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Relationship of Acetaminophen and Alcohol to Incipient Renal Insufficiency: The Role of Race in Estimating Glomerular Filtration Rate

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Abstract

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Doctoral Study Submitted in Partial Fulfillment

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Abstract

There are increasing concerns about the incorporation of race in the estimated glomerular filtration rate (eGFR) prediction equation. which has been used to measure renal function in studies that have shown a relationship between therapeutic dose of acetaminophen and light-moderate alcohol use to incipient renal insufficiency. The purpose of this study was to assess the same relationship, using a redefinition of renal insufficiency based on the chronic kidney disease–epidemiology collaboration creatinine-based eGFR, with and without race, and exploring the potential impact of race in the hypothesized relationship. Data from the 2003-2004 National Health and Nutrition Examination Survey were analyzed using multi-variable logistic regression. Results, after adjusting for hypertension, diabetes, and obesity, showed a statistically significant association of therapeutic dose of acetaminophen and light–moderate alcohol to incipient renal insufficiency, regardless of whether the eGFR prediction equation included race, OR = 2.65, 95% CI [1.74, 4.09], or did not include race, OR = 2.43, 95% CI [1.88, 3.14]. Thus, the hypothesized relationship of therapeutic dose of acetaminophen of light to moderate amount of alcohol to incipient renal insufficiency is ordered-preserved. Therefore, future largescale epidemiological studies to further investigate this issue are warranted. Implications for social change include designing awareness messages that target all racial groups about the effect on the kidneys of light drinking with a therapeutic dose of acetaminophen. With more awareness, individuals may be able to adjust their behavior to prevent kidney damage.

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Dedication

I dedicate this study to my mom, Ms. Cecilia Eledu; my brother, Smart Eledu and my wife, Cynthia Eledu, for their support and encouragement.

Acknowledgments

I want to thank my chair, Professor Ndetan Harrison, and my committee member, Dr. Vasileios Margaritis, for their guidance and aid, especially Professor Harrison for his push and persistence in this process.

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Section 1: Foundation of the Study and Literature Review

Pain continues to be a major medical burden in the United States (Zelaya et al., 2020) and is the main reason people self-medicate. Acetaminophen, also known as paracetamol, is the most widely used and readily available over-the-counter analgesic and antipyretic in the country (Consumer Healthcare Products Association, 2020; Food and Drug Administration, 2020; da Rocha et al., 2015). Acetaminophen use by individuals who lack the ability to safely self-medicate may have harmful implications for kidney health. Some noticeable kidney diseases include nephrotoxicity, which can be induced by drugs such as acetaminophen when used inappropriately (Chen et al., 2015). Nephrotoxicity, alongside adverse immunological reactions, causes high mortality in most adults worldwide (Sohail et al., 2019).

Furthermore, acetaminophen can have adverse health impacts when used with alcohol. Alcohol in heavy amounts can have harmful toxic effects (Kaartinenet al., 2009) and can contribute to acetaminophen toxicity in the kidney (Lesser et al., 1996). These effects are concerning because of the prevalence of alcohol use in the United States. In research by the National Institutes for Health (2020), 70% of respondents said they had a drink within the past 12 months, and 55.3% said they drank alcohol within the past 30 days. Also, among youth ages 12 to 17, an estimated 401,000 had alcohol use disorders, including 227,000 females and 173,000 males (National Institutes for Health, 2020).

Although some research has found that drinking in moderation seems to help the heart and cardiovascular system, research shows that heavy drinking and binge drinking come with a host of short- and long-term health effects (National Institutes for Health,

2020). One focus of these adverse health impacts is the kidney. The kidney is one of the human body's most sensitive and dynamic organs. It is useful for the excretion of toxic metabolites, detoxification, and protection of homeostasis or homeostatic mechanisms within and outside of the body (National Institutes for Health, 2020). The kidney, accordingly, can be affected by different diseases, including drug-induced-kidney diseases that can affect kidney functioning in a way that may be dangerous to human health (Reddyhoff et al., 2015). The sensitivity of the kidneys has fueled the collaboration of the pharmaceutical industry and researchers to tackle kidney diseases induced by drugs (Schwarzinger et al., 2017). The observed increased specific risks for hepatotoxicity due to both acetaminophen and alcohol have been shown to share a similar metabolic pathway involving catalase and cytochrome P450 2E1 (CYP2E1; Heit et al., 2013; Tanaka et al., 2000).

These impacts are concerning because individuals who experience a hangover after social drinking may self-medicate with over-the-counter acetaminophen to resolve the hangover. According to a 2018 analysis, among 1,179 National Health and Nutrition Examination Survey (NHANES) respondents who reported consuming acetaminophen, including in combination with other pills, 1,104 (93.64%) ingested therapeutic doses, among which 622 (56%) also consumed light-moderate amount of alcohol (Ndetan et al., 2018). Thus, it is a significant public health concern to know whether these two highly prevalent substances in U.S. society, if chronically used, even in normal (light-to-moderate) amounts, may contribute towards renal insufficiency. This question spurred Ndetan and colleagues (2018, 2020) to explore the potential effect of therapeutic doses of

acetaminophen in combination with light-to-moderate amounts of alcohol on kidney functions. They reported an increased risk of early-stage kidney disease potentially associated with the consumption of therapeutic doses of acetaminophen concomitantly with light-to-moderate amounts of alcohol. In their analyses, early-stage kidney disease was defined based on estimated glomerular filtration rate (eGFR) equations, including race (Ndetan et al., 2018, 2020). However, the inclusion of race in an eGFR equation has come under increased scrutiny recently because race can differentially influence access to care and kidney transplantation with a national call to re-evaluate the use of race in eGFR equations in the United States (Delgado et al., 2022).

In the United States, Black people experience kidney failure 4 times as often as Whites, yet they are less likely to receive timely referrals to a specialist. Doctors detect kidney functions using eGFR, which predicts the ability of the kidneys to filter creatinine. However, race is factored in the eGFR prediction equation to adjust for higher creatinine levels in Black people, typically resulting in higher values than other ethnicities. Many members of the medical community believe that levels of creatinine, a waste product of muscle metabolism, are higher in Black people who are claimed to have greater muscle mass than other racial/ethnic groups. (Delgado et al., 2022).

The adjustment of creatinine levels in the eGFR equation for Black people has the potential to make the kidneys of Black people appear healthier than they are, thus delaying life-saving transplants; such delays are now looked upon as an element of racial discrimination (Delgado et al., 2022).

Experts, including those from the National Kidney Foundation and the American Society of Nephrologists, are reviewing the ramifications of eliminating race in the estimation of GFR. It is imperative that claims based on the inclusion of race in the estimation of GFR be revisited, according to Delgado et al. (2022). In this study, I examined the hypothesized association of therapeutic doses of acetaminophen with light-to-moderate amounts of alcohol and early-stage kidney disease using the chronic kidney disease-epidemiology, collaborating (CKD-EPI) creatinine-based eGFR equation with and without race. Assessing the inclusion of race in estimating GFR may contribute to the larger conversation about racial disparities in kidney health. In this section, I provide an overview of the study and review key literature related to the study topic. I also discuss the potential significance of the study.

