more attention. Further investigation was needed to clarify the mechanism of these associations.

In a separate research study conducted in the United Kingdom, Melzer, Osborne, et al. (2012) inspected association of BPA and CVD. Among the 591 participants, 385 patients reported severe coronary artery diseases (one to three vessels), along with a median BPA urinary concentration of 1.53 ng/ml. One hundred twenty participants with normal coronary arteries were found to have a lower concentration of urinary BPA (1.28 ng/ml). Melzer, Osborne, et al. concluded that larger studies were needed to fully explore the association of CVD and BPA. Melzer, Osborne, et al. also established the need for studying the mechanism underlying the association of CVD and BPA. CRP might be the intermediate variable in a pathway between CVD and BPA.

CRP was chosen for this study because it is the major protein secreted during an inflammatory response (Erlinger, Platz, Rifai, & Helzlsouer, 2004). Erlinger et al. (2004) ascertained higher CRP concentration was associated with the presence of cancer, CVD, fibrosis, and sleep apnea. The CRP level was found to be 2.69 milligrams per liter in individuals with colon cancer, in comparison to an average of 1.97 milligrams per liter in healthy individuals (Erlinger et al., 2004). According to Erlinger et al., organs, such as the colon, were more susceptible to cancer while inflamed. To lower the risk of colon cancer, researchers used anti-inflammatory drugs (Baron et al., 2003). In patients with coronary artery diseases, the level of CRP dropped after interventional exercise programs (Jialal et al., 2001). Jialal et al. (2001) provided evidence of the presence CRP with

higher lipid profiles. They indicated that once the lipid level was controlled, the level of CRP dropped (Jialal et al., 2001).

Teitel (2013) indicated that the level of CRP was elevated in patients with chronic renal failure, obstructive sleep apnea, stroke, and severe peripheral vascular disease. The level of CRP as a systemic marker of inflammation was used in this study as a marker for the effect of BPA on the body. CRP, the substance that is increased during systemic diseases, was worth studying to correlate its level with the level of urinary BPA. Little is known about the long-term effects of BPA on the body's level of CRP. My intent in this study was to extend understanding of the role of CRP on CVD and BPA.

Problem Statement

BPA is a synthetic substance used in polycarbonated plastic. Researchers estimated the total annual production of BPA at more than 2.2 million metric tons (Melzer, Rice, et al., 2010). The primary use of BPA is to harden the plastic and to aid in its durability (Vogel, 2009). BPA is also found in drinks, food packaging, and in the production of epoxy resin used in the lining of cans for the food industry (Vogel, 2009). People are exposed to BPA through dietary intake, dental sealants, drinking water, and dermal and respiratory assimilation of household dust (Vogel, 2009). Researchers estimated that, during their lifespan, 90% of the general population will be exposed to BPA (Calafat, Ye, Wong, Reidy, & Needham, 2008), with a human serum level ranging from 0.3 to 4 ng/ml (Taylor et al., 2011).

The chemical bond of BPA with plastic is disrupted when exposed to high heat, which releases BPA into the food or beverage (Vogel, 2009). The leaked BPA takes its

route into the human body through beverages and food via oral exposure. According to Vogel, BPA is an endocrine disruptor and belongs to a group of chemicals known as xenoestrogens that react in a biological reaction comparable to estrogen. BPA binds to the estrogen receptors of relevant cells and impairs development, health, and reproductive systems of life (Vogel, 2009).

BPA was associated with liver damage (Bindhumol et al., 2003) and was associated with disrupting pancreatic functions, often resulting in diabetes (Repero et al., 2008). According to Newbold et al. (2008), BPA was also correlated to obesity and thyroid function disruption. Melzer, Rice, et al. (2010) assessed the association of BPA and CVD using data from NHANES collected in 2003/2004 and 2005/2006. However, in the data collected in 2005/2006, concentrations of urinary BPA were lower than in data collected in 2003/2004, yet there was an association between BPA and CVD. Melzer, Rice, et al. recommended replication of the study to further explore and to clarify the association between BPA and CVD. While CVD were associated with unhealthy lifestyle choices, socioeconomic factors, diabetes, and dyslipidemia, less is known about any association of CVD and environmental contaminants. Nash et al. (2003) and Weisskopf et al. (2009) reported association of CVD with heavy metals (arsenic and lead), air pollutants, and other persistent organic pollutants. Only Melzer, Rice, et al. found an association between CVD risk and environmental phenols, which provided support for this study.

Using this study, I attempted to replicate and expand Melzer, Rice, et al. (2010) results by inspecting the association of BPA with CVD. In this cross-sectional study, I

assessed the association of urinary BPA with CVD using a different data set (2009/2010 NHANES) than that used by Melzer, Rice, et al.. The addition of the CRP to the analysis tested the effect of inflammation on the mechanism by which BPA might cause CVD. According to Melzer, Rice, et al., there seemed to be an association between BPA and CVD; however, Melzer, Rice, et al. did not pursue the mechanism by which BPA and CVD were associated and recommended replication of their study to confirm their findings. With this study, I used multivariate analysis to assess the association between BPA and the presence of CVD. I also inspected the effect of BPA on serum CRP. According to Hennig et al. (2002), BPA induced oxidative stress to normal vascular endothelial cells leading to inflammatory changes.

Purpose of the Study

In this quantitative study, I explored the association of urinary BPA with CVD. Then, I assessed the association between serum CRP and urinary BPA. Urinary BPA was the independent variable, while reporting of CVD was the dependent variable with CRP acting as a moderating variable.

Research Questions and Hypotheses

The following two research questions along with respective hypotheses guided this study:

Research Question 1 (RQ1): Is there an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine?

The null and research hypotheses are as follows:

Null Hypothesis 1 (H_01): There is no association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Hypothesis 1 (H_{a1}): There is an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Question 2 (RQ2): Is there an influence of C-reactive protein on the relationship between BPA and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine?

The null and research hypotheses are as follows:

Null Hypothesis 2 (H_02): There is no influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Hypothesis 2 (H_{a2}): There is an influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

To account for urinary concentration, researchers on BPA such as Calafat et al. (2008), Melzer, Rice, et al. (2010), and Melzer, Osborne, et al. (2012) suggested adjusting for urinary creatinine because it concentrates urine and leads to false positive BPA reporting. I adjusted for urinary creatinine concentration as well.

The level of urinary BPA was the independent variable and reporting of CVD was the dependent variable. I designed my research to assess the hypothesis that, excluding all other extraneous variables, CVD reporting indicated a higher level of BPA. In this case, the variables were CVD and BPA concentrations. BPA was the independent variable

because BPA was thought to influence, affect, or cause variation in reporting CVD (the dependent variable). To limit confounders and their influence on the results, I employed a multiple regression model to evaluate the odd ratio (OR) with 95% confidence interval (CI) after adjusting for confounders such as gender, age, race/ethnicity, arthritis, and urinary creatinine (to account for urine concentration).

The relevance of CRP as moderating variable was that inflammation is a dynamic response of cardiovascular tissues to injury (Hennig et al., 2002). In this research, I attempted to examine if excessive exposure to BPA had an effect on triggering the inflammatory process in cardiovascular tissues. According to Melzer, Rice, et al. (2010), excessive exposure to BPA might lead to oxidative stress on cardiovascular tissue and might lead to endothelial damage. The addition of CRP tested the hypothesis by Melzer, Rice, et al. through assessing serum CRP in the moderation analysis.

Theoretical Framework

The advanced model of the triangle of epidemiology was the model best suited for the study. The model was first adapted for infectious diseases, but it can be expanded to include chronic diseases (Merrill, 2010). Scholars have recognized chronic diseases to be the leading cause of death in many nations, and the advanced model of the triangle of epidemiology was proposed by Merrill as a way to reflect on the multifaceted causes of chronic diseases, such as behavior, lifestyle, environmental contaminants, and physical factors. As such, the new triangle of epidemiology takes into accounts the complex arrays of factors causing chronic diseases (Merrill, 2010).

In such chronic diseases as CVD, the advanced triangle of epidemiology shows the complex interactions and interdependence of causative factors, that is, environmental, behavior, cultural, physiological, and ecological factors (Merrill, 2010). Chronic diseases are also peculiar to the environment in which a population resides, and with time, diseases may develop and may expand to the lifespan of individuals causing the burden of chronic diseases (Merrill, 2010).

The environmental factors of the advanced triangle of epidemiology model focus on the biological and chemical stresses in triggering chronic diseases (Merrill, 2010). The surroundings in which a chemical exists are also important in developing chronic diseases. The socioeconomic status, social support, and social network are important in combating chronic diseases. Moreover, the environment plays a role in developing CVD because of limited healthy choices. The time plays a crucial role in developing chronic diseases as these healthy choices, and environmental contaminants, have to be persistent over time in developing chronic diseases (Merrill, 2010).

According to Yach, Hawkes, Gould, and Hofman (2004), the primary mission of public health is prevention. Breaking one of the legs of the triangle would fulfill the mission of public health leading to positive social change that coincides with Walden University's (2014) mission.

Rudestam (2007) ascertained that the adoption of the research model affects the final form of the dissertation. Regardless of the design, most studies have explored an association between two variables or a comparison between two groups. Through this quantitative cross-sectional study, I employed a correlation approach to examine the

effect of urinary BPA on reporting of CVD using the NHANES collected in 2009/2010. The risk ratio or odds ratio (OR) was the tool that gave the relative risk of exposure to BPA. According to Rudestam, in a correlation study several statistical techniques are employed such as a simple regression to establish the correlation. In correlation studies, several statistical controls are used to remove the influence of variables other than the major independent variable. It is the design of the study that controls the type of statement or correlation that is established among variables and not the statistical approach (Rudestam, 2007).

The purpose of this study was to provide a set of research questions through a different perspective to the issue of BPA. As such, the approach of the study was not about proving that the stakeholders in BPA were right or wrong but rather the intention was to provide a different lens to examine the issue of BPA. This new dimension of exploring the association between BPA and the presence of CVD was an effective way of dissecting the controversial issue of BPA.

In a theoretical framework, researchers launch their intentions on the current issue and provide a set of assumptions and goals that need to be addressed (Rudestam, 2007). The developed proposition of BPA and CVD was to explore the association between these two variables. The BPA and CVD association proposition existed within a conceptual framework, and it was my intention behind this research to clarify the relationship between these variables. According to Rudestam, conceptual framework is a less developed form of a theory and comprised of statements to link concepts into empirical data. Thus, the research questions answered through this research were not

simply to explore a relationship between variables but rather to put meaning into such relationship by strengthening past and future research on BPA. I intended through this study to contribute to scholarly literature and to trigger positive social change towards safer plastic industry by questioning items used in people's daily lives.

Nature of the Study

The research was a population-based study with a quantitative approach. The purpose of this study was to assess the association between urinary BPA and reporting CVD in adults and children participants of the NHANES collected in 2009/2010. Then I assessed the influence of BPA on serum CRP. In this study, I used secondary data from NHANES collected in 2009/2010 because these years were the most recent years in which both BPA and CRP were measured. Newer NHANES data are available but for unknown reasons, the Centers for Disease Control and Prevention (CDC, 2014d) did not gather serum CRP levels in NHANES 2011/2012.

The urinary concentration of BPA was the independent variable, while reporting of the presence of CVD was the dependent variables. Serum concentration of CRP acted as a moderating variable. Throughout this research, I adjusted for the following confounders: gender, age, race/ethnicity, arthritis, and urinary creatinine (to adjust for urine concentration). I did this to limit the effect of these confounders and to focus on the main issue of BPA, CVD, and CRP.

I used SPSS version 21.0 to run simple regression analysis to examine the association between BPA and CVD. Urinary concentration of BPA was the independent variable, and the reporting of CVD was the dependent variable. The influence of

confounders on the result was limited by using multiple regression and by calculating the OR with 95% CI after adjusting for gender, age, race/ethnicity, arthritis, and urinary creatinine.

The NHANES sampling methodology has gone through various modifications over the years. According to the CDC (2011), the sampling method included Hispanic and not just Mexican Americans. Among each race/ethnicity domains, information on certain ethnic/race group in a domain of 0 to 5, 6 to 11, 12 to 19, 20 to 39, and 40 to 59 years of age was created; the data fit my research as studies on BPA have agreed on its effect on adults of all age including children. In total, the sample size in my research was 1,465 participants with target gender of both males and females, while the target age was 6 to 65 years old (CDC, 2011b).

Definitions

Operational definitions important for the study were included herein:

Bisphenol A (BPA): This was the independent variable. BPA is a chemical used in plastic to add durability and rigidity to plastic. It is widely found in many household products such as compact discs, dental sealants, and epoxy resin lining of canned food (National Institute of Environmental Health Sciences, 2013)

Cardiovascular Disease (CVD): This was the dependent variable. For the sake of this study, CVD was defined as any reporting of heart attack, angina, coronary heart diseases, and congestive heart failure.

C-reactive protein (CRP): CRP was a moderating variable. CRP is a protein secreted by the liver in response to inflammation (Ridker, 2003).

Estrogen: Secreted by ovaries in female and testes in male, estrogen is a hormone that influences the female reproductive tract development, function, and maturation. The main forms of estrogens are estradiol and estrone (National Cancer Institute, 2010b).

Estrogen receptors: The target tissues for binding and reacting to estrogen. Estrogen exerts effects only on tissues that have estrogen receptors (National Cancer Institute, 2010a).

National Health and Nutrition Examination Survey (NHANES): The NHANES is a program of the CDC that assesses the U.S. population health and nutritional status. NHANES is special because it combines interviews along with physical examinations and laboratory assessment (CDC, 2014).

Xenoestrogen: Groups of chemicals that exert a biological reaction comparable to that of estrogens, bind to the estrogen receptors of relevant cells, and impair development, health, and reproductive systems of life. BPA is an example of xenoestrogen (Vogel, 2009).

Inflammation: A process by which the body, through the white blood cells, reacts and protects itself against foreign substances, such as allergens, bacteria, and viruses (National Library of Medicine, 2011).

Obesogens: Chemical compounds that affect normal development through disruption of lipid metabolism leading to obesity (Kirchner et al., 2010).

Carcinogen: According to the American Cancer Society (2013), carcinogens are substances and exposures (such as radiation) that can trigger cancer.

Assumptions

In this study, there were several assumptions. First, I assumed that the data gathered were representative of the United States population. According to the CDC (2013b), every person selected to participate in NHANES represented 65,000 similar people in the United States. Second, I assumed that the level of urinary BPA and serum CRP were reliable and reflected the accuracy of the laboratory instrument used. This was ensured by the vigorous CDC's quality control program that was certified by CLIA (CDC, 2013b). Third, holding all other aspects of health constant, I assumed that the increase in serum CRP was related to the increase in the urinary BPA concentration. Fourth, I assumed that verbal reporting of having a heart attack, angina, coronary heart diseases, or congestive heart failure was enough to report the presence of CVD.

Holding these assumptions, it was to the best of my knowledge that the participants answered the survey questionnaire honestly and that their confidentiality was maintained. Furthermore, the participants were volunteers, and they had the option to withdraw from the survey at any given time and were not in any way forced to participate (CDC, 2013b).

Scope and Delimitations

Due to accessibility of data, I chose the NHANES to study the relationship between BPA, CVD, and CRP. NHANES is a rich source of variables that can be studied, and generalizations can be extrapolated based on the data. The data gathered through NHANES were representative of the U.S. population and demonstrated trends and aspects of health and nutrition in the U.S. population (CDC, 2013b). According to the

CDC (2013b), many improvements in the health and diet of people living in the United States have been attributed to trends and analysis of the data gathered through NHANES.

Delimitations of the study included the choice of individuals from the NHANES data that reported CVD. CVD was defined in NHANES as any reports of heart attack, angina, coronary heart diseases, and congestive heart failure. The research questions were also delimiters because the scope of the study was to explore the association between BPA, CVD, and CRP. The choice of correlation study model was a factor mandated to by the type of research questions posed.

The scope of the study was the U.S. population. However, it was demonstrated throughout the world and by studies done on BPA that generalization could be extrapolated. Studies done in Japan on BPA were also valid in the U.S. population and vice versa (Lang et al., 2008; Li et al., 2013; Okada et al., 2008).

Limitations of the Study

In this study, I described the characteristics of BPA within a representative sample of the U.S. population. Larger sample size was desirable to maintain the reliability of the results (Hackshaw, 2008). The main result of this research had 95% CI because the width and depth of the study depended on sample size. According to Hackshaw, the larger the sample size, the more the narrow intervals are and, therefore, more precise results are achieved. When comparing the concentration of urinary BPA and that of serum CRP, the size of the study mattered and it affected the outcome of the study. According to Hackshaw, effect size can be measured by the relative risk or odd ratio.

A possible bias in this study was that CRP was also elevated in other diseases. Efforts were made to include participants reporting only CVD. Providing empirical generalization to the larger population was the goal of this quantitative study. I achieved this goal by controlling for confounders through statistical regression analysis. Other unknown confounders could be controlled through generalization.

Significance

Building on previous reports on BPA, I assessed the association between BPA and CVD in participants of NHANES collected in 2009/2010. Melzer, Rice, et al. (2010) recommended replication of their study so that the association between BPA and CVD was established and confirmed. While the factors contributing to CVD have been established (complex interaction between diet, genetic, and lifestyle factors), the contribution of environmental contaminants (such as BPA) received poor attention from researchers. There was a clear need for such research as this study to ensure that the findings of Melzer, Rice, et al. were robust and grounded.

Based on the results of the research, the implications for positive social change are numerous. Aligned with Walden University's (2014) mission in creating the scholar-practitioner graduate, my intention through this study was to generate knowledge that articulates justification for a policy shift among plastic industries. The positive social implications of my research were first to increase the recognition of BPA as a chemical that needed further scrutiny and study than just simply advising people not to boil food in plastic as stated by the FDA (2013). Second, recognizing the association among BPA, CRP, and CVD may pose a different perspective on chronic diseases leading to effective

strategies for prevention of future chronic diseases. Third, by creating potential positive social change, the study attempted to decrease the burden of financial costs associated with chronic diseases.

Summary

Chapter 1 introduced the different views on BPA and examined the stance of independent researchers and the FDA on BPA. Chapter 1 introduced BPA and explored the problem surrounding this chemical. This chapter also explored the background and statement of the problem, the significance of the problem, research questions and hypotheses, along with the data analysis plan.

Chapter 2: Literature Review

Introduction

This research was a cross-sectional study with a quantitative approach. Using a multivariate approach, and after adjusting for confounders, I assessed whether higher levels of urinary BPA and serum CRP had an influence on reporting CVD. In this study, I used secondary data from NHANES collected in 2009/2010 because the NHANES 2009/2010 survey was the latest survey in which the CDC collected laboratory data on both urinary BPA and serum CRP. Newer NHANES data were available but, for unknown reasons, the CDC did not gather serum CRP levels in NHANES 2011/2012 (CDC, 2014d).

In this chapter, the major findings and theories regarding BPA are discussed. The chapter starts with an overview on the search strategy employed to find articles and studies on BPA, CVD, and CRP. Specifically, this chapter describes the scope of the literature review in regards to the association of BPA with diseases. I also discuss the name and theoretical foundation of the study. In particular, the literature reviewed includes previous theories employed in studying BPA. I also describe the practical application of these theories as they relate to the current study. Several key variables important for the current study are discussed with justification of the selected theory. The chapter concludes with various studies in relation to the current study's independent and dependent variables to point out the gap left by researchers, justifying the need for my current study.

Chapter 2 supports the two research questions introduced in Chapter 1 of this study: (a) What is the relationship between urinary BPA and CVD? (b) How does the addition of CRP influence the relationship between BPA and CVD? A thorough review of the literature was required to support the need for the study and to present research opportunities for other researchers by shedding light from a different perspective on the issue of BPA.

Literature Search Strategy

For this literature review, I used PlosOne, the U.S. National Center for Biotechnology Information (NCBI), Environmental Health Perspective, Reproductive Toxicology, and the American Medical Association Journal. Several research databases were also used, such as Walden Academic Search Complete, ProQuest, and ScienceDirect. I also searched the FDA, CDC, and the National Centers for Health Statistics (NCHS) websites in accessing valuable information for a comprehensive review on BPA, CVD, and CRP.

Key terms used in that search included *bisphenol A*, *BPA*, *CVD*, *coronary artery disease*, *congestive heart failure*, and *C-reactive protein*, *CRP*. In addition, the search was narrowed by using terms such as *AND*, *OR*, and *NOT*. I also utilized advanced search to include peer-reviewed articles. I then filtered the results to include studies done in the last 5 years.

I began the literature review by exploring the strategy employed in such review. Initially, my intention was to present a chronological order of studies associated with BPA based on the views of independent researchers and the FDA. However, I found it

appropriate to present the studies associating BPA with diseases and then to explore the stance of the FDA in regards of these findings. I never intended for this study to present attacks and counterattacks between independent researchers and the FDA. In my research, I focused on presenting unbiased findings and reporting the gap in the literature to support the need for this study.

Theoretical Foundation

The advanced model of the triangle of epidemiology was the model best suited for this study. The model was first adapted for infectious diseases, but it was expanded to include chronic diseases (Merrill, 2010). Chronic diseases are recognized by most researchers to be the leading cause of death in many nations, and the advanced model of the triangle of epidemiology was proposed by Merrill as a way to reflect on the multifacet causes of chronic diseases, such as behavior, lifestyle, environmental contaminants, and physical factors. The new triangle of epidemiology takes into accounts the complex arrays of factors causing chronic diseases (Merrill, 2010).

The epidemiology triangle is the foundation for epidemiology (Ghimire, 2014). The triangle has been applied to injury, defects, disorders, and diseases. It is an indispensable tool for epidemiologists. With the advent of chronic diseases as the leading cause of death, the advanced triad model was adopted to take into accounts lifestyle, behavior, ecological elements, physical factors, and environmental causes (Ghimire, 2014).

The framework was based on the following criteria (Ghimire, 2014):

- Causative factors such as BPA as a possible factor influencing the incidence of CVD.
- Environmental behavior as people using more plastic in their daily life. Environmental circumstances include time for diseases to thrive, spread, and survive. Time is an important factor with chronic diseases, such as CVD, as chronic diseases develop over a certain period of time and not as a sudden incidence in time (incubation period in case of infectious diseases).
- Group or their population such as participants of NHANES as representative of the whole U.S. population.
- Diseases in the epidemiological triad include infectious, communicable, and chronic diseases. The triad was used to analyze the role and interaction of these three factors (causative agent, environment, and population) to study the effect of each factor in the advent of chronic diseases (such as CVD in the case of this study; Ghimire, 2014).

The result of all these complex factors could be depicted in the advanced model of the triangle of epidemiology (Figure 1).

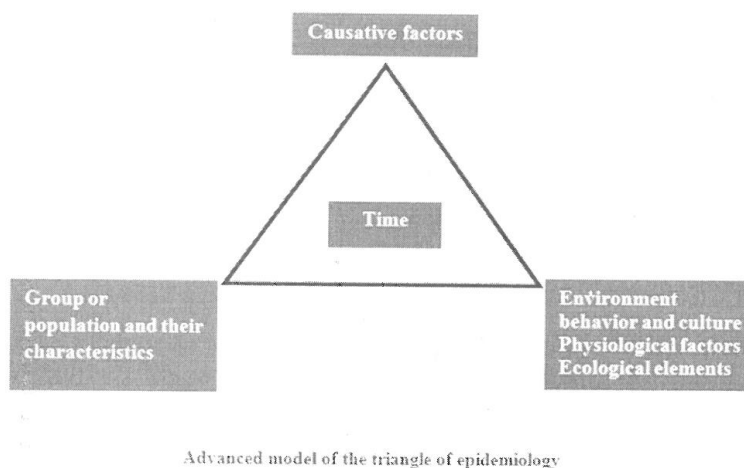


Figure 1. The advanced model of the triangle of epidemiology reflects major factors affecting the emerging of chronic diseases. It takes into account chronic diseases issues found in modern time such as behavior and lifestyle. Adapted from “The advanced triangle of epidemiology” by Ghimire (2014). Retrieved from <http://umeshg.com.np/advanced-triangle-of-epidemiology>

The various factors of the advanced model of the triangle of epidemiology are interrelated and interact in a complex manner (Ghimire, 2014). The model was useful to understand the complex interactions of these factors when applied to BPA, CRP, and CVD. The causative agent is delineated in the advanced model to include environmental contaminants, chemical solvents, injury, or death. The host is the individual that harbors the condition. In this study, host was represented by NHANES participants who reported CVD. The environment refers to those favorable surroundings and conditions that allow the diseases. The modern lifestyle and being surrounded with plastic containing BPA fall into this category, too. Time accounted for the incubation period, or the period elapsed between exposure to BPA and reporting of CVD (if any; Ghimire, 2014).

Sherwin, Mausner, and Kramer (1985) applied the advanced model of the triangle in developing of coronary heart diseases. The various causative agents of unhealthy diet

of saturated fat, lack of physical activity, and decreased level of low-density lipoprotein constituted heart diseases promoters (Sherwin et al., 1985). Other causative factors included smoking and increased salt intake. These factors were exacerbated with the environment and culture of these individuals affected by coronary heart disease in terms of availability of health choices and accessibility to better food alternatives. According to Sherwin et al., the groups or population affected by coronary heart disease, were men and women under stress and women taking oral contraceptive and thus increasing the level of estrogen. These multifaceted factors all interacted with time and contributed to the advent of coronary heart disease in those individuals. The advanced model was successful in including all factors affecting coronary heart disease (Sherwin et al., 1985). Similar analogy was followed in this study.

The triangle of epidemiology has long been applied to communicable diseases as it showed the complex interaction between the agent, host, and time (Merrill, 2010). The triangle was used by epidemiologists extensively in infectious disease investigations during outbreaks. Because infectious diseases are caused by single agent, it is fairly easy to apply the triangle of epidemiology but still not comprehensive or complete. With chronic diseases and their various causative agents, from social to lifestyle and genetic predisposition, the model is useful in recognizing that the conditions affecting a population are complex and that the causative agents are various and versatile (Merrill, 2010). The concept of an agent is replaced by causative factors to imply the need to identify multiple etiologic factors of diseases, specifically CVD as applied in my study. The advanced model is an effective model into investigation of chronic diseases because

it comprises the importance of including the many factors to various maladies (Merrill, 2010).

Fawcett and Downs's (1986) correlation study showed the relationship between characteristics of a certain phenomenon under study. The correlation theory was the theory adopted for this study because it examined association between two variables, the independent urinary BPA, and the dependent reporting of CVD and serum CRP concentrations.

The theoretical proposition I presented in this dissertation was simple: Is there an association between urinary BPA and reporting of CVD, and how does the addition of CRP influence the relationship between BPA and CVD? The proposition was adopted from the assumption that, holding all other confounders constant, the rise in CVD reporting (if any) was attributed to rise in concentration of urinary BPA. Holding all other aspects of individual constant, such as gender, age, race/ethnicity, arthritis, and urinary creatinine (to account for urine concentration), I demonstrated the association between BPA on the presence of CVD. As precautionary measures, I assumed that all laboratory assays employed in detecting BPA and CRP were accurate and that they complied with the United States Clinical Laboratory Improvement Amendments (CLIA) of 1988, which govern the regulatory standards in laboratory testing (FDA, 2010). CLIA assures quality in laboratory testing through ensuring the accuracy and reliability of patient test results (FDA, 2010).