Background

Acetaminophen is commonly used to treat mild-to-moderate pain and liver infections (Zhang et al., 2015). In addition, it is sometimes used for self-medication and to help with hangovers induced by alcohol (Wang et al., 2018). However, research shows that the combination of alcohol and acetaminophen can result in adverse health effects. Combined use affects the kidneys and other organs like the liver (acetaminophen-induced hepatotoxicity; Wang et al., 2018). Further studies point out that acute kidney injury (AKI) is one of the most severe complications of hospitalized patients and may be associated with an increased risk of death and higher costs of hospitalization (Ruiz-Criado et al., 2015; Sykes et al., 2018). Drugs are the third to the fifth leading cause of AKI in hospitalized patients (Kane-Gill & Goldstein, 2015). Drug-induced acute kidney

injury (D-AKI) is defined as kidney injury caused by drugs or their metabolites within 7 days after using one or more drugs (Awdishu & Mehta, 2017). D-AKI is increasingly recognized as a common adverse drug reaction in clinical practice. In the United States, 18%–27% of hospital-acquired AKI cases are caused by drugs (Pierson-Marchandise et al., 2017; Taber & Pasko, 2008).

The negative effect of acetaminophen on the kidneys is not widely recognized due to the limited interaction of the kidneys and acetaminophen (Braueret al., 2015). The effect is manifested on the liver when used in massive quantities because it associates itself with the drug metabolism. However, the combination of acetaminophen and alcohol may cause adverse health effects on the liver and renal problems (Rocha et al., 2015). Studies show that the use of acetaminophen in people with kidney diseases may be harmful (Braueret et al., 2015; Rocha et al., 2015), and hence the National Kidney Foundation recommended that the drug be optional for people with kidney difficulties or renal failure (Rocha et al., 2015). Rocha et al. (2015) showed that people's continued use of acetaminophen to reduce pain could cause renal impairment and Cystatin-C drug-induced renal diseases. This research suggests the negative effect of acetaminophen on the kidneys.

Problem Statement

Because pain continues to be a major burden in the United States (Zelaya et al., 2020) and still is the main reason people self-medicate, acetaminophen has become the most used over-the-counter analgesic (Consumer Healthcare Products Association, 2020; Food and Drug Administration 2020). However, acetaminophen use is associated with

renal toxicity (Chen et al., 2015). Also, alcohol consumption is highly prevalent in the U.S. general population (National Institutes for Health, 2020), and studies have shown that it contributes to acetaminophen toxicity in the kidney (Zelaya et al., 2020). Because the prevalence of both acetaminophen and alcohol, especially in normal amounts, is high in the U.S. general population, chances are also high that concurrent use is widespread, especially among active youth who experience a hangover after social drinking and self-medicate with acetaminophen (Ndetan et al., 2018).

The specific research problem addressed in this study is that although a statistically significant association between concomitant use of a light-to-moderate amount of alcohol with therapeutic doses of acetaminophen and the risk of incipient kidney dysfunction has been reported, (Ndetan et al., 2018).

this observed association requires further examination. In the analyses of this association, a key measure for renal dysfunction was prediction equations for eGFR that included race. However, such practice has been viewed as problematic recently, with a national call for race to be eliminated from eGFR prediction equations and recommendations from a national task force to evaluate the potential impact of such practices on the prediction of kidney function (Delgado et al., 2022).

Purpose of the Study

The purpose of this quantitative secondary data analysis was to investigate the impact of eliminating race from the CKD-EPI creatinine-based eGFR prediction equation to assess the relationship of therapeutic doses of acetaminophen and light-to-moderate amount of alcohol to incipient renal insufficiency. This investigation required first

confirming the existence of the hypothesized relationship using the CKD-EPI creatinine-based eGFR prediction equation with race, then without race and subsequent control of factors such as diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity. In addition, other potential disparities based on sociodemographic characteristics were explored. I utilized data from the 2003–2004 NHANES, the latest available data that includes all required variables, especially analgesic pain relievers (including acetaminophen-containing pills).

Research Questions and Hypotheses

I answered the following research questions (RQs) and hypotheses for this study:

RQ1**:** Using the CKD-EPI creatinine-based eGFR prediction equation with race, is there an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income)?

$H_0$1: Using the CKD-EPI creatinine-based eGFR prediction equation with race, there is no association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income).

H_a1: Using the CKD-EPI creatinine-based eGFR prediction equation with race, there is an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income).

RQ2**:** Using the CKD-EPI creatinine-based eGFR prediction equation without race, is there an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income)?

$H_0 2$: Using the CKD-EPI creatinine-based eGFR prediction equation without race, there is no association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol, and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity as well as sociodemographic (such as education and household income).

$H_a 2$: Using the CKD-EPI creatinine-based eGFR prediction equation without race, there is an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which

predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income).

Race, age, and gender were incorporated in the eGFR prediction equation and thus abhorrent to further control to avoid overadjustment bias (see Gilthorpe et al., 2015).

Theoretical Foundation

Two theories provided the theoretical foundation of this quantitative study: the theory of reasoned action and the theory of planned behavior. TRA, developed by Fishbein and Ajzen, explores the likelihood that individuals will engage in a particular behavior by seeing their attitudes and the norms under which they subject themselves (Linke et al., 2013). Based on TRA, TPB contends that individuals tend to adopt a behavior they perceive to be valuable and impactful to their lives and social environment; the opinions, beliefs, and thoughts of influential figures that shape that thinking process. As an extension of TRA, TPB was formulated on similar constructs, attitudes, and norms with the addition of perceived behavioral control elements (Linke et al., 2013). According to TPB, the belief on how likely or hard it is to adopt a behavior figures out whether the behavior is adopted while acknowledging the role of contributing factors (Godin, 1994). TRA, however, looks at a person's views regarding their ability to perform the specific behavior and how the behavior change can be prompted amongst a diversified population with different health behaviors.

TRA and TPB describe how one’s health behavior is based on their intent, which is, in turn, influenced by their attitude toward the behavior; subjective norms, such as social and environmental surroundings; and their perceived control over their behavior

(Fishbein & Ajzen, 2009). In this research study, the attitude and behavior of interest were the intakes of acetaminophen and alcohol (potentially concomitantly), reasoned actions, planned behaviors, and/or attitudes associated with social norms. I posited that a lack of knowledge about the potential adverse effects of these behaviors tends to encourage them. In contrast, sound knowledge, often created or influenced by health care providers and other influential figures with knowledge of adverse effects such as renal and other toxicities (potentially associated with concomitant use of acetaminophen and alcohol), may deter individuals from these behaviors. (Go et al., 2001; McDonald, 2009; Matsushita et al., 2010). Sociodemographic characteristics play a role in perceived self-efficacy related to health habits and warrant controlling for investigations that assess the relationship between specific health behavior and health outcome. Racial groups tend to have distinct social norms that may play a role in their health behavior concerning alcohol and acetaminophen consumption and its potential effect in predicting kidney functions based on eGFR, which incorporates race. These theoretical frameworks were the basis for selecting variables that defined the health behaviors of interest (acetaminophen and alcohol consumption) and health outcome (renal insufficiency), analyzing the results, and interpreting the findings.