Based on the research questions, the following two hypotheses were presented:

Hypothesis 1

H_01 : There is no association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

H_a1 : There is an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Hypothesis 2

H_02 : There is no influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

H_a2 : There is an influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Exploring these hypotheses relied on the accuracy of detecting urinary BPA and serum CRP concentrations, and on honest reporting of the presence of heart attack, angina, coronary heart diseases, and congestive heart failure (the definition of CVD for the sake of this research). Such accuracy was important to explore the research questions and to understand the relationship between BPA, CRP, and CVD.

Studies done on BPA were mostly quantitative studies and of the correlation type. There were studies that correlated BPA and major health effects, such as celiac disease (Collin, Kaukinen, Valimaki, & Salmi, 2002), disruption of endocrine functions (Collin et al., 2002), diabetes (Lang et al., 2008), prostate cancer (Prins, 2008), heart diseases (Melzer, Rice, et al., 2010), breast cancer (Acevedo, Davis, Schaeberle, Sonnenschein, &

Soto, 2013), and obesity (Li et al., 2013). Following in the path of these studies, I used a correlation study to understand the relationship between BPA, CRP, and CVD. The effect of BPA on the human body was best assessed by correlating the concentration of urinary BPA and other body markers, such as CVD and CRP in the case of the current study.

The challenge in the current study was to acquire accurate laboratory assessment of BPA and CRP. This was achieved through the selection of secondary data from NHANES collected in 2009/2010. The NHANES sampling methodology has gone through various modifications in previous years. According to the CDC (2013b), the sampling method included Hispanic (not just Mexican American) participants. Among each race/ethnicity domain, information on certain ethnic/race groups in a domain of 0 to 5, 6 to 11, 12 to 19, 20 to 39, and 40 to 59 years of age was created. This study had a sample size of 1,465 participants with target gender of both males and females while the target age was 6 years and older (CDC, 2013b).

Review of Literature Related to Key Variables and/or Concepts

Review of literature of BPA revealed a focus on its harmful effect as a way to demonstrate its toxicity. Correlating BPA with different diseases was the trend in BPA history, a norm that this study explored, but from a different perspective. The new perspective was to examine the association of urinary BPA concentration with reporting of CVD and then to assess the impact of such reporting by adding the CRP concentration to the picture.

Researchers studied BPA in the United States using correlation studies and extracted secondary data from NHANES. Correlation studies were chosen because of

their inherent strengths and the absence of a control group (Rudestam, 2007). Correlation studies show the strengths of association between two variables and act as a platform for more research to explore this association in further details. Weaknesses of correlation studies are its failure to assume cause and effect relationships between variables as it is impossible to know which variable preceded the other in time (Rudestam, 2007).

Using NHANES data, Melzer, Rice, et al. (2010) correlated BPA with CVD, liver diseases, and diabetes. The researchers explored 1,493 participants from NHANES data collected in 2003/2004 and in 2005/2006. Levels of urinary BPA were found to be higher in individuals reporting CVD by 1.33 ng/ml in the survey collected in 2003/2004 and 1.79 ng/ml in the survey collected in 2005/2006. Melzer, Rice, et al. concluded that a higher urinary BPA associated with CVD was a significant finding that needed more attention, and further investigation was needed to clarify the mechanism of these associations. Melzer, Rice, et al. recommended replication of the study so that the association between BPA and CVD would be established and confirmed. While CVD were associated with unhealthy lifestyle choices, socioeconomic factors, diabetes, and dyslipidemia, less was known about any association of CVD and environmental contaminants. Nash et al. (2003) and Weisskopf et al. (2009) reported association of CVD with heavy metals (arsenic and lead), air pollutants, and other persistent organic pollutants. Only Melzer, Rice, et al. found an association between CVD risk and environmental phenols (such as BPA), providing support for this study. Using this research study, I attempted to replicate, expand, and reference Melzer, Rice, et al.'s results by investigating the association of BPA with CVD. In this cross-sectional study, I

assessed the association of urinary BPA with CVD using a different data set (NHANES 2009/2010) than that used by Melzer, Rice, et al.

Melzer, Osborne, et al. (2012) also investigated the association of BPA and CVD in a separate research in the United Kingdom. Among the 591 participants, 385 patients reported severe coronary artery diseases (one to three vessels) along with a median BPA urinary concentration of 1.53 ng/ml. 120 Participants with normal coronary arteries were found to have a lower concentration of urinary BPA (1.28 ng/ml). Melzer, Osborne, et al. concluded that larger study was needed to fully explore the association of CVD and BPA. Through this study, I reassessed the same variables used by Melzer, Osborne, et al. but with a larger sample size from NHANES (representing the whole United States population) to fully expand and replicate the association between BPA and CVD. Melzer, Osborne, et al. also established the need for studying the mechanism underlying the association of CVD and BPA. CRP might be an intermediate variable for such mechanism.

In a meta-analysis of several studies on human and animal, Vandenberg et al. (2007) explored the harmful effect of BPA on the development of human fetus and its role as an estrogen disruptor. The researchers reported that the level of urinary BPA in these studies was high enough to induce human fetal anomalies. Not only BPA was detected in urine but also in other human fluids such as fluids in the abdomen, joints, and in blood (Vandenberg et al., 2007). According to Vandenberg et al., high concentration of BPA stimulated the inflammatory response similar to acute and chronic diseases. CRP is an inflammatory substance that is secreted during acute and continuous inflammation and

assessing its effect on reporting CVD with higher urinary BPA was worth exploring in this study.

The direct evidence of the high binding ability of BPA to estrogen receptors in the body was the conclusion of a study done in Japan by Okada et al. (2008). The human estrogen-related receptor (ERR) attached strongly to BPA if found in the body. The maximum binding concentration of BPA to achieve full binding capacity with ERR was 14.4 nmol/ml (Okada et al., 2008). Okada et al. concluded that to totally impair the function of estrogen in the body; the BPA concentration needs to be 14.4 nmol/ml. Okada et al. demonstrated that even with such low concentrations of BPA in the body, BPA was still able to bind to ERR leading to disruption of the endocrine system and inflammation.

Lang et al. (2008) associated higher concentration of urinary BPA with CVD, liver diseases, inflammation, and glucose homeostasis. In comparison with participants reporting neither CVD nor diabetes or inflammation, the urinary BPA concentration was higher in patients with CVD by 1.63 ng/ml per 1 standard deviation (SD) (Lang et al., 2008). The concentration of urinary BPA in diabetic patients was higher by 1.39 ng/ml per 1 SD, and that of inflammation (measured by the concentration of liver enzymes excluding other diseases) was 1.29 ng/ml per 1 SD (Lang et al., 2008). Lang et al. found also that while holding all confounders constant, higher concentration of urinary BPA was associated with higher inflammation reflected in the level of liver enzymes gamma glutamyltransferase (1.29 ng/ml increase for every 1 SD increase in BPA) and alkaline phosphatase (1.48 ng/ml increase for every 1 SD increase in BPA). Lang et al. concluded that there was an association between urinary BPA and health anomalies in community-

dwelling adult population of the United States. The researchers recommended the replication of these findings to provide robust correlation and to unveil evidence on whether the association was causal. I, through this study, expanded on these results and explored further the association among urinary BPA, CVD, and serum CRP.

Acevedo et al. (2013) investigated the effect of BPA on mammary gland hyperplasia by injecting female rats with various levels of BPA. The levels were 0, 0.25, 2.5, 25, and 50 micrograms of BPA per kilogram (kg) of body weight per day. Acevedo et al. concluded there was 100% detection of unconjugated form of BPA in sera of female rat and in 33% of their offspring when the female rats were exposed to 250 microgram of BPA per kg per day (within the levels found in human). Preneoplastic lesions were found in BPA-exposed female offspring across all doses as early at day 50 post-delivery (PND50). Acevedo et al. reported the development of mammary gland adenocarcinoma in BPA-exposed offspring by PND90. Wadia et al. (2013) (as cited by Acevedo et al., 2013) reported that low level of BPA (250 mg per kg body weight per day) altered the composition of extracellular matrix and accelerated the maturation of presumptive fat pad, a process necessary for ductal invasion.

Li et al. (2013) found BPA to be associated with overweight and obesity in school aged children in Shanghai. More than 98% of the students participating in the study had more than 2 micrograms per milliliter of BPA in their urine (Li et al., 2013). Those who had 2 micrograms/ml of urinary BPA were also found to be overweight and obese indicating a possible association between BPA and obesity (Li et al., 2013). The researchers found a dose-response relationship between BPA and body weight suggesting

that BPA might be a new environmental obesogen and contributing to the worldwide obesity epidemic (Li et al., 2013).

CRP rises in the blood of individuals in response to inflammation (Teitel, 2013). CRP activates the complement system by binding to phosphocholine found on the surface of dying cells and bacteria. It is synthesized by the liver in response to factors released by macrophages due to acute and chronic inflammatory conditions such as infection (bacterial, viral, and fungal), and in response to malignancy, rheumatoid arthritis, tissue necrosis, and environmental factors such as BPA (Teitel, 2013).

Teitel (2013) stated that during the acute inflammatory response, the level of CRP increased to 50,000 folds within 6 hours of inflammation. It peaked at 48 hours to decline in a half-life of 18 hours. CRP level was elevated in many conditions and measuring its level simply indicated an inflammation and/or infection. According to Teitel, an elevated level of serum CRP did not diagnose a specific disease, but indicated the presence of inflammation in the body. I, through this study, investigated whether an elevated level of serum CRP along with elevated level of urinary BPA were associated with reporting of CVD.

Erlinger et al. (2004) reported that CRP was elevated during cancer, among individuals with CVD, fibrosis, and sleep apnea. CRP level was found to be 2.69 milligrams per liter in individuals with colon cancer, in comparison to an average of 1.97 milligrams per liter in healthy individuals (Erlinger et al., 2004). Some organs, such as the colon, were more susceptible to cancer while inflamed, and some attempts were made to use anti-inflammatory drugs to lower the risk of colon cancer (Baron et al., 2003). In

patients with coronary artery diseases, the level of CRP dropped after interventional exercise programs were implemented (Jialal et al., 2001). Jialal et al. concluded that the elevated level of CRP was correlated with higher lipid profile and once the lipid level was controlled, the level of CRP dropped. Jialal et al. concluded in their study that CRP provided a picture on the inflammatory process of coronary artery diseases in the human body.

Summary and Conclusions

The purpose of this research was to assess the association of urinary BPA, reporting of CVD, and serum CRP in participants of the NHANES collected in 2009/2010. The preceding literature review supported the need for this study. Following in the footsteps of many researchers on BPA, I used a correlation approach to examine the association between urinary BPA and reporting of CVD. The research used a very reliable source of secondary data that was the cornerstone of many studies on BPA, namely the CDC's NHANES.

Studies done on BPA were mostly quantitative studies and of the correlation type. There were studies that correlated BPA and major health effects, such as CVD, liver diseases, and diabetes (Melzer, Rice, et al., 2010), coronary artery disease (Melzer, Osborne, et al., 2012). BPA was also found to induce fetal anomalies through disruption of estrogen receptors (Vandenberg et al., 2007), and BPA was found concentrated not only in urine but also in other human bodily fluids such as fluids in the abdomen, joints, and in blood (Vandenberg et al., 2007). Higher concentration of urinary BPA was also

associated with CVD, liver diseases, inflammation, and glucose homeostasis (Lang et al., 2008).

As demonstrated by Teitel (2013) level of CRP was elevated in patients with chronic renal failure, obstructive sleep apnea, stroke, and severe peripheral vascular diseases. Acting as a systemic marker of inflammation, the level of CRP was interesting enough to use it as a marker for the effect of BPA on the body. There was no doubt that CRP, the substance that increased during all of these systemic diseases, was worth studying to investigate its level with the level of urinary BPA and reporting of CVD.

This study attempted to replicate and expand on the findings of these researchers by examining the association of BPA with CVD. In this cross-sectional study, I assessed the association of urinary BPA with CVD using NHANES collected in 2009/2010. The addition of the CRP to the analysis explored the mechanism by which BPA might cause CVD. According to Melzer, Rice, et al. (2010), there seemed to be an association between BPA and CVD; however, Melzer, Rice, et al. did not pursue the mechanism by which BPA and CVD were associated and recommended replication of the study using a different set of data to confirm their findings. Lang et al. (2008) recommended replication of these findings on correlating BPA with CVD, liver diseases, inflammation, and glucose homeostasis to provide robust association and to unveil evidence on whether the association was causal. I, through my research study, expanded on these results and explored further the association among urinary BPA, CVD, and serum CRP.

To fully expand the findings of these researchers, a robust research method and design were indispensable to fully understand the interaction of BPA, CVD, and CRP.

The research method and design were explored in Chapter 3 along with sample size justification, threat to validity and reliability, and other legal and ethical issues pertaining to recruitment of participants.

Chapter 3: Research Method

Introduction

In this quantitative study, I examined the association of BPA and CVD in participants of NHANES collected in 2009/2010. I used a multivariate approach to examine the effect of CRP on the analysis. The addition of CRP to the analysis allowed me to explore the mechanism by which BPA might be associated with CVD. According to Melzer, Rice, et al. (2010), there seemed to be an association between BPA and CVD; however, Melzer, Rice, et al. did not pursue the mechanism by which BPA and CVD were associated. Melzer, Rice, et al. recommended replication of the study using a different set of data to confirm their findings. This study used multivariate analysis to assess the association between BPA and the presence of CVD. The study inspected the changes in reporting CVD after adjusting for CRP. According to Melzer, Rice, et al., BPA might induce oxidative stress to normal vascular endothelial cells, leading to pro-inflammatory changes. I used my research study to explore inflammation, as measured by CRP, and I assessed its relevance to CVD. In this analysis, urinary BPA was the independent variable, while the presence of CVD was the dependent variable with serum CRP acting as a moderating variable.