Nature of the Study

I employed data-driven hypotheses. To address the RQs in this quantitative study, I performed a secondary data analysis of the 2003-2004 NHANES data (National Center for Health Statistics [NCHS], n.d.). I first ensured that NHANES captured the required variables. NHANES is a series of cross-sectional, nationally representative surveys of the

U.S. noninstitutionalized population conducted by the NCHS. The general purpose of NHANES is to assess the health and nutritional status of adults and children in the United States. ("National Health and Nutrition Examination Survey") NHANES applies a complex sample survey design structure within a multistage probability design. NCHS researchers use U.S. counties as primary sampling units and select individuals (persons) to be interviewed from clusters of households randomly sampled from the counties. [NCHS], n.d.). They combine interviews with physical and laboratory examinations and store data in separate subsamples. Any analyses using NHANES data must apply the complete multistage probability design structure with appreciate sample weights, cluster, and strata variables to yield accurate national population estimates (NPEs) and corresponding weighted percentages (frequencies), standard errors, and estimates effect measures.[NCHS], n.d.).

The key variables for this analysis included variables applied to generate the CKD-EPI creatinine-based eGFR (with and without race). From these variables, I further defined the dependent variable computed from serum creatinine, age, sex, and race. The independent variables were ingestion of acetaminophen (determined from analgesic pain relievers and their frequency, quantity, and strength) and light-to-moderate alcohol consumption (defined using quantity and frequency of alcohol use). Covariates included diabetes (defined using blood sugar measurements), hypertension (defined from multiple measures of systolic and diastolic blood pressure), obesity (defined by body mass index [BMI]), age, gender, race, education level, and household income. All the required variables—serum creatinine, analgesic pain relievers (types, frequency of consumption,

quantity, and strength), alcohol consumption (types, quantity, and frequency of consumption), blood sugar measurements, systolic and diastolic blood pressure, BMI, age, gender, race, education level, and household income—were captured in NHANES 2003-2004. Data management and operationalization of the variables are described in Section 2's Methodology subsection. All the required variables to answer the RQs were defined as categorical and analyzed using multi-variable logistic regression models that featured the complex survey design structure. Analyses were limited to those aged 18 years and above.

Literature Search Strategy

To obtain articles on the given topic, I used keywords such as pain, acetaminophen, Tylenol, analgesic pain reliever, alcohol, kidney disease, renal failure, kidney dysfunction, renal dysfunction, renal insufficiency, renal injury, NHANES, prescription pain reliever, creatinine-based estimated glomerular filtration rate, race-based estimated glomerular filtration rate and non-race-based estimated glomerular filtration rate. The search was done mostly by using the Walden University Library and accessing key databases and search engines, including CINAHL Plus, MEDLINE, Science Direct, Google Scholar, PLOS ONE, Gale OneFile, Academic Search Complete, ProQuest Health & Medical Collection, EBSCO, CINAHL & Medline, ProQuest, and PubMed. In addition, I narrowed the search to peer-reviewed articles, specifically those published between 2010 and 2020.

Literature Review Related to Key Variables and Concepts

Renal Disease and Markers of Renal Function

Kidney failure has become a common global health problem. The health problem is more severe in industrialized nations, including the United States. The condition is most common in adults 45 years and above with renal failure (Rocha et al., 2015). Studies highlight that the leading cause of kidney failure or kidney diseases is glomerulonephritis, followed by diabetes and hypertension (Braueret et al., 2015). Chronic kidney disease puts patients at a substantial risk of requiring renal replacement or dialysis to sustain long-term survival. Kidney function is assessed by examining the glomerular filtrate in which creatinine or cystatin concentration is included in the equation and demographic data (Braueret et al., 2015).

Chronic kidney disease is classified into five stages by the National Kidney Foundation Disease Outcome Initiative (More et al., 2016). Stage naming depends on the severity of the health conditions. Stages 1 and 2 have mild complications such as kidney damage manifestation and erythrocytosis, macro- or micro-albuminuria on renal ultrasound (Zhang et al., 2017). Therefore, determining the glomerular filtration rate in the early stage of kidney complications is simplified because it requires distinguishing between Stages 1 and 2 (between 60-80 mL or eGFR > 90 min-1 per 1.73m^2, respectively). Initial stages of kidney infection are usually asymptomatic; however, the kidney might normally function but with a significant risk of disease progression (Yoon et al., 2016).

Determining GFR using creatinine is not limited to standardizing the analytical method, but other sources of error occur. For example, variation in tubular secretion and production. According to Munt et al. (2017), Cystatin-C was developed as an alternative for determining the GFR. The alternative requires no tubular secretion and minimal extra-renal elimination. Thus, the blood concentration in Cystatin-C is entirely influenced by GFR and not affected by malignant or inflammatory diseases, diet, or nutritional status, (Wendon et al., 2017).

Recognizing incipient chronic kidney disease or renal insufficiency using Cystatin-C does not require the correction of anthropometric data or age (Rajaram & Subramanian, 2018). Researchers have used various equations involving serum creatinine concentrations to estimate the GFR in children. These include the Schwartz formula but lack the substitute for accurately determining glomerular filtration rate by biomarkers (Rocha et al., 2015).

Effect of Combining Acetaminophen and Alcohol on Renal Tubule Function

Acetaminophen is a pain reliever with no harmful effects as per the recommendation of the National Institute of Diabetes and Digestive and Kidney Diseases arm of the National Institutes of Health. People can use acetaminophen at a therapeutic dose not exceeding 4g per day (Koning et al., 2015). Using acetaminophen beyond the prescribed dosage presents health complications to the kidney and other sensitive organs like the liver that involves itself while breaking down drugs. According to Koning et al. (2015), acetaminophen should not be consumed beyond the limit of 325 mg per tablet or pill, and the prescription of products having high dosages is heavily prohibited. An

overdose of acetaminophen is known to cause acute renal failure and end-stage renal disease. Koning et al. (2015 reported a dose-response relationship between acetaminophen ingestion and the ratio for end-stage renal disease. In addition, Koning et al. observed the dose-response relationship between serum alanine aminotransferase with reoccurring doses of acetaminophen at a recommended level of 4g without using other pain relievers such as opiates.

The daily use of acetaminophen for a long time is not advisable as it results in a three-fold risk of kidney failure after adjusting for aspirin and phenacetin (Teschke et al., 2018). For example, a study conducted in 1999 on the use of acetaminophen in patients with the renal tubular and glomerular disease showed a significant increase in β2-microglobulin excretion and creatinine levels in all three groups (Park et al., 2019). The results helped to determine the toxicity of acetaminophen. However, most researchers argue that using acetaminophen at a therapeutic level is safe for human health (Molnar et al., 2016). Therefore, the effect could have originated from using more acetaminophen than recommended by the National Institute of Diabetes and Digestive and Kidney Diseases arm of the National Institute for Health (Munt et al., 2017).

Alcohol and acetaminophen act on the same pathway; therefore, their combination causes a health effect on the renal tubular as it increases the risk for nephrotoxicity and hepatotoxicity (Sheehan et al., 2016). There were 1997 case studies on hepatotoxicity and nephrotoxicity from concurrent use. However, they have sparked debate on the frequent combination of acetaminophen and alcohol versus acute incipient renal insufficiency (Sheehan et al., 2016).

In the United States, renal toxicity is severe among alcohol users who frequently use acetaminophen to relieve a hangover (Braueret al., 2015). However, other factors predispose people to the same health condition rather than the combination of alcohol and acetaminophen drugs (Schwarzinger et al., 2017). Research in health care settings show that for every autopsy performed on a man who died from hepatic necrosis, acute epithelial cell desquamation, tubular injuries, and loss of microvilli are common (Munt et al., 2017).

Metabolism and Reaction of Acetaminophen on Sensitive Body Organs

The literature shows that the kidney and liver metabolize acetaminophen in the body through the P450 enzymes (Quigley et al., 2019). Therefore, no toxicity is seen when acetaminophen is administered at a therapeutic level (Assari & Caldwell, 2017). However, using acetaminophen in large doses above 2,000 mg/kg leads to hepatotoxicity and nephrotoxicity in the liver and kidney, respectively (Assari & Caldwell, 2017).

Acetaminophen metabolites react with sulfhydryl and glutathione groups on critical proteins resulting in renal and hepatic toxicity and cellular dysfunction (Major et al., 2016). The characteristics of P450 metabolizing enzymes differ between the kidneys and the liver. Renal toxicity is influenced by several factors ranging from gender conditions that alter the metabolism of the P450 enzyme system to liver disease and concurrent renal insults (Rocha et al., 2015). The last stage of renal toxicity, Stage 5, is characterized by a cellular injury that mostly occurs on the proximal tubule. Furthermore, the rate of glomerular filtration is reduced at a significant level (Rocha et al., 2015).

According to Koning et al. (2015), no conclusive evidence exists that analgesic nephropathy and chronic disease are caused by chronic administration. However, research shows that the combination of acetaminophen and alcohol contributes to such health conditions (Lipman et al., 2017). Furthermore, reports show that chronic administration of the combination of acetaminophen and aspirin or other drugs is likely to cause damage to the nephrons and liver (Rocha et al., 2015).

Relationship of Therapeutic Dose of Acetaminophen and Renal Dysfunction in Social Drinkers

Independently, acetaminophen ingestion at doses above the recommended levels and heavy consumption of alcohol are associated with end-stage renal disease and acute renal failure. For example, a 2011 study reported trends in emergency department visits in the United States for renal-related issues over 14 years attributable to acetaminophen overdoses (Li & Martin, 2011). In addition, clinical and pathophysiological manifestations of acetaminophen-induced nephrotoxicity have also been reported (Mazer & Perrone, 2008). These reports include AKI associated with acetaminophen intoxication (Chen et al., 2015), particularly with chronic acetaminophen use (Kelkar et al., 2012). In a similar vein, excessive use of alcohol has been known to be associated with kidney malfunction alone (Kaartinen et al., 2009; Schaeffner et al., 2005) and concomitantly with acetaminophen use (Schmidt et al., 2002; Tanaka et al., 2000).

Although a dose-response relationship is well established between excess use of acetaminophen and/or alcohol with renal dysfunction, the therapeutic use of acetaminophen and light- to- moderate drinking remains understudied. One of the earliest

studies that reported on this use was in 1986 by Lesser and colleagues, who reported a lethal enhancement of therapeutic doses of acetaminophen by alcohol. While reporting similar observations, some researchers have argued that the problem may be related to inadvertent overdoses, holding that routine use at normal doses is extremely safe (Dart & Bailey, 2007).

An analysis of a national representative sample of 9,643 U.S. non-institutionalized civilians within the 2003-2004 NHANES data set projected an NPE of 286,222,757 in 2018 (Ndetan et al., 2018). It also suggested a relationship between therapeutic doses of acetaminophen and light-to-moderate alcohol drinking to early signs of renal dysfunction, separately and in combination (Ndetan et al., 2018). The study results showed that individuals not exposed to therapeutic doses of acetaminophen had reduced odds of renal dysfunction compared to those exposed to therapeutic doses of acetaminophen, especially with light-to-moderate drinking. The reported effect measures ordered were preserved in size, directionality, and statistical significance even after adjusting for factors predisposing the kidney to acetaminophen toxicity, such as diabetes, hypertension, and obesity (Ndetan et al., 2018).

The outcome measure or dependent variable for this analysis was kidney function measured in various ways, including self-report of whether a doctor had told the study participants that they had kidney disease or laboratory results of kidney function tests such as serum creatinine (SCr), blood urea nitrogen (BUN), or some combination of these such as GFR, and urinary albumin/creatinine ratio (ALBCR). These were all coded as binary categorical variables with early-stage kidney abnormalities (defined respectively,

SCr > 1.0 mg/dL, BUN> 23mg/dL, GFR<90mL/Minute/1.73m^2, and ALBCR > 17mg/g, male; 25mg/g, female) otherwise the kidney function was considered normal, making easy to test the existence of association with the exposure (or independent) variables as well as with adjusting for the controlled factors using the multivariable logistics regression model (Ndetan et al., 2018).

The use of varied approaches for assessing kidney function in this analysis was desirable for exploring the hypothesized relationship. Interestingly, although there seemed to be variations in the prevalence of kidney malfunction based on the various markers (31.53%,6.54, 34.40%, and 15.90%, respectively, based on SCr, BUN, GFR, and ALBSR), statistically significant increased odds were observed in all cases (Ndetan et al., 2018). Furthermore, a follow-up re-analysis of the same data sample to explore the existence of early disparate signs of kidney function associated with the same exposures seemed to confirm similar observations with noted disparities in age, educational levels, and income (Ndetan et al., 2020). The results suggest that these variables call for further consideration.

Estimated Glomerular Filtration Rate (eGFR) Prediction Equationswith and Without Race

The outcome variable for this study is incipient renal insufficiency measured in terms of eGFR. Over the years, several different equations have been used to predict eGFR. For example, when they first hypothesized and explored the relationship of the therapeutic dose of acetaminophen and light-to- moderate drinking to early-stage kidney disease, Ndetan et al. (2018) used the National Kidney Foundation's (2002) prediction

equation to define eGFR. The equation, which was first published in 2002, combines serum creatinine, blood urea nitrogen, gender, age, and race. In their 2020 study that looks at disparities in the observed relationship, they resorted to the 2009 CKD-EPI creatinine-based prediction equation which accounted for the physiological contribution of muscle mass on serum creatinine by adding age, gender, and race (Ndetan et al., 2020). They noted as part of their limitation that members of the CKD-EPI Collaboration had long contemplated its accuracy and consequently developed a 2012 version touted more accurate.

The 2012 version included cystatin C on claims that equations with multiple endogenous filtration markers are more precise (Inker et al., 2012; Levey et al., 2014). However, the inclusion of race in eGFR prediction equations has come under increased scrutiny recently on claims that such practices can differentially influence access to care and kidney transplantation with a national call to eliminate race from eGFR equations (Delgado et al., 2022).