In this chapter, research method and design are explored. I start this chapter with a brief introduction about the purpose of the study and then proceed to highlight the research design and methodology. I also define the population under study and the method utilized in drawing samples. This is done to justify the sample size in comparison to the population. Although this study used secondary data from the CDC, the procedures

for recruiting participants and their eligibility for participation are discussed in addition to legal documents obtained throughout the process. The threat to validity and the reliability of the data are then discussed. The chapter concludes on the overall method used and comments on any ethical concerns posed during and after the data collection process.

Research Design and Rationale

In this study, I used a quantitative, nonexperimental cross-sectional design with a correlation approach to assess the relationship between the concentration of urinary BPA and reporting of CVD. The sample was representative of the general adult U.S. population with target age of 18 to over 80 years. The urinary concentration of BPA was the independent variable, and reporting of CVD was the dependent variable. Serum concentration of CRP was a moderating variable. The plan was to assess how the amount of serum CRP affects the relationship between BPA and CVD. The research questions and the null and alternate hypotheses directing this study were as follows:

Research Question 1 (RQ1): Is there an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine?

The null and research hypotheses are as follows:

Null Hypothesis 1 (H_01): There is no association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Hypothesis 1 (H_a1): There is an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Question 2 (RQ2): Is there an influence of C-reactive protein on the relationship between BPA and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine?

The null and research hypotheses are as follows:

Null Hypothesis 2 (H_02): There is no influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Hypothesis 2 (H_a2): There is an influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

To account for urine concentration, researchers on BPA such as Calafat et al. (2008), Melzer, Rice, et al. (2010), and Melzer, Osborne, et al. (2012) suggested adjusting for urinary creatinine because it concentrates urine and leads to false positive BPA reporting. I adjusted for urinary creatinine concentration as well.

Rudestam (2007) ascertains that the adoption of the research model affects the final form of the dissertation. Regardless of the design, most studies explore a correlation between two variables, or a comparison between two groups. I employed a correlation approach to examine the effect of urinary BPA on reporting of CVD using data from NHANES collected in 2009-2010. Specifically, I employed a cross-sectional study design with a quantitative approach. A quantitative method was chosen for this study because this method helps collecting numerical data, analyzes the data, and then explains phenomena at stake (Creswell, 2009). Specifically, a quantitative approach has helped

explore the association among BPA, CVD, and CRP. I used quantitative analysis tools to answer the research questions by analyzing the relationship between key variables, whether these variables were continuous, ordinal, or integers. A qualitative approach was not suitable for the study because of the type of the numerical data collected from NHANES. A qualitative study is suitable for such data as opinions, behaviors, values, and social context of a population (Creswell, 2009). As such, the numerical data of NHANES imposed a quantitative approach that answered how BPA, CVD, and CRP are associated.

I chose a cross-sectional design for the study because it involved collecting data from a population at a specific period of time (Creswell, 2009). Unlike case-control design, a cross-sectional design provides data on the entire population, whereas case-control design provides data on specific people within a population with certain characteristics. Because data are collected within a certain period, a cross-sectional design is limited in providing a cause-effect relationship among variables. Regardless of such limitation, a cross sectional design would be typical for this correlation study that investigated an association among BPA, CVD, and CRP. Other quantitative designs such as experiment, quasi-experiment, and ex post facto designs were not appropriate for the study. Experimental design was not appropriate for the study because an experimental design investigates the impact of a treatment, a program, or a procedure on an outcome (Creswell, 2009). Experimental design controls all other factors that might affect the outcome. A quasi-experiment aims at controlling various factors affecting the outcome and then identifies the variable responsible for the change in outcome (Creswell, 2009).

Ex post facto shows that the independent variable is causing changes in the dependent variable. Ex post facto classifies sample based on a criterion they have such as wearing glasses, working aged men, and so forth. A cross-sectional design was appropriate for this study because it enabled me to estimate the prevalence of factors in the sample and then draw conclusions to generalize the results into larger population. This study investigated the association of urinary BA, CVD, and CRP in representative sample of the U.S. population using data from NHANES collected in 2009/2010.

Methodology

Population

NHANES is an ongoing program that collects data about the health and nutritional trends in adults and children of the United States (CDC, 2013b). The earliest NHANES survey (NHANES I) was conducted in 1971-1975. The survey was then carried out every 2 years until 1999, when the survey data started to be collected on an annual basis. The latest NHANES survey collected and published was NHANES 2013/2014 (CDC, 2013b). According to the CDC (2013a), the total distribution of the civilian, noninstitutionalized U.S. population for the midpoint of 2009-2010 surveyed totaled 301,943,719, distributed among White, African American, Hispanic, and non-Hispanic.

In the NHANES collected in 2009/2010, 13,272 persons were selected for the sample. Only 10,537 individuals (79.4%) were surveyed (CDC, 2013c). The response rate differed between age group. The response rate fluctuated between 86.9% (for 16- to 19-year-old participants) to 55.2% (for participants over the age of 80 years). These

individuals were recruited randomly with selected sample representative of 15 individuals visited every year to follow on their dietary and health status. The sample selected represents the total U.S. population of all ages. To produce reliable results, oversampling was recommended for individuals 60 and older, Hispanics, Asians, and African Americans. The oversampling was justified because the U.S. population is expanding exponentially with elderly people, Hispanics, Asians, and African Americans. As a result, these groups of individual play a dramatic role in the health trends of the U.S. population, and hence need to be replicated (CDC, 2013c).

Sample and Sampling Procedures

NHANES used a complex probability sampling method (CDC, 2013b). With such complex sampling methods, adjustments need to be incorporated in the statistical analysis to project accurate and unbiased national estimates. Ignoring the complex sampling design leads to standard errors of estimates. The complex sampling in NHANES used multistage probability sampling design to select representatives of the civilian, noninstitutionalized U.S. population. The sampling method took into account nonresponse, oversampling, and poststratification. In participants aged 60 and older, Hispanics, African Americans, and Asians, oversampling was utilized to increase the precision and reliability of the health indicators. Each selected person represented 65,000 similar people in the United States (CDC, 2013b).

The NHANES 2009/2010 survey examined nationally 10,537 persons with a response rate as low as 55.2% and as high as 86.9%, depending on the age of participants (CDC, 2013c). Data were collected between January 2009 and December 2010. The

sample individuals were selected based on a complex statistical process. In brief, the United States was divided into communities, and communities into neighborhoods. Neighborhoods and houses within these neighborhoods were randomly selected to participate. Interviewers then asked selected houses a few short questions to determine their eligibility to participate. Participants were selected based on their health status, gender, age, race, and ethnicity. Only the selected individuals could participate; no substitutes were allowed, even if participants dropped their participation.

The sample person was assigned a weight equivalent to the reciprocity of the final probability.

Sample person's base weight = $1 / \text{final probability}$, where final probability was defined as:

Final probability = probability of being selected

x probability of a segment being selected

x probability of a household being selected

x probability of an individual being selected (CDC, 2012).

Power analysis. Power analysis refers to the probability of failing to reject a false null hypothesis (Sullivan, 2010). It is affected by sample size and statistical significance (also known as alpha). Alpha level is the probability of having a Type I error. Type I error arises when the null hypothesis is rejected while in fact it is true. The preferred determined alpha level for this study was set at 0.05 because adding more restriction (such as setting alpha at 0.01 or 0.001), when a sample size was fixed, would increase Type II error, failing to reject the null hypothesis when it was actually false. Therefore,

setting alpha at 0.05 was a good compromise between the likelihood of getting Type I or Type II errors (Sullivan, 2010).

Sample Size Justification

To conduct power analysis, I used G*power 3.1.7. The study used multivariate logistic regression. The multiple binary logistic regression used in Research Questions 1 and 2 were posed to have an identical number of covariates, and power analysis was conducted using a binary regression model with two tails. This analysis was used to determine the power of the study given the original sample size. The OR was chosen to be 1.10 based on suggestions posed by Hsieh, Block, and Larsen (1998). Considering a multiple binary logistic regression with a very small effect size (OR = 1.10), a confidence level of 95% ($\alpha = .050$), a sample size of 1,465, the power was 0.31 (Faul, Erdfelder, Buchner, & Lang, 2013). If the effect was of a medium size (i.e., OR of 3.5), the power was calculated to approach .99. Thus, there was sufficient power to reject the null hypothesis if it was false using such analyses.

Procedures for Recruitment, Participation, and Data Collection

NHANES is the National Center for Health Statistics' most in-depth and comprehensive survey of the United States population. The survey is administered out of mobile examination units that travel into the randomly selected sites throughout the country. The survey combines personal interviews, laboratory tests, and physical examination to gather data about current trends in the U.S. population in terms of diagnosed and undiagnosed conditions, nutrition and diet, growth and development, overweight and obesity, risk factors, and environmental exposures (CDC, 2013b).

Using the most current census information, participants for the 2009/2010 survey were recruited through a complex statistical process (CDC, 2013b). The United States was divided into 15 regions called primary sampling units (PSU) based on specific characteristics. Each PSU was then divided into segments in which 20 to 24 of these small segments were selected. Among the segments selected, a sample of about 30 households was selected. Finally, NHANES interviewers conducted a brief interview to gather basic information such as race, age, sex, and general income level. A computer algorithm then selected all households, one or more, or none to participate in NHANES survey. Participants were selected based on age, sex, and racial/ethnic background. Once participants were selected, a unique health profile was created for each. No person could substitute for any missing or dropped participants (CDC, 2013b). Each selected person represented 65,000 similar people in the United States (similar in age, sex, ethnicity, and race). At any given time, participants had the ability to leave the survey with no retribution. Dropped participants were treated as missing data and could not be substituted by anyone, not even an immediate family member. Fifteen sample representatives were randomly selected and visited throughout the year to follow up on their dietary and health status (CDC, 2013b).

Selected participants were provided with informed consent. NHANES participants were protected by the Public Health Act that deals with authorization for collecting information from participants. Participants were also protected by the Privacy Act of 1974 and by the Confidential Information Protection and Statistical Efficiency Act

that prohibits disclosure of participants' information without their own authorization (CDC, 2013b).

The Division of Health Examination Statistics (DHANES) was responsible for releasing data from NHANES (CDC, 2013b). The DHANES policy mandated the accuracy of released information as well as the confidentiality of participants. According to 2009/2010 NHANES policy, accuracy of released data was as important as making these data as practicable as possible (CDC, 2013b). The dissemination procedure called for maintaining accuracy in collecting the data as well as during the input process. To maintain accuracy and due to the large dataset and the large post-collection processes, NHANES data are released twice a year to make sure all data are available to the public. The data are released after proper documentation, review, cleaning, and editing, and within 3 months of the collection process. The public nature of the NHANES data requires no special release agreement between the CDC and any researchers except in special circumstances where datasets are not yet released to the public (CDC, 2013b).

Instrumentation and Materials

The CDC used 2009/2010 NHANES to collect wide varieties of data. The survey included such instruments as interviews, health assessment, risks factors, nutritional and laboratory data (CDC, 2013b). This study had an interest in interviews and in the laboratory data.

The 2009/2010 NHANES laboratory tests were based on the participants' gender and age at the time of the interview. Samples were collected in a Mobile Examination Center with certified phlebotomist and technologists from the American Academy for

Clinical Pathologists or other organizations (CDC, 2011a). Samples collected include urine, vaginal swabs, blood, and other bodily fluids. Urine was assessed for the presence of glucose, protein, pregnancy, and other environmental chemicals (such as BPA). The blood samples were assessed for various indicators, such as CBC, cholesterol level, and CRP. The procedure for urine collection included collecting and processing the specimen for health indicators and for pregnancy. The procedure for collecting blood samples included a brief questionnaire to screen participants for conditions that excluded them for blood sample (CDC, 2011a).

There were numerous steps taken to ensure reliability and validity of the data collected (CDC, 2011a). First, all laboratory staff went through certification process in laboratory science. Technologists running the specimen and involved in other sample collection held a baccalaureates in medical technology. Phlebotomists were certified with extensive training in pediatric venipuncture, laboratory safety, patient confidentiality, and cardiopulmonary resuscitation. Second, for each method used in the survey, there was clear instruction in the NHANES Laboratory/Medical Technologists Procedures Manual on proper collecting, labeling, preserving, and processing samples. Third, the laboratory results were entered directly into the NHANES system. Any very high or very low values were verified for a second time by NCHS staff with numerous consistency checks verified at all time. Fourth, blind split samples were analyzed and compared with the published results (CDC, 2011a).

This study examined the association among urinary BPA, reporting of CVD, and serum CRP. In NHANES dataset, urinary BPA had an item ID of URXBPH, CVD

reporting was represented by CDQ_F, and that of serum CRP concentration was represented by LBXCRP. Urinary BPA samples were processed, stored at -20°C, and shipped to Division of Environmental Health Laboratory Sciences, National Center for Environmental Health where they were analyzed (CDC, 2014c). The reporting of CVD was collected through a questionnaire that asked participants whether they had experienced chest pain (angina), were diagnosed with congestive heart failure, heart attack, coronary heart diseases, and congestive heart failure (CDC, 2014b). CRP samples were collected, processed, and shipped to University of Washington, Seattle, WA, where they were analyzed for CRP (CDC, 2014a). The detection limits of BPA were 0.1-2.0 ng/ml, while the lowest detection level of CRP was 0.02 ng/ml. The detection limit of 0.1-2.0 ng/ml for BPA was within the limit permitted for non-occupational exposure (CDC, 2014c).

Study variables and covariates. A list of the study variables (independent and dependent), and covariates are provided herein. The urinary BPA was the independent variables, and reporting CVD was the dependent variable. The independent and dependent variables, and their covariates are explained in Table 1.