Black Americans experience kidney failure four times as often as White Americans, yet they are less likely to receive prompt referrals to a specialist. Doctors detect kidney functions using eGFR predicts the ability of the kidneys to filter creatinine. The race is factored in this equation to adjust for higher creatinine levels in Black people, typically resulting in other ethnicities. The medical community holds an age-old belief that levels of creatinine, a waste product of muscle metabolism, are higher in Black people, who are claimed to have greater muscle mass than other racial/ethnic groups. This can potentially make some Black people's kidneys appear healthier than they were,

thus delaying life-saving transplants, which are now looked upon as an element of racial discrimination (Delgado et al., 2022).

Although a national taskforce of experts, including the National Kidney Foundation, American Society of Nephrologists and others continue to review ramifications surrounding the elimination of race in estimating GFR, it is imperative that claims based on models that have included race in the estimation of GFR be revisited (Delgado et al., 2022). This national taskforce recommendation is the fundamental basis for this study.

Theoretical Framework

The TRA and TPB supported this study. In 1975, Fishbein and Ajzen developed TRA as part of their exploration of the likelihood that individuals will engage in a particular behavior by observing their attitudes and the norms under which they subject themselves (Linke et al., 2013). In 1980, they extended the theory as the TPB by including perceived behavioral control elements (Linke et al., 2013). The premise of TPB is that individuals tend to adopt a behavior they perceive to be valuable and impactful to their lives and their social environment, including opinions, beliefs, and thoughts of influential figures, which tend to shape that thinking process. According to TPB, the belief on how likely or hard it is to adopt a behavior determines whether the behavior is adopted while acknowledging the role of contributing factors (Godin, 1994). TRA, however, looks at a person's views on their ability to perform the specific behavior and how the behavior change can be prompted amongst a diversified population with different health behaviors.

Together, TRA and TPB have been used to explain a wide range of health behaviors and intentions like smoking, drinking, health services utilization, and substance use in many aspects of social life and interactions by linking behavioral achievements to both motivations (intentions) and abilities (behavioral controls). Six constructs collectively represent a person's actual control over the behavior (Cheon et al., 2012). These include.

- Attitudes refer to the degree to which a person has a favorable or unfavorable evaluation of the behavior of interest. It entails a consideration of the outcomes of performing the behavior. ("The Theory of Planned Behavior - Boston University") The Theory of Planned Behavior Boston University)
- Behavioral intention refers to the motivational factors that influence a given behavior where the stronger the intention to perform the behavior, the more likely the behavior will be performed. ("The Theory of Planned Behavior - Boston University") (Behavioral Change Models; Boston University)
- Subjective norms refer to the belief about whether most people approve or disapprove of the behavior. It relates to a person's beliefs about whether peers and people of importance to the person think they should engage in the behavior.
- Social norms refer to customary codes of behavior in a group, people, or a larger cultural context. Social norms are considered normative, or standard, in a group of people. (The Theory of Planned Behavior Boston University")

- Perceived power refers to the perceived presence of factors that may ease or impede the performance of a behavior. Perceived power contributes to a person's perceived behavioral control over each of those factors. (“Behavioral Change Models - Boston University”)
- Perceived behavioral control refers to a person's belief of the ease or difficulty of performing the behavior of interest. Perceived behavioral control varies across situations and actions, which results in a person having varying beliefs of behavioral control depending on the situation (Cheon et al., 2012). (“Behavioral Change Models - Boston University”)

Both TRA and TPB describe how one’s health behavior is based on their intent, which is in turn informed by one’s attitude towards the behavior and subjective norms, such as social and environmental surroundings, and one’s perceived control over their behavior (Fishbein & Ajzen, 2009). In this research study, the attitude and behavior of interest are the intakes of acetaminophen and alcohol (potentially concomitantly), reasoned actions, planned behaviors and/or attitudes associated with social norms. I posit that lack of knowledge about the potential adverse effects of these behaviors tends to encourage them, whereas sound knowledge, often created or influenced by health care providers and other influential figures with knowledge on adverse effects such as renal and other toxicities (potentially associated with concomitant use of acetaminophen and alcohol), may deter individuals from these behaviors. Socio-demographic characteristics tend to play a role in perceived self-efficacy related to health habits and warrant

controlling for in investigations that assess the relationship between specific health behavior and health outcome.

An essential element of the fundamental relationship to be examined in this study is the definition of the outcome or dependent variable: kidney function using the 2012 CKD-EPI creatine-based prediction equation for eGFR (Inker et al., 2012; Levey et al., 2014; Ndetan et al., 2020). Furthermore, this equation has typically adjusted for the effect of race which has been a subject of a broader national debate on segregation related to access to health care. Thus, exploring the theoretical bases of race in the fundamental relationship becomes critical.

Social identity development and social norm adherence are two fundamental social processes for which race is central. One's ethnic/racial group membership is integral to one's identity and serves as a relevant source of psychological well-being and a lens through which others perceive them (Rivas-Drake et al., 2014). For example, the kidney function prediction equation remained predominant because many members of the medical community conceived people of African American descent as being muscular, which intends to affect the role of creatinine in kidney filtration (Delgado et al., 2022). The scientific basis of this claim is currently being scrutinized (Delgado et al., 2022). Social norms, broadly defined as the shared ideals and standards that guide or regulate the behaviors of members of a group (Cialdini & Trost, 1998), increasingly affect an individual's intergroup behavior and explicit attitudes (Nesdale, 2004; Rutland, 2004). It is theorized to work harmoniously with social identity to help individuals formulate

strong group identities and understand proper intragroup and intergroup behaviors (Nesdale, 2011).

Included in the TPB (Godin & Kok, 1996), social norms play an integral role in social psychology, health behavior change, and health communication (Bell & Holder, 2019; Rimal & Real, 2005). The work of Perkins and Berkowitz using the framework of social norms to study health behaviors (Smith & Christakis, 2008; Perkins & Berkowitz, 1986) has inspired a proliferation of research, interventions, and policies to modify social norms and behavior change related to alcohol use (Perkins & Berkowitz, 1986). For example, an individual may adopt the normative attitudes and behaviors of family and friends (proximal others) to which they feel close and identify (Cho, 2006) and because of the desire to belong and maintain social cohesion (Boyington et al., 2008) tend to be influenced by their behaviors.

A few factors complicate the degree to which social dorms influence behaviors. For example, social acceptance and identification mechanisms could affect distal norms and health behaviors, such as simultaneous intake of alcohol and drug use among racial groups in settings where they are in the minority. The distinction between descriptive (beliefs of others' behaviors) and injunctive (guiding collective ideals about what behaviors are regarded as acceptable or unacceptable) norms (Berkowitz, 2004) may further complicate how race and social norms affect the intake of alcohol and use of acetaminophen and their interaction with the kidneys.

Apart from adjusting for the race in the 2012 CKD-EPI creatinine-based eGFR, age is another typical variable that is adjusted for. Others have looked at early desperate

signs of kidney function associated with alcohol and acetaminophen based on race, age, and other sociodemographic (Ndetan et al., 2020). However, the interaction of age in a race and social norms is not as essential. While there seemed to be no convergence in alcohol use across a life course (age) with race (Caetano & Kaskutas, 1995), the interplay with acetaminophen and how it affects the kidney warrants further investigation.