Table 1

Independent, Dependent, and Covariate Variables of the Study, NHANES 2009/2010

Variable Type	Variable Name	Variable Source	Potential Responses	Level of Measurement
Independent variable	BPA	NHANES data file EPH_F.xpt	Values between 0.1-2.0 nanogram per deciliter	Continuous
Dependent variable	CVD	NHANES data file CDQ_F.xpt	79.4%	Dichotomous
Moderating variable	CRP	NHANES data file CRP_F.xpt	More than 0.02 nanogram per deciliter	Continuous

Data Analysis Plan

Upon approval from Walden Institutional Review Board (approval number is 05-28-15-0182468) I obtained data files for the NHANES collected in 2009/2010 from the CDC website in SAS file format. Data was entered into SPSS version 21.0 for Windows. I conducted descriptive statistics to describe the sample demographics and the research variables used in the analysis. I also calculated frequency and percentages for nominal data such as instances of CVD, and means/standard deviations for continuous data, such as BPA and CRP levels (Howell, 2010).

Preanalysis Data Screening

Survey respondents included secondary data from the CDC. I screened the data for missing data, outliers, or extreme cases. Descriptive statistics and frequency distributions were conducted to determine that responses were within statistically acceptable range of values and that the data was not distorted by outliers. I assessed the

presence of outliers by the examination of standardized residuals. I created standardized values for each subscale score and examined cases for values that fall above 3.29 and values that fall below -3.29, indicating an outlier, and removed these participants (Tabachnick & Fidell, 2012). I examined cases with missing data and for nonrandom patterns. Participants who did not complete major sections of the survey were excluded.

Descriptive statistics. I used frequency tables to create descriptive statistics for the dependent, independent and covariate. I calculated percentages of occurrence of the study population to show the central tendency. Central tendency included the mean, median, mode, minimum and maximum, and standard deviation. Summary of the ordinal and categorical variables were presented in frequency tables to show frequency distribution.

The following two research questions along with respective hypotheses guided the study:

Research Question 1 (RQ1): Is there an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine?

The null and research hypotheses are as follows:

Null Hypothesis 1 (H₀₁): There is no association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Hypothesis 1 (H_{a1}): There is an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Question 2 (RQ2): Is there an influence of C-reactive protein on the relationship between BPA and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine?

The null and research hypotheses are as follows:

Null Hypothesis 2 (H_02): There is no influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Hypothesis 2 (H_a2): There is an influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

To test the two research questions, I conducted a binary multivariate logistic regression. Binary logistic regression was appropriate because CVD (the dependent variable) was dichotomous, meaning there are two possible outcomes for the dependent variable so one can directly estimate the probability of an event's occurrence (Stevens, 2009). This type of analysis can be used especially when the predictor variables are continuous, discrete, or a combination of continuous and discrete. This analysis permitted the evaluation of the odds of membership in one of the two groups based on the combination of predictor variable values. In my analysis, urinary BPA concentration was the independent, or predictor variables of focus. Presence of CVD was the dependent variable. CVD was dichotomous, which means a participant either was or was not considered to have CVD. I considered participants to have CVD if they reported any one

or more of the following: angina, coronary heart disease, heart attack, or congestive heart failure. Urinary BPA and serum CRP concentrations were both scale level variables.

To address the possibility that confounding variables might have an effect on instances of CVD, I implemented several controls. To control for a range of these potential confounding factors, I included the following controls: age, gender, ethnicity/race, arthritis, and urinary creatinine levels. These control measures were entered into the first step of the regression to determine the degree to which they contributed to instances of CVD. In the second block, BPA levels were added to the regression. By examining both steps, I was able to determine the degree to which BPA predicts instances of CVD beyond what I accounted for with these confounding factors (Tabachnick & Fidell, 2012).

Inferential statistics. Inferential statistics refers to drawing conclusions from a sample of data representing the population (Sullivan, 2010). Inferential statistics allows the generalization of findings into the whole population from which the sample was drawn. There are two methods of inferential statistic: estimation of parameter and testing of statistical hypotheses. Testing of statistical hypothesis was the method appropriate for the study. Specifically, I used multivariate logistic regression in this study, as it was best suited since the dependent variable (CVD) was dichotomous while the independent variable (BPA) was continuous. Logistic regression, by design, overcomes many of the restrictive assumptions of linear regression (Sullivan, 2010). For example, in logistic regression linearity, normality, and equal variances are not assumed, nor is it assumed that the error term variance is normally distributed. The major assumptions are that the

outcome variable must be discrete, and that independent variables are not too highly correlated (absence of multicollinearity). I assessed the absence of multicollinearity by using Variance Inflation Factors (VIFs); any independent variable was determined to have a VIF greater than or equal to ten, they were considered too related and removed from the model (Tabachnick & Fidell, 2012).

I examined the overall model significance for the logistic regression by the effect of the independent variable presented with a χ^2 coefficient. The Nagelkerke R^2 was reported and used to determine how much variance in the dependent variable can be accounted for by the set of independent variables. I used Wald statistics to determine the significance of each predictor, and standardized beta coefficients (β) to determine predicted probabilities of having CVD based on BPA and CRP levels (Tabachnick & Fidell, 2012).

Validity of Study

Internal and External Threats to Validity

According to Creswell (2009), there are two types of threats to validity: internal and external. Threat to internal validity reflects our confidence in concluding that the relationship between the independent variable and the dependent variable is not due to chance, other systemic errors, or bias. It also reflects the ability of other researchers to conduct the study under the same conditions and still reach similar conclusion (Creswell, 2009). External validity refers our confidence in applying our results to other group under the same condition of study. It is the ability to generalize or to draw inferences to other situations and other people (Creswell, 2009).

Creswell (2009) ascertains that threats to validity are inevitable and can occur at the collection of data, analysis, study design, and interpretation of results. According to the CDC (2014), NHANES has undergone extensive testing and demonstrated criterion validity, predictive validity, content and construct validity, internal consistency, measurement invariance, test-retest reliability to assure validity and usefulness of the data presented to researchers. Threats to validity were controlled through the vigorous training of individuals conducting the interviews, performing the laboratory testing, and analyzing the findings. Minimizing threats to validity was also maintained by automated and computerized data entry of results, CLIA-certified technicians performing laboratory testing, and by using forms approved by various ethical committees (CDC, 2011a).

Potential Bias

According to Creswell (2009) the potential for bias governs any research. Regardless of the vigorous training of personnel, and extensive ethical standards of NHANES, bias and limitations did exist. Bias in NHANES included measurement bias and selection bias.

Measurement bias. Measurement bias refers to misclassification or lack of accuracy in obtaining data from participants. NHANES was subject to three different types of measurement bias: recall bias, interviewer bias, and measurement variations. Recall bias occurs when participants erroneously report data. Recall bias was minimized in NHANES by probing questions that detected irregularity in responses (CDC 2014a, 2014b, 2014c, 2014d). Interviewer bias occurs when interviewers record inaccurate data into the form or pose questions in a way to elicit a specific favorable response.

Measurement variations occur when performing laboratory testing. The CDC (2014a, 2014b, 2014c, 2014d) minimized interviewer bias and measurement variations by extensive personnel training of field staff, and protocols that reviewed responses and testing results. Annual training, refresher courses, and quality control programs put forth by the CDC enhanced the reporting of accurate and reliable data from NHANES.

Selection bias. Selection bias refers to error in choosing participants for a study. Selection bias also occurs at the data analysis stage specifically during the measurement of association (risk ratio, rate ratio, or OR). To limit selection bias, the CDC (2013b) used complex, multi-stage, and stratified method of probability sampling. Initial sampling was performed on 15 regions called PSU that were divided into blocks or clusters of households. Individuals from each household were randomly selected to participate. Such sampling reduced risks for selection bias and ensured fair selection participants. NHANES probability sampling method took into account nonresponse, oversampling, and post-stratification. In participants aged 60 and older, Hispanic, African Americans, and Asians, oversampling was utilized to increase the precision and reliability of the health indicators. The sample weight was the number of people in the population represented by that sample. Each selected participants represented 65,000 similar people in the United States (CDC, 2013b).

Ethical Procedures

In this research, I used secondary archived data from NHANES. The data was available from the CDC website. It was considered public data and could be used without special authorization from the CDC. Being public, the data could be accessed at any time

and from any device with Internet connection. To make sure this data was accessible at all time and for easy retrieval, the data were downloaded into a password-protected personal computer owned and accessed by the researcher of this study and in the same format as the original downloaded data from the CDC website (SAS format) for the duration of this research and for 5 years after.

NHANES data was approved by the National Center for Health Statistics Ethics Review Board before the data was released to the public. All participants' information was confidential and protected in accordance to Federal laws such as the Public Health Service Act (42 USC 242k), The Privacy Act of 1974 (5 USC 552A), and the Confidential Information Protection and Statistical Efficiency Act (PL 107-347). Information that identified participants was not giving without a prior consent from participants. Laboratory samples and survey data were coded with numbers in place of names or other personal identifiers (CDC, 2013b).

According to the CDC (2013b), all participants were provided with privacy statement notice disclosing their rights for review and consideration. All participants were assured that they could withdraw their participation at any stage of the survey. Participants were provided with informed consent from the Ethics Board Review of the National Center for Health Statistics.

The CDC (2013b) released the 2009/2010 NHANE secondary data for public use. As such, the data used by the study was not intended to breach confidentiality of any participants, or to misuse the data released. In accordance with Walden University ethical

standards, I obtained approval for this study from Walden University Institutional Review Board prior to data analysis.

This study was part to fulfill the requirements for the Doctor of Philosophy, Public Health and Epidemiology at Walden University. I certify herein that I seek no financial interest in this study other than fulfilling the requirement for a doctoral degree. I also claim no conflicts of interest with other party.

Summary

In Chapter 3, I discussed the method used in this study to investigate the association among BPA, CVD, and CRP. I also presented the research design and rationale, methodology, procedures for recruiting participants, instrumentation and materials, data analysis plan. In Chapter 3, I also discussed the threats to validity and ethical procedures governing this study. This quantitative study used secondary data from NHANES collected in 2009/2010 with a sample size of 1,465 from civilian, non-institutional subjects representing the US population. I carried out the data analysis only after getting approval from Walden University Institutional Review Board. In Chapter 4 I presented the research results with discussion of these findings presented in Chapter 5.

Chapter 4: Results

Introduction

Using this study, I attempted to replicate and expand Melzer, Rice, et al.'s (2010) results by inspecting the association of BPA with CVD. In this cross-sectional study, I assessed the association of urinary BPA with CVD using a different data set (2009/2010 NHANES) than that used by Melzer, Rice, et al. The addition of the CRP as covariates to the analysis enabled me to test the effect of inflammation on the mechanism by which BPA might cause CVD while controlling for inflammation from CRP. According to Melzer, Rice, et al., there seemed to be an association between BPA and CVD; however, Melzer, Rice, et al. did not pursue the mechanism by which BPA and CVD were associated and recommended replication of their study to confirm their findings. With this study, I used multivariate analysis to assess the association between BPA and the presence of CVD.

The study presented the following research questions:

Research Question 1 (RQ1): Is there an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine?

The null and research hypotheses are as follows:

Null Hypothesis 1 (H_01): There is no association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Hypothesis 1 (H_a1): There is an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Question 2 (RQ2): Is there an influence of C-reactive protein on the relationship between BPA and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine?

The null and research hypotheses are as follows:

Null Hypothesis 2 (H₀₂): There is no influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Research Hypothesis 2 (H_{a2}): There is an influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

Using these research questions as guidelines, I started Chapter 4 by examining the data collection process and the timeframe through which NHANES data were collected. The data collection process overview includes the sampling methods, how participants were recruited, and any discrepancies in the data collection process. After introducing basic descriptive statistics, I presented the results in tables extracted from SPSS 21.0. I also reported statistical analysis, findings, and statistics associated with the data such as intervals, probability values, and effect size as appropriate. Chapter 4 concludes with a summary and a transition to Chapter 5.

Data Collection

Handling of Data and Data Files

NHANES is an ongoing program that collects data about the health and nutritional trends in adults and children of the United States (CDC, 2013b). According to

the CDC (2013a), the total distribution of the civilian, noninstitutionalized U.S. population for the midpoint of 2009-2010 surveyed totaled 301,943,719, distributed among White, African American, Hispanic, and non-Hispanic. The 2009/2010 NHANES data were collected between January 2009 and December 2010 (CDC, 2013c). Because I used secondary data from the CDC, there were no discrepancies between the data plan presented in Chapter 3 and obtaining the data from the CDC.

Data presented in NHANES collected in 2009/2010 included 13,272 persons who were selected for the sample. Due to nonresponse factors, only 10,537 individuals (79.4%) were surveyed (CDC, 2013c). The response rate differed between age group. The response rate fluctuated between 86.9% (for 16- to 19-year-old participants) to 55.2% (for participants over the age of 80 years). These individuals were recruited randomly with selected sample representative of 15 individuals visited every year to follow on their dietary and health status. The sample selected represents the total U.S. population of all ages. To produce reliable results, oversampling was recommended for individuals 60 and older, Hispanics, Asians, and African Americans. The oversampling was justified because the U.S. population is expanding exponentially with elderly people, Hispanics, Asians, and African Americans. These groups of individual play a dramatic role in the health trends of the U.S. population and hence need to be replicated (CDC, 2013c). According to the CDC (2013a), every person selected to participate in NHANES represented 65,000 similar people in the United States.

After obtaining approval from Walden University's Institutional Review Board, the data were downloaded from the CDC website in SAS format. The independent

variables of interest, namely the urinary BPA and the moderating variable (serum CRP) were located in a different baseline data files. The dependent variable, the dichotomous reporting of CVD, was also located in the NHANES data files and compiled using SPSS 21.0 into one file, keeping only the relevant variables for this study. Data were merged using the participants' identification number.

Data Treatment

Data were collected from the CDC's NHANES 2009/2010 database, which had a total of 10,537 participants' survey responses. I used a sample of 1,465 participants of the NHANES 2009/2010, because only these participants had completed responses for all of the variables of interest for the study. Of the 1,465 participants with complete surveys, I assessed for outliers via standardized values. Any standardized value, or *z* score, greater than 3.29 or less than -3.29 were removed (Stevens, 2009). The researcher found six outliers for BPA levels and six outliers for urinary creatinine levels. With the outliers removed, the final data set was comprised of 1,453 participants.

Descriptive Statistics

Of the final 1,453 participants, 724 were male (50%) and 729 were female (50%). Of the race/ethnicity options, the majority of the participants reported to be non-Hispanic White (661, 46%), with 20% reported as Mexican American ($n = 293$), 17% reported as non-Hispanic Black ($n = 253$), 11% as other Hispanic ($n = 164$), and 6% as other or multiracial ($n = 82$). The majority of the participants reported to not have arthritis (1,444, 99%), and the majority reported to not have CVD (1,360, 94%). Of those who were classified as having CVD based on the criteria, 35 (38%) reported being diagnosed with

congestive heart failure, 46 (49%) reported being diagnosed with coronary heart disease, 28 (30%) reported at least one past heart attack, and 28 (30%) reported angina pectoris. Because participants could have one or more of the aforementioned diagnoses (i.e., diagnoses are not mutually exclusive) to be classified as having CVD, these frequencies summed to greater than 93, but represented frequencies of those 93 participants only. The frequencies and percentages of demographics are presented in Table 2.

Table 2

Frequencies and Percentages for Sample Demographics

Demographic	<i>n</i>	%
Gender		
Male	724	50
Female	729	50
Race/Ethnicity		
Non-Hispanic White	661	46
Other	792	55
Non-Hispanic Black	253	17
Mexican-American	293	20
Other Hispanic	164	11
Other/Multiracial	82	6
Arthritis		
Yes	9	1
No	1444	99
CVD		
No	1360	94
Yes (based on below classifications)	93	6
Congestive heart failure	(35)	(38)
Coronary heart disease	(46)	(49)
Heart attack	(28)	(30)
Angina pectoris	(28)	(30)

Note. Due to rounding error, not all percentages may sum to 100. Participants with CVD could have one or more classifying condition.

The age of the participants at the time of the survey ranged from 20 years to 69 years with mean of 43.56 years ($SD = 14.10$). The creatinine levels ranged from 4 mg/dL to 382 mg/dL with a mean of 127.08 and standard deviation of 75.71. BPA levels ranged from 0.28 ng/mL to 112.00 ng/mL with a mean of 3.29 and standard deviation of 5.71. Values for CRP ranged from 0.02 mg/dL to 8.76 mg/dL with mean of 0.39 and standard deviation of 0.65. Descriptive statistics of the continuous variables are presented in Table 3.

Table 3

Descriptive Statistics of Continuous Variables

Continuous Variables	<i>Min.</i>	<i>Max.</i>	<i>M</i>	<i>SD</i>
Age	20	69	43.56	14.10
Creatinine (mg/dL)	4	382	127.08	75.71
BPA levels (ng/mL)	0.28	112.00	3.29	5.71
CRP (mg/dL)	0.02	8.76	0.39	0.65

Results

The following results were based on the two research questions. The findings suggested that there was a significant relationship between the controls, independent variables, and the dependent variable. However, the binary logistic regression indicated that the only significant predictor was the control, age. As such, there was not sufficient evidence to prove an association between BPA levels and CVD. Based on these findings, a moderation analysis could not be conducted as there was no relationship on which to assess moderating effects. In an ancillary analysis, I found BPA and CRP to have a significant relationship using a Spearman correlation; however, upon examination of a

plot of the two variables, this relationship could not be supported. The results are detailed in the following sections.

Detailed Analysis

Research Question 1

Is there an association of bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine?

H_0 1: There is no association of bisphenol A (BPA) and CVD, after adjusting for age, gender race/ethnicity, arthritis, and urinary creatinine.

H_a 1: There is an association of bisphenol A (BPA) and CVD, after adjusting for age, gender race/ethnicity, arthritis, and urinary creatinine.

I proposed a stepwise binary logistic regression to examine Research Question 1 with the first step posed to analyze the relationship between the controls and presence of CVD, and the second step posed to analyze the influence the controls and the independent variable (i.e., BPA levels) had on CVD. The first step of the binary logistic regression suggested that the controls were significant in predicting CVD ($\chi^2(5) = 83.72$, $p < .001$, $R^2 = .15$). The Nagelkerke R^2 , or coefficient of determination, indicated that the controls explain approximately 15% of the variance in instances of CVD. Upon examination of the individual variables, the only significant control variable was age ($p < .001$), which had a direct effect on CVD; in other words, the regression analysis suggested that a 1-year increase in age caused a 1.08 factor increase in the odds of being diagnosed with CVD.

The second step of the binary logistic regression included the controls and BPA level in the model together. The regression analysis suggested that there was a statistically significant relationship between the controls and independent variable to predict the dependent variable ($\chi^2(6) = 83.76, p < .001, R^2 = .15$). However, the Nagelkerke coefficient of determination did not increase from the 15% explained by the controls, and BPA level was found to be an insignificant predictor of CVD ($p = .853$). Therefore, the results suggested that there was not a significant relationship between BPA and CVD. As such, the null hypothesis was accepted, and there was not sufficient evidence to indicate a relationship between BPA levels and instances of CVD. Results for the stepwise binary logistic regression are presented in Table 4.

Table 4

Two Step Binary Logistic Regression with Covariates and BPA Levels to Predict Having CVD

Source	<i>B</i>	<i>SE</i>	Wald	<i>p</i>	<i>OR</i>
Step 1 (Nagelkerke $R^2 = .15$)					
Gender	.23	.23	.96	.327	1.25
Age	.08	.01	61.24	< .001	1.08
Ethnicity	.13	.22	.33	.567	1.14
Arthritis	.16	1.10	.02	.887	1.17
Creatinine Levels	.00	.00	3.27	.070	1.00
Step 2 (Nagelkerke $R^2 = .15$)					
Gender	.23	.23	.97	.325	1.26
Age	.08	.01	61.26	< .001	1.08
Ethnicity	.13	.22	.32	.571	1.14
Arthritis	.15	1.10	.02	.892	1.16
Creatinine Levels	.00	.00	2.99	.083	1.00
BPA Levels	.00	.02	.04	.853	1.00

Note. Step 1: $\chi^2 (5) = 83.72, p < .001$, Nagelkerke $R^2 = .15$. Step 2: $\chi^2 (6) = 83.76, p < .001$, Nagelkerke $R^2 = .15$.

For this regression analysis, I examined the classification table to detail the model's goodness of fit. The classification table suggested that 93.60% of responses were correctly classified using the single dichotomous predictor variable. Upon further examination, the classification table predicted all 1,453 cases as not having CVD. This was likely due to the unequally sized groups, in which a majority was represented in the "Not having CVD" group. A total of 1,360 (93.60%) of the overall sample were observed within this group. Table 5 provides the classification table for this regression model.

Table 5

Classification Table for CVD as Examined in Research Question 1

Observed	Predicted		% Correct
	Does not have CVD	Does have CVD	
Does not have CVD	1360	0	100
Does have CVD	93	0	0

Note. Overall, correct classification of 88.40%.

Research Question 2

Is there an influence of C-reactive protein on the relationship between BPA and CVD?

H_0 2: There is no influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

H_a 2: There is an influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for age, gender, race/ethnicity, arthritis, and urinary creatinine.

I proposed a moderation analysis with a binary logistic regression to assess Research Question 2. One of the assumptions of a moderation analysis concluded that there was a significant relationship between the independent variable (i.e., BPA) and the dependent variable (i.e., CVD) before including the moderator variable (i.e., CRP). Results for Research Question 1 indicated that the relationship between BPA and CVD was not statistically significant, so I was unable to conduct a moderation analysis. Thus, I

was not able to reject the null hypothesis, as I could not assess the effects of moderation given there was no observed relationship.

Ancillary Analysis

Following the planned analyses, it was determined that there might be an association between the study variables of BPA and CRP, regardless of the inability to determine a link with CVD. To assess this potential relationship, a single Pearson correlation was to be conducted between the variables of BPA and CRP. Prior to analysis, the assumptions of the Pearson correlation were assessed. Normality was assessed using a normal P-P plot to determine the distribution of error around the line of best fit. The plot (found in Appendix A) indicated that the error was not normally distributed, and this assumption was violated (Stevens, 2009). In addition, examination of the standardized residual plot was used to examine the homoscedasticity of the relationship, and this indicated that the linear relationship was heteroscedastic and this assumption was also violated (Stevens, 2009). As such, I conducted the non-parametric equivalent of the Pearson correlation. The non-parametric equivalent of the Pearson correlation is the Spearman correlation, and this analysis does not require that the same restrictive assumptions are met (Lehmann, 2006).

Results of the Spearman correlation indicated that there was a significant relationship between measures of urinary BPA and urinary CRP levels ($r_s = .06, p = .015$). Though this relationship was found to be significant beyond the .05 level, examination of the Spearman correlation coefficient (r_s) using Cohen's (1988) guidelines indicated that this represented a very weak association. In addition, upon examination of

a scatterplot between the two variables I determined that significant findings might be due to the tendency of both variables to cluster around zero, and I observed no linear relationship. This observation held true after I filtered the outliers from the plot. A scatterplot between both variables was assessed with outliers in Figure 2 and further assessed without outliers in Figure 3.

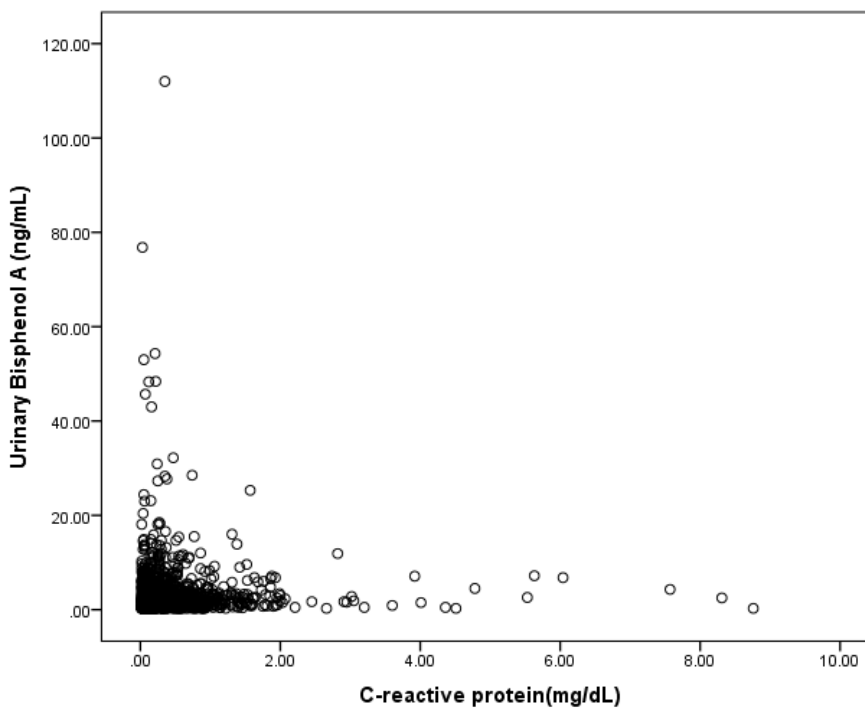


Figure 2. Scatterplot between urinary BPA and serum CRP measurements with outliers.

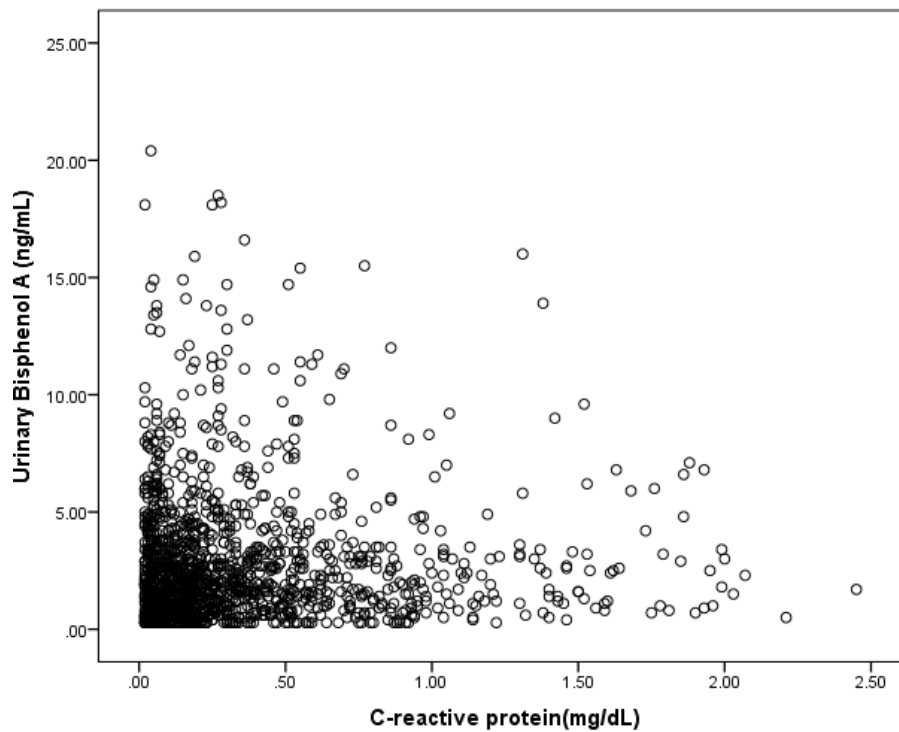


Figure 3. Scatterplot between urinary BPA and serum CRP measurements without outliers.

To explore the relationship between BPA and CRP further, I produced a logarithmic base scale of 10 transformations for these two variables. Log base 10 transformation was the best transformation to use in this situation. The results of the logarithmic scale are depicted in Figure 4 and Figure 5.