Gender is also adjusted in the NKD-EPI 2012 prediction equation. While gender is not the subject of scrutiny, its role in alcohol use and its interplay with race and social norms is critically important to understanding its etiology and consequences on the kidney. The intersection of race and gender in trajectories of alcohol and acetaminophen may shed light on potential emerging disparities in this relationship. While social norms regarding substance use are changing for women (Goodwin et al., 2009; Keyes et al., 2008a, 2010), drinking remains less acceptable compared to men (Ahern et al., 2008; Keyes et al., 2011). The evidence suggests that Whites are more susceptible to influence from social norms about alcohol, with more positive attitudes toward drinking than Black people (Keyes et al., 2012). In general, at equal levels of alcohol consumption relative to their White counterparts, Black women are reported to have higher rates of alcohol-related problems. Among those with low levels of heavy drinking, Black men have higher rates of alcohol-related problems (Witbrodt et al., 2014). Thus, examining the intersection of race and gender when examining alcohol and acetaminophen consumption patterns on kidney function may yield important insights into the processes underlying racial/ethnic differences and social norms.

Finally, socio-economic status is another key factor that may further complicate how race manifests in the fundamental relationship of alcohol and acetaminophen with kidney function. Although it has been hypothesized that socio-economic indicators could fully account for racial/ethnic differences in age-related variation (Watt, 2008), the exact extent of how it plays in this relationship still is a dilemma. According to little available evidence, while income is positively associated with alcohol use in general (Keyes & Hasin, 2008), among those in poverty, Black men have higher rates of heavy drinking compared to their White counterparts (Ford et al., 2007; Gilman et al., 2008).

Thus, TPA extended from TRA theoretical framework was the basis for my understanding and selection of variables that define the health behaviors of interest (acetaminophen and alcohol consumption as well as other potentially complicating factors) and health outcome (renal insufficiency), and analyses and the resulting interpretation of its findings.

Definitions

The variables within this study and other pertinent terms are defined as follows:

*Acetaminophen (therapeutic amount)***:** It is a non-prescription medicine with a usual dose of 325 mg to 650 mg taken every 4 to 6 hours, with the maximum varying from 3,000 mg to 4,000 mg (Garriettes et al., 2021). Therefore, the patient must take less than 4,000 mg in 24 hours. Acetaminophen is used to minimize mild to moderate pain resulting from headaches: muscle aches, and menstrual pain and minimizes fever (Garriettes et al., 2021). In addition, acetaminophen is to reduce osteoarthritis pain which is arthritis caused by the breakdown of the lining of the joints. Accordingly,

acetaminophen is in a group of medications known as analgesics and antipyretics, which operate by alternating the body's senses and pain and acts as a body-coolant.

Diabetes Harreiter and Roden (2019) define diabetes as a chronic health condition that affects an individual's body while turning food into energy. Most of the eaten food is broken down into sugar (glucose) and released into an individual's bloodstream. When blood sugar increases, it signals the pancreas' release of insulin. So, insulin is key to let blood sugar into an individual's body cells for use as energy. Unfortunately, the body of a diabetic person either does not make enough insulin or efficiently uses the insulin it makes as it should. When insufficient insulin or cells respond to insulin, too much blood sugar stays in an individual's bloodstream. Over time, serious health problems, such as heart disease, vision loss, and kidney disease, are caused.

Incipient kidney abnormality: According to Morgensen et al. (1983), incipient kidney abnormality, alias incipient nephropathy, is the first presence of limited and abnormal urine albumin, known as microalbuminuria.

Hypertension Evidence from Giles et al. (2010) highlights hypertension as blood pressure higher than the normal level. An individual's blood pressure changes throughout the day based on their activities. Blood pressure measured consistently above the normal level results in a diagnosis called hypertension.

Obesity: This is the excess accumulation of fats that risks an individual's health status. A BMI beyond 25 is considered overweight, and 30 and beyond is obese (Panuganti et al., 2021). The problem has expanded to epidemic proportions as four million people perish annually due to being overweight (Panuganti et al., 2021). The

number of adults who are overweight and obese has been rising in the last four decades. For example, from 1975 to 2016, the number of overweight and obese individuals aged 5 to 9 years was increased to 18% from 4% (World Health Organization, 2020). Obesity is a double-burden malnutrition and research show that the biggest population of people in Asia and Africa are obese compared to overweight. Obesity is only considered to be a problem in developed nations (World Health Organization, 2020).

Social drinking (light- to- moderate amount of alcohol) Fillmore and Vogel (1996), define social drinking as individuals who regularly drink alcohol in various social settings. However, drinking neither changes their lifestyles nor creates severe problems. Social drinking is an important culture in America. Alcohol in America is present everywhere, for example, in bars, restaurants, and residents. Alcohol is a common way of socializing, relaxing, and celebrating occasions. Occasional drinking is termed to be normal and less harmful. However, the ingrained cultural effect is unchallenged and there is no clear clarification of the point where social drinking is a problem.

Assumptions

The NFK spurred on by the first success of its 1995 initiative to develop clinical practice guidelines for dialysis patients, and health providers approved a proposal known as the Kidney Disease Outcomes Quality Initiative (K/DOQITM). It aimed to improve the health status of all individuals with kidney disease, from the earliest kidney damage through the various stages of progression to kidney failure. The guidelines have become the centerpiece for evaluating, classifying, and stratifying chronic kidney disease. In this case, I relied on these guidelines for this study because they are authoritative and

constitute a comprehensive assimilation of information derived from other authoritative guidelines and reliable and well-known large data sources.

Acetaminophen and alcohol at high doses cause kidney damage, and this study supplied information at lower doses of the effect. However, the study was exploratory and only provided preliminary evidence of whether the interaction between acetaminophen, alcohol and other factors is important. A much larger study will be required to investigate the interaction between these factors in detail effectively.

Scope and Delimitations

With a clear understanding of the hierarchy of study designs to demonstrate evidence and an outlining of inherent limitations, this study settles on the analysis of secondary data derived from a cross-sectional design. Although this is not the best option for investigating this type of issue, it has a significant potential for providing useful preliminary information that may be incorporated in the future in dept and well-structured epidemiological designs like my study in which I would be taking advantage of data set capture by the NCHS.

As mentioned on many occasions, this study used data-driven hypotheses, analyzing data from 2003-2004 NHANES. These data stand for the entire U.S. non-institutionalized population (the target population) captured through a multistage probability survey design. Thus, all the complex survey design structures, such as survey weights, strata, and clusters, were applied to generate NPEs.

Limitations

This quantitative study analyzed secondary data from NAHNES 2003-2004. The main limitations are those inherent in secondary data analysis. Specifically, the data were not collected for the specific purpose of this study. So, there is a lot of possibility for where assumptions are made. For example, the main exposure variable for this study is the ingestion of acetaminophen. In NHANES 2003-2004 a separate module captured information about respondent use of over-the-counter analgesic pain relievers. It is based on these that I plan to capture acetaminophen usage. However, since so many compounds containing acetaminophen are sold over the counter, some respondents may not know they have taken a product that has the ingredient. Therefore, underreporting of its use is possible. Moreover, so many combination pills having acetaminophen cannot properly be delineated for acetaminophen use alone.

There is also the possibility of sampling and no sampling errors, including measurement errors. NHANES captures data using a questionnaire, medical examinations, and laboratory testing. Questionnaire data are based on self-reports with the potential for recall bias, while laboratory data are subject to measurement variation and examiner effects. However, it is worthwhile to acknowledge the extremely ambitious standards of the NHANES program that minimizes no sampling and measurement errors in data collection. Furthermore, this study used the NHANES 2003-2004 conducted almost 18 years ago. This is a limitation in that it is an old data set. It is usually desired to have a more recent data set in assessing public health situations as that may be easily

applicable to current trends. However, this is the latest series that captured data on analgesic pain relievers which helps define the key exposure variable for this study.

Ingrasciotta et al. (2014), in critical reviews of the epidemiologic literature, highlighted several deficiencies in studies investigating analgesic use and chronic renal failure. These deficiencies included most studies that did not have goal diagnostic criteria, which presented difficulty in identifying patients early enough in the disease process to ensure that exposure predated the outcome. Usually, patients with chronic renal insufficiency, once diagnosed are directed to stop aspirin and other NSAIDs as these drugs increase the risk of bleeding. These patients are advised to use acetaminophen instead for pain relief (Ingrasciotta et al., 2014). This cannot be fully addressed in this study either. Therefore, I only attempt to define renal insufficiency using eGRF based on measured serum creatinine incorporated in the prediction equation.

Finally, I acknowledge that NHANES is based on a cross-sectional design. Cross-sectional study designs are limited in how much value it contributes to research. Experimental and analytical observational designs (such as cohort and case-control) are preferred to establish claims (Davidson & Iles, 2013). However, that is not a limitation specific to this secondary data analysis, as I have no control over that.

Significance

Pain is one of the most common symptoms among the public and is also most frequently self-treated with over-the-counter analgesics such as acetaminophen. The prevalence of alcohol consumption among adults is also remarkably high. The toxic effects of both acetaminophen and alcohol, separately on the kidney at high doses, have

been well established. This is not the case in therapeutic doses of acetaminophen with light-to-moderate amounts of alcohol, respectively. However, extraordinarily little, if any, information is available on the simultaneous consumption of therapeutic amounts of acetaminophen in combination with low/moderate amounts of alcohol. Therefore, I hypothesized that incipient kidney disease (with no clinical manifestation) might develop in subjects with no previous history of exposure to therapeutic amounts of acetaminophen in combination with low/moderate amounts of alcohol. Particularly those with factors that increase their risk of acetaminophen toxicity.

This study investigated the potential effect of ingestion of therapeutic doses of acetaminophen in combination with light-to-moderate amounts of alcohol on kidney functions among adolescents and adults. To investigate the hypotheses, several methodological issues were overcome. These included the appropriate definition of a case of early kidney toxicity, the best markers and lowest cut-off point kidney function (test), the role of elevated liver enzymes in case definition, the nature of the proposed interaction (whether additive or multiplicative), the implications of slightly elevated levels of, and the exact role of predisposing factors including genetic susceptibility and of which future investigations need to address. This study began with exploring some of those important methodological challenges. For example, what is the appropriate definition of a case of early kidney toxicity? Much as the toxic effects of acetaminophen on the kidney at high doses are well established, the threshold dose at which these effects begin to occur is unknown. What does the lowest cut-off point of eGFR, which will be associated with these early toxic effects if present?

The overarching goal was to estimate the risk of early changes in kidney function tests due to ingesting therapeutic amounts of acetaminophen alone, low to moderate amounts of alcohol alone, and ingesting various amounts of both acetaminophen and alcohol combined. The presence of any interaction between acetaminophen and alcohol ingestion in the occurrence of these changes in kidney function tests was explored. Definitions of a case based on the 2009 CKD-EPI eGFR prediction equation with and without race were explored by distinguishing cases from controls. The study sought to identify the lowest doses of acetaminophen and alcohol associated with abnormal kidney function tests and the earliest change in kidney function tests detectable.

The study can provide preliminary data showing whether early toxic effects seen with the ingestion of therapeutic amounts of acetaminophen alone or in combination with alcohol are influenced by the presence of factors other than genetic susceptibility believed to enhance acetaminophen toxicity. Apart from providing evidence supporting the hypothesis that ingestion of therapeutic amounts of acetaminophen may cause early toxic effects on the kidney, this study can help identify other design methods that could be considered in the design of future large-scale epidemiologic studies. Also, the findings in this study can be found useful by the public health department in understanding the correlation between alcohol, acetaminophen, and renal failure. There still exists an unmet need for acute treatment options because current therapies are not always effective, especially for long-term migraine sufferers, who may have unwanted side effects, or are contraindicated for people with cerebra-cardiovascular disease. (“Full article: The current state of acute treatment for migraine in ...”) Recently approved therapies that include oral

CGRP receptor antagonists, a 5-HT1 F receptor agonist, and neuron-modulation devices may help address this unmet need because they do not induce vasoconstriction. In addition, it may be necessary to counsel patients on lifestyle modifications and behavioral strategies to manage alcohol consumption, acetaminophen intake, and renal failure. Finally, the recent uproar on potential racism associated with the inclusion of race in the eGFR definitions was explored and the findings from this study may provide important insights to contribute to the broader debate on race and the assessment of kidney function.

Summary and Conclusions

It is well understood that alcohol and acetaminophen have toxic effects on the kidney. For public health professionals, prevention is the goal; having proper exposure and outcome definitions to properly understand the situation is key. Two relevant questions are in order. The first was on exposure definition: What is the minimum exposure to both alcohol and acetaminophen that will be associated with renal failure? A preliminary step toward answering this question is to investigate whether a normal amount of these two substances will be associated with renal toxicity. The second and more relevant question was on outcome definition: What is the earliest sign of renal toxicity associated with exposure to a normal amount of these common substances (acetaminophen and alcohol) with potential toxicity to the kidney? Thus, the first premise of the study is that incipient kidney diseases with no clinical manifestation develop in subjects who never suffered from the illness exposed to therapeutic amounts of acetaminophen in combination with low to moderate amounts of alcohol. Although

previous researchers attempted to establish a relationship linking the therapeutic amount of acetaminophen and light-to-moderate alcohol to incipient kidney abnormalities, the findings were based on the definition of kidney function using a raced-based eGFR. A recent call by a national task force of experts has recommended a re-evaluation of kidney function assessment using a non-race-based prediction equation which is the bases of the current study. Confirming the previous findings using recommended non-race-based eGFR will have potential positive social change implications. It should spur health care and public health professionals to educate patients about the risk of kidney disease. When statistically significant associations are observed, this study can unearth many methodological challenges that need to be overcome to design a large-scale definitive study on this issue. That the analyses were performed with eGFR prediction equations with and without race also contributed to the broader debate on race and the assessment of kidney function.