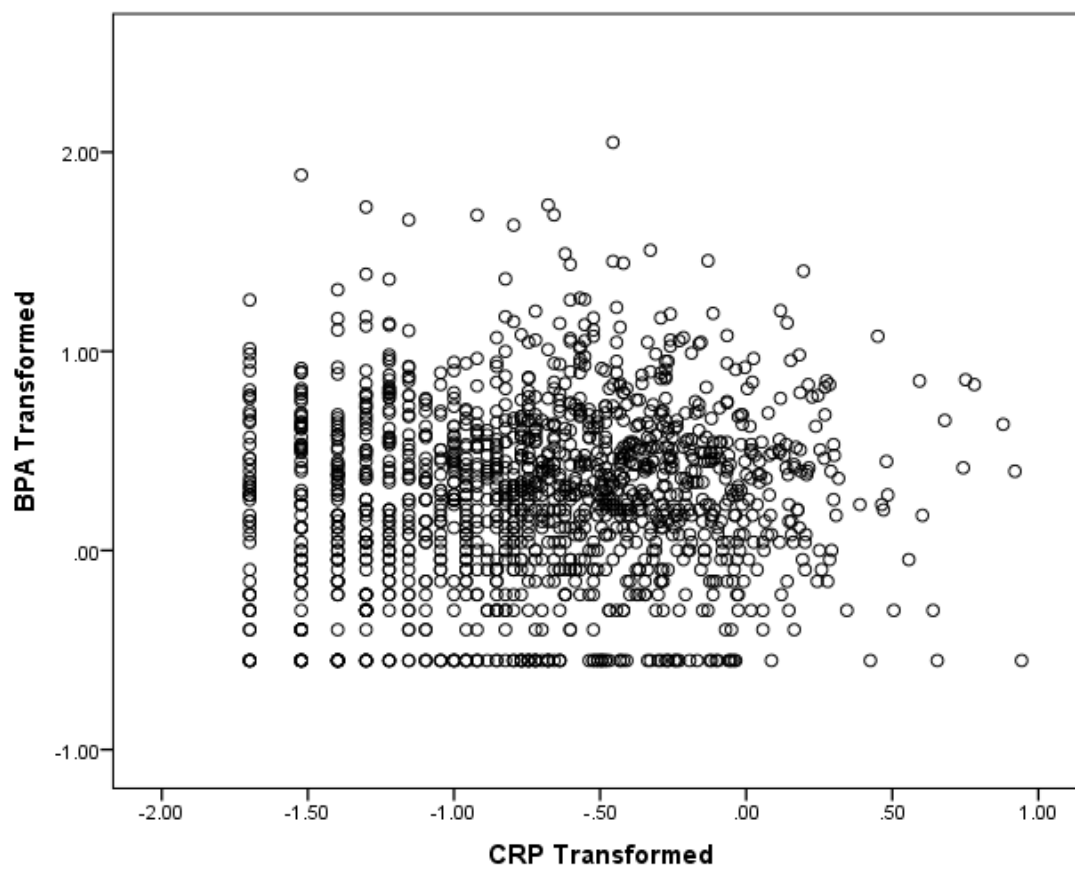


Figure 4. Scatterplot between urinary BPA and serum CRP transformed to base-10 logarithmic scale with outliers.

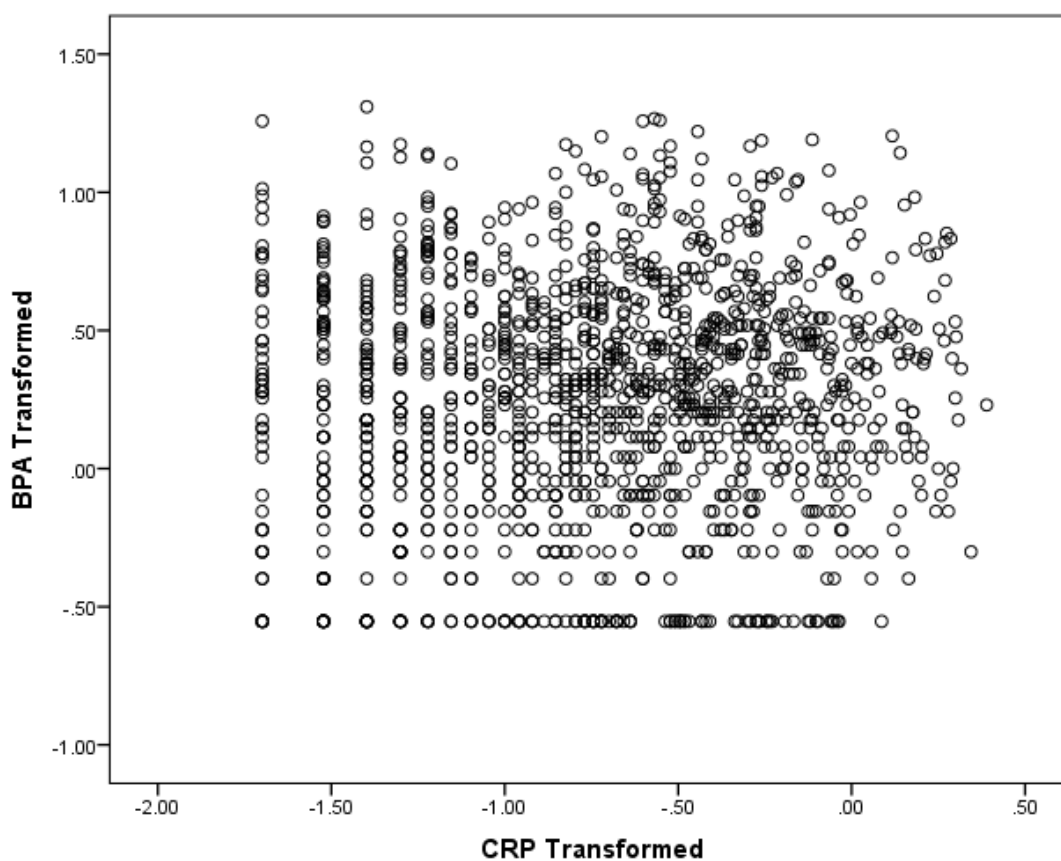


Figure 5. Scatterplot between urinary BPA and serum CRP transformed to base-10 logarithmic scale without outliers.

The logarithmic 10-scale transformation did not show any linear relationship between BPA and CRP. There seemed to be a tendency towards a central cluster that might be skewing things to look like there was a relationship when I conducted the Spearman correlations.

Summary

Chapter 4 included a restatement of the problem and purpose to contextualize the preceding results. This statement was followed by a report on the demographic features of the collected sample and brief summary of the study findings. The research questions

were then analyzed in detail and the results were organized by the relevant research question. These results were interpreted to determine whether the appropriate null hypothesis for each research question could be rejected. In Chapter 5, these results are compared against the existing data from prior studies and interpreted as they fit into the existing body of knowledge. Chapter 5 also contains a synthesis of the findings and suggestions for future study.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

Chapter 5 discusses the results of the study to answer the two research questions investigated by this study. Possible explanations for the results of the study are presented, conclusions are drawn from the results, and recommendations for future research are made. I also present in this chapter the limitations of the study and recommendations for positive social change. The discussion begins by examining the statistical findings as they related to the research questions.

The main purpose of the study was to explore the association between BPA and CVD. The current study is a continuation of a study done by Melzer, Rice, et al. in 2010 in which they found an association between BPA and CVD. Using data from NHANES collected in 2003/2004 and 2005/2006, Melzer, Rice, et al. assessed the association between BPA and CVD; however, concentrations of urinary BPA in 2005/2006 were lower than 2003/2004, yet there remained an association between BPA and CVD (Melzer, Rice, et al., 2010). Melzer, Rice, et al. recommended a replication of the study to establish and confirm the association between BPA and CVD, and this study was born. Using this study research, I attempted to replicate and expand Melzer, Rice, et al.'s results by examining the association of BPA with CVD. In this cross-sectional study, I assessed the association of urinary BPA with CVD, using a different dataset (NHANES 2009/2010) than that used by Melzer, Rice, et al. The addition of the CRP as a moderating variable was halted due to the insignificant association between BPA and CVD.

The analysis of the NHANES 2009/2010 data revealed that the association of BPA and CVD was not statistically significant. Further exploration of the addition of the CRP to the analysis was not possible because of the insignificant association between BPA and CVD. Regardless of the association between BPA and CVD, an analysis was also carried out to show if there was a possible association between BPA and CRP. The association between BPA and CRP was also found to be statistically nonsignificant.

Interpretation of the Findings

The results of the study indicated that there was no association between BPA and CVD. The findings suggested that there was a significant relationship between the controls, independent variables, and the dependent variable. However, the binary logistic regression indicated that the only significant predictor was the control, age. As such, there was insufficient evidence for an association between urinary BPA level and reporting of CVD. Based on this finding, a moderation analysis could not be conducted as there was no association between BPA and CVD on which to assess moderating effects. In an ancillary analysis, BPA and CRP were found to have a significant relationship using a Spearman correlation ($r_s = .06, p = .015$). Though I found this relationship to be significant beyond the 0.05 level, examination of the Spearman correlation coefficient using Cohen's (1988) guidelines indicated that this represented a very weak association. Further examination of a scatterplot between the two variables (Figures 2 and 4) indicated that significant findings may be due to the tendency of both variables to cluster around zero, and therefore no linear relationship was observed. This observation held true after outliers were filtered from the plot (Figures 3 and 5).

Urinary BPA and Reporting of CVD

The focus of the first research question was to examine the association between BPA and CVD in participants of NHANES 2009/2010. I examined the possible relationship between BPA and CVD using a stepwise binary logistic regression. The first step analyzed the relationship between CVD and the following controls: age, gender, race/ethnicity, arthritis, and urinary creatinine. The second step analyzed the influence of the independent variable (i.e., BPA levels) and controls (i.e., age, gender, race/ethnicity, arthritis, and urinary creatinine) on CVD.

The first step of the binary logistic regression (Table 4) suggested that the controls were significant in predicting CVD ($\chi^2(5) = 83.72, p < .001, R^2 = 0.15$). The Nagelkerke R^2 , or coefficient of determination, indicated that the controls explained approximately 15% of the variance in instances of CVD. Upon examination of the individual variables, the only significant control variable was age ($p < .001$), which had a direct effect on CVD; in other words, the regression suggested a 1-year increase in age caused a 1.08 factor increase in the odds of being diagnosed with CVD.

The second step of the binary logistic regression (Table 4) included the controls and BPA level in the model together. The regression suggested that there was a statistically significant relationship between BPA and age, gender, race/ethnicity, arthritis, urinary creatinine ($\chi^2(6) = 83.76, p < .001, R^2 = .15$). However, the Nagelkerke coefficient of determination did not increase from the 15% explained by the controls, and BPA level was found to be an insignificant predictor of CVD ($p = .853$). Therefore the results suggested that there was no significant relationship between BPA and CVD. As

such, I was unable to reject the null hypothesis based on a lack of evidence to indicate an association between BPA and CVD.

Reflecting on the literature presented in Chapter 2, Melzer, Rice, et al. (2010) correlated BPA with CVD using two sets of data combined: NHANES 2003/2004 and NHNAES 2005/2006. The 2005/2006 concentrations of urinary BPA were lower than 2003/2004, yet there remained an association between BPA and CVD. Melzer, Rice, et al. recommended a replication of the study to establish and confirm BPA and CVD association and this study was intended to confirm such association. While BPA was associated previously with several health anomalies such as breast and prostate cancers, CVD, obesity, reproductive anomalies, and neurological problems (Bindhumol et al., 2003; Melzer, Rice, et al., 2010; Newbold et al., 2008; Repero et al., 2008), the current study concluded that an association with CVD was not statistically significant, adding more controversy to the issue of BPA.

The Office of Food Additive Safety (OFAS) of the FDA reviewed studies concerning BPA and found no evidence of toxicity, especially at the low level people exposed (FDA, 2013). OFAS ascertained that the level of BPA in adults and children was less than the toxicity level of these chemicals. While OFAS is assuring the public that BPA is safe at typical exposure levels from food and drink, they have encouraged consumers to limit the exposure of infants and children to BPA, especially through baby bottles and "Sippy" cups. Such studies funded by the FDA coincided with the findings of this study indicating no association between BPA and CVD.

This study suggests that BPA warrants further investigation in light of conflicting reports on its adverse effect on the human body. The purpose of this study was to provide a set of research questions through a different perspective on the issue of BPA. The results of this research extended the findings of other reports indicating the need for further investigation and scrutiny of household items containing BPA that are used on a daily basis.

The theoretical framework that guided this research was the advanced triangle of epidemiology. The model was first adapted for infectious diseases, but it was later expanded to include chronic diseases (Merrill, 2010). Chronic diseases are recognized to be the leading cause of death in many nations, and the advanced model of the triangle of epidemiology reflects the multifaceted causes of chronic diseases, such as behavior, lifestyle, environmental contaminants, and physical factors. As such, the new triangle of epidemiology takes into account the complex arrays of factors causing chronic diseases (Merrill, 2010).

The current study coincided with this view of chronic diseases as having multiple etiologic factors. By excluding BPA as an etiologic factor for heart diseases (per the findings of this study), the view was shifted to consider other causes of CVD such as behavior, lifestyle, environmental contaminants, and physical factors. The study was guided by the advanced triangle of epidemiology to look into the whole concept of host as a group of populations and their characteristics. The representative population in the current study was NHANES with its representation of the whole U.S. population. This study took into account the factors of age, gender, race/ethnicity, arthritis, urinary

creatinine, and BPA as a way to look into the causes of chronic diseases such as CVD. Time in this study accounted for the incubation period or life expectancy of NHANES participants. Time was considered as the duration of developing CVD and the accumulation of BPA and CRP in such participants.

Although there was no association between BPA and CVD or between BPA and CRP, the advanced triangle of epidemiology served as a guide for this study to investigate some of the factors that contribute to chronic diseases. The study was aligned with its theory by examining some of the factors related to chronic diseases and maladies in populations.

Urinary BPA and Serum CRP

Following the nonsignificant statistical association between BPA and CVD, a possible association between BPA and CRP was investigated. To assess such relationship a single Pearson correlation was conducted between BPA and CRP. Prior to the analysis, the assumptions of the Pearson correlation were assessed. Pearson correlation is used with data that exhibits normal distribution (Lehmann, 2006). Normality was assessed using a P-P plot. The plot (found in Appendix A) indicated that the data were not normally distributed, and thus the assumption to use Pearson correlation was violated. Another assumption to use Pearson correlation was also violated, namely the homoscedasticity of the relationship between BPA and CRP. The relationship between BPA and CRP was found to be heteroscedastic, violating the Pearson assumption again. The other alternative, nonparametric equivalent of the Pearson correlation method was

Spearman correlation, which was conducted. Spearman analysis does not require the same restrictive assumptions as Pearson analysis (Lehmann, 2006).

Spearman correlation for the two variables, BPA and CRP, was .06 ($p = .015$), indicating a significant association between BPA and CRP. The positive Spearman correlation indicated a positive association between BPA and CRP. As urinary BPA level increases, serum CRP level also increases.

Though the relationship between BPA and CRP was found to be significant beyond the 0.05 level, examination of the Spearman correlation coefficient (r_s) using Cohen's (1988) guidelines indicated that this represented a very weak association. In addition, examination of a scatterplot between the two variables (Figure 2) indicated that significant findings might be due to the tendency of both variables to cluster around 0, and no linear relationship was observed. This observation held true after outliers were filtered from the plot (Figure 3).

The focus of the association between BPA and CRP was later shifted to examine the cluster of the measurements of both BPA and CRP around the zero. To examine such cluster fully, I conducted a logarithmic 10-scale with outliers (Figure 4) and without outliers (Figure 5). The logarithmic 10-scale transformation did not show any linear relationship between BPA and CRP. There seemed to be a tendency towards a central cluster that might be skewing things to appear that there was a relationship when conducting the Spearman correlations.

CRP is the major protein secreted during an inflammatory response (Erlinger et al., 2004). Erlinger et al. ascertained higher CRP concentration was associated with the

presence of cancer, CVD, fibrosis, and sleep apnea. The current study ascertained that an association between BPA and CRP existed but not at a significant level using Spearman correlation ($r_s = .06, p = .015$). According to Cohen (1988), Spearman correlation coefficient (r_s) of .29 and below indicates weak association. Spearman correlation coefficient (r_s) between .3 and .39 constitutes a medium strength correlation and that of 0.5 and above indicates high strength association. Spearman correlation coefficient for BPA and CRP in the current study was .06 ($p = .015$), indicating a very weak association.

Further investigation of the association between BPA and CRP using a scatterplot (Figures 2 and 3) also indicated weak association, although the scatterplot was later scaled at a 10 logarithmic scale (Figures 4 and 5). The reporting of CRP elevation from NHANES participants supported the literature on CRP as a systemic marker for inflammation and other anomalies not related to BPA. According to Erlinger et al. (2004), organs, such as the colon, were more susceptible to cancer while inflamed. To lower the risk of colon cancer, researchers have used anti-inflammatory drugs (Baron et al., 2003). In patients with coronary artery diseases, the level of CRP dropped after interventional exercise programs (Jialal et al., 2001). Jialal et al. provided evidence of the presence CRP with higher lipid profiles. They indicated that once the lipid level was controlled, the level of CRP was noticed to drop (Jialal et al., 2001). Teitel (2013) indicated that the level of CRP was elevated in patients with chronic renal failure, obstructive sleep apnea, stroke, and severe peripheral vascular disease. While the level of CRP as a systemic marker of inflammation was used in this study to show any possible

effect of BPA on the body, the findings showed that higher level of urinary BPA was not statistically significant predictor of higher level of serum CRP.

Limitations of the Study

The current study is limited due to use of secondary data that could not be verified and was conducted under the auspices of the CDC. The original sample had 10,537 participants but due to data filtering and processing the ending sample size was 1,465 participants. Larger sample size is desirable in research to reflect reliability of the data. The resulting sample size used in the logistic regression conveyed high level of power and hence the sample size was verified to be valid and trustworthy. There could be higher reliability with larger sample size but data processing limited the sample size to 1,465 participants. The final sample size limited generalization from NHANES samples to the whole U.S. population.

Another limitation for this study is that the level of CRP is also raised in other conditions. To limit this confounder, the study controlled for age, gender, race/ethnicity, arthritis, and urinary creatinine. The reporting of CVD is also limited to heart attack, angina, coronary heart diseases, and congestive heart failure, with exclusion of many other heart conditions.

Recommendations

I suggest extending the definition of CVD to be more inclusive. Future researchers can include pericarditis, abnormal heart rhythm, heart valve diseases, and aorta diseases. Broader definitions of CVD would include higher sample size and improve the generalization and reliability of the study. To see the immediate effect of

BPA on CVD, future researchers can use animal models in experiments that include a treatment group, which is followed over the course of their lifetime measuring urinary BPA output and development of CVD. Comparing the level of BPA before and after reporting CVD would clarify the relationship, which may be dose dependent. Any accidental acute exposures of humans to BPA should also be investigated and a long term study measuring BPA, CRP, and CVD could be carried out with this population.

Other recommendations include controlling for other causes of CRP elevation. The current study controlled for age, gender, race/ethnicity, arthritis, and urinary creatinine. Recommendations for this aspect of the study include controlling of such disease as chronic renal failure, obstructive sleep apnea, stroke, and severe peripheral vascular diseases. The use of a larger sample size is also desirable in future research to better represent the US population. For better understanding of BPA, it is also recommended to compile data from other countries in a meta-analysis of the effect of BPA on other chronic disease other than CVD.

There are an opportunity for future researchers to explore the possible association between age and BPA, and between age and CRP. It was observed from the results of this study that age is the only predictor of CVD. The analysis suggested that 1 year increase in age caused 1.08 factor increase in the odds of being diagnosed with CVD. Further analysis is needed to explore such association in more details to fully understand the interaction of age, BPA and CRP.

Implications

There are numerous positive social changes implicated from the results of the current study at the various level of society. For individuals, the current study joins voices with the FDA to refrain from boiling food in plastic until further testing of the chemicals used in plastic is completed. On the family level, individuals are encouraged to buy safe products and to question ingredients found in household items. On the organizational level, institutions are encouraged to have a broader approach on the cause of CVD and hence effective prevention strategies. On the society/policy level, BPA is recognized as a chemical that needs further research and testing. On the research level, the importance of the current study is that it adds to the body of knowledge as aligned with Walden University's mission statement.

This study provided a different perspective on chronic diseases, especially CVD. While the factors contributing to CVD have been established (complex interaction between diet, genetic, and lifestyle factors), the contribution of environmental contaminants (such as BPA) received poor attention from researchers. There was a need for research such as this to shed a new light on the causes of CVD and contribute to the development of more effective strategies for prevention.

Conclusions

The results of this study indicated that the association between BPA and CVD is not statistically significant within the parameters of this study. The two step binary logistic regression with covariates and BPA levels to predict CVD showed no change in the Nagelkerke coefficient of determination, which did not increase from the 15%

explained by the controls. BPA level was found to be a nonsignificant predictor of CVD ($p = .853$). In particular, the analyses revealed that among other confounders, age was the only predictor of CVD. The regression suggested a one-year increase in age causes a 1.08 factor increase in the odds of being diagnosed with CVD.

In an ancillary analysis, there seemed to be an association between BPA and CRP ($r_s = .06, p = .015$); however, upon further analysis, it was determined that the association was not statistically significant and was due to the tendency of both variables to cluster around zero, and no linear relationship was observed.

Although no significant association was found between BPA and CVD or between BPA and CRP in this study, further investigation is needed to confirm such results and to include more confounders and to increase sample sizes and hence increasing the reliability for possible generalization to the whole US population. Incidents of acute exposure of humans and animals, if available, should be investigated. Experiments using animal models should be conducted to determine the dose-response relationship between BPA, CRP, and CVD. It is also highly recommended to explore the interaction of age, BPA, and CRP. Further research to identify other possible causes of CVD and elevation of CRP is recommended.

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Appendix A: SPSS Output for BPA and CRP

The SPSS outputs for BPA and CRP are listed here.

Table A1

Spearman's Correlation Between BPA and CRP

Spearman's Correlations			Urinary Bisphenol A (ng/mL)	C-reactive protein(mg/dL)
Spearman's rho	Urinary BPA (ng/mL)	Correlation	1.000	.064*
		Coefficient		
		Sig. (2-tailed)	.	.015
		N	1453	1453
	CRP (mg/dL)	Correlation	.064*	1.000
		Coefficient		
Sig. (2-tailed)		.015	.	
	N	1453	1453	

Note. Correlation is significant at the 0.05 level (2-tailed).

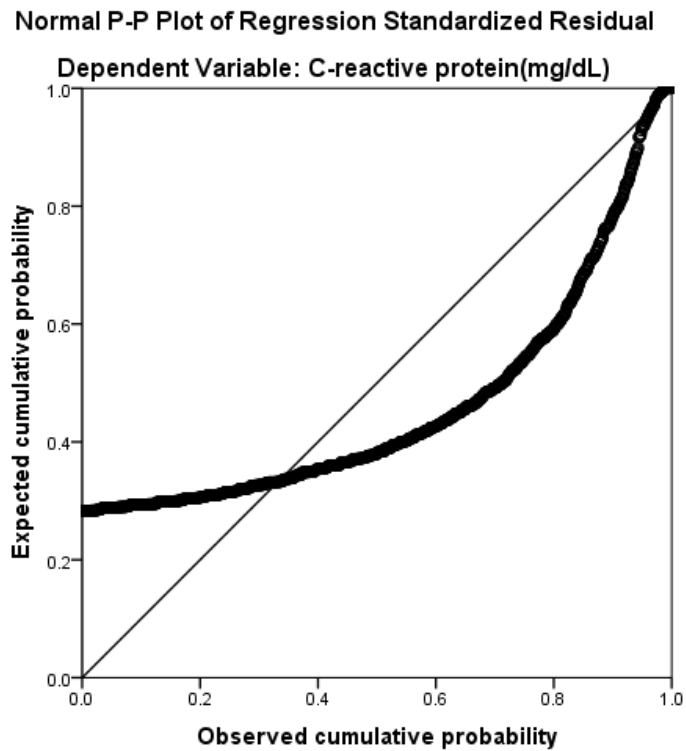


Figure A1. Normal P-P plot to determine the distribution of error around the line of best fit.

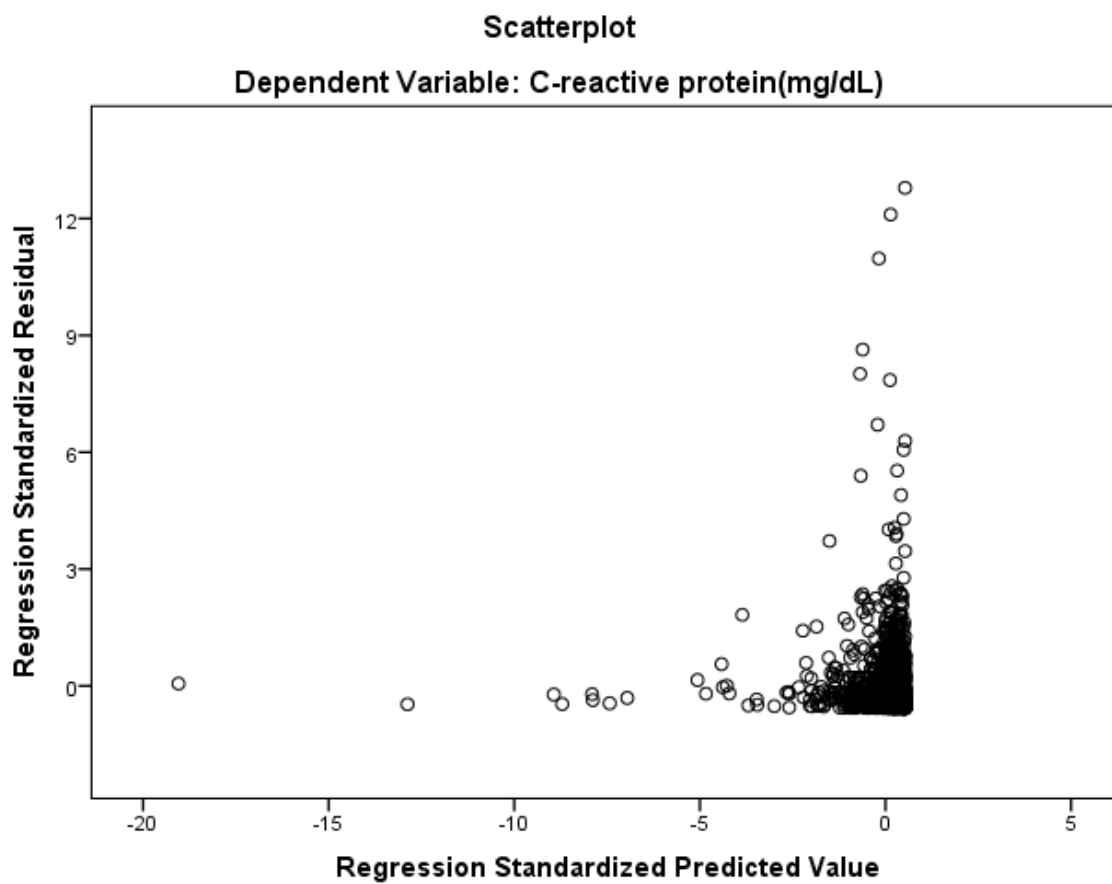


Figure A2. Standardized residual scatterplot between urinary BPA (IV) and serum CRP (DV) for examining homoscedasticity.