In this section, I outlined the premise upon which this investigation was based with a clear research problem, purpose, RQs and hypotheses, theoretical framework, significance, assumptions, limitations, and delimitation. I have also reviewed the literature to provide a historical foundation and rationale. In the next section, I described the methodological framework of the proposed study with a clear study design, study population, sampling method, definitions (types and measurement levels) of the key variables and analytical plan.

Section 2: Research Design and Data Collection

Introduction

In this quantitative secondary data analysis, I investigated the impact of dropping race from the CKD-EPI creatinine-based eGFR prediction equation to assess the relationship of therapeutic doses of acetaminophen and light-to-moderate alcohol to incipient renal insufficiency. This investigation required first confirming the existence of the hypothesized relationship using the CKD-EPI creatinine-based eGFR prediction equation with race and then without race. Then, I examined the next control of factors such as diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, and explored any potential disparities based on sociodemographic characteristics. In this section, I discuss the research design and rationale and the study's methodology, including sample size, data analysis, threats to validity, and ethical considerations.

Research Design and Rationale

For this quantitative study, I performed a data-driven testing of hypotheses using secondary data. Data from the 2003–2004 NHANES were analyzed using SPSS Version 27 following ethics approval from the Walden University Institutional Review Board. NHANES 2003-2004 is the latest available data and includes all required variables, especially analgesic pain relievers (including acetaminophen-containing pills), for the analysis.

Often, data collected by another researcher can be an excellent means of exploring other aspects of a specific topic, but with a different intent or purpose (Payne &

Payne, 2004). When using secondary data analysis as a research design, the researcher re-processes the data, and then use their findings as evidence to justify reasoning different from what the original data were intended for (Payne & Payne, 2004). Secondary data are more cost-efficient to analyze, and their use can shorten the study process because data are already collected (Payne & Payne, 2004). One consideration in using secondary data is to ensure that the sample is large enough and representative of the expected study population.

Methodology

This section includes a description of the study population, sample size, and procedures used to collect the data based on the data set and materials provided by the secondary source. Furthermore, the instruments, operationalization for each variable, and the data analysis plan are discussed.

Population

The population was the U.S. noninstitutionalized general population of adults aged 18 and above who took part in the 2003-2004 NHANES surveys. The analytical samples included only those who did not consume an excess of light-to-moderate alcohol within the past 12 months following the survey, and who were aged 18 to 84 years, with no frank kidney disease or ingestion of acetaminophen above therapeutic doses.

Sampling and Sampling Procedures

NHANES is a series of cross-sectional, representative surveys of the national U.S. non-institutionalized population. It is a complex sample survey, involving the use of a multistage probability design with primary sampling units being U.S. counties. Study

samples for the survey are individuals selected from clusters of households from these counties. In addition, the survey combines interviews with physical and laboratory examinations. (NHANES, 2004)Thus, any analysis of such data must be design-based, considering the complex multi-stage probability design structure, and use proper differential selection probabilities (survey weight) and geographic clustering/stratification, which allows for generating unbiased parameter and variance estimations (NHANES, 2004).

Inclusion Criteria

I limited the analyses to those aged 18 and above and adults under 85. Only those with complete information on the key variables involved in exposure (alcohol and acetaminophen) and outcome (eGFR prediction equation) definitions were included in the analyses.

Exclusion Criteria

I excluded NHANES participants who had frank kidney diseases (based on eGFR thresholds defined in methods), those who ingested more than therapeutic doses of acetaminophen, and heavy alcohol consumers from the main analyses. In addition, NHANES does not include ages above 85 years and groups all ages 85 and above as 85. Thus, for analytical purposes, individuals aged 85+ were not included in this analysis as the exact age cannot be delineated when defining eGFR. (NHANES, 2004)

Power Analysis and Sample Size

I performed a secondary data analysis and made use of all available data sets. There were 10,122 participants in NHANES 2003-2004. Although the prevalence of

incipient kidney disease among those who ingest both therapeutic amounts of acetaminophen and light-to-moderate amount of alcohol may be less than 23%, this still gives enough samples to afford the study enough statistical power. To determine the requisite sample size, I used G*Power 3.1.9.2 software (Faul et al., 2007). RQ1 explored the relationship between the ingestion of a therapeutic dose of acetaminophen and alcohol to incipient kidney abnormality in persons who are social drinkers and who consume light-to-moderate amount of alcohol while controlling for predisposing factors.

This relationship's outcome (dependent) variable was incipient kidney disease, a binary categorical variable. The main predictor was the ingestion of therapeutic dose of acetaminophen among light-moderate alcohol consumers, also defined as binary categorical. Investigating a similar relationship as in RQ1, albeit using a different definition for kidney function, Ndetan and colleagues (2018) reported an estimated adjusted odds ratio of 2.05. Using this estimated odds ratio at 80% power and a Type I error rate of 5%, the requisite sample was 504. This sample size was readily available in the data set.

Instrumentation and Operationalization of Constructs

For this study, I analyzed data from the 2003–2004 NHANES. NHANES 2003–2004 data sets are publicly available through the NCHS website (NCHS, n.d.). This latest data version has all the study's aspects as described in this subsection. Specifically, this version of the data set is attractive because of the available data on analgesic pain relievers needed to define the key exposure variable for this study.

The questionnaire, medical examination, and laboratory data files (18 separate files) were imported into the statistical analysis system from NHANES using SPSS. Important variables kept for analytical purposes include serum creatinine, analgesic pain relievers (types, frequency of consumption, quantity, and strength), alcohol consumption (types, quantity, and frequency of consumption), blood sugar measurements, systolic and diastolic blood pressure. Others were BMI, age, gender, race, education level and household income, respondent sequence number, SEQN, full sample 2-year interview weights (WTINT2YR), full sample 2-year MEC exam weights (WTMEC2YR), the masked variance pseudo-primary sampling unit (SDMVPSU) and masked variance pseudo-stratum (SDMVSTRA) that was required to generate accurate and bias-free NPEs. Most of the imported variables were re-categorized and re-coded to address the specific aims of this study.

Operationalization of Variables

In this study, I investigated the impact of eliminating race from the CKD-EPI creatinine-based eGFR prediction equation to assess the relationship of therapeutic doses of acetaminophen and light-to-moderate amounts of alcohol to incipient renal insufficiency, by seeking to answer the following RQs:

RQ1: Using the CKD-EPI creatinine-based eGFR prediction equation with race, is there an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income)?

RQ2: Using the CKD-EPI creatinine-based eGFR prediction equation without race, is there an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income)?

To answer these questions, I operationalized the required variables from the available data.

Dependent Variable. The outcome (dependent) variable for this study was a binary categorical variable denoting whether the study participant has incipient kidney abnormality defined by the glomerular filtration rate (GFR)<90mL/Minute/1.73m^2. GFR was estimated using the 2009 CKD-EPI creatine and cystatin C-based prediction equation (Inker et al., 2012; Levey et al., 2014):

$eGFR_{race} = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if Black] ("The CKD-Epi Equation: An Improved MDRD? - Renal Fellow Network")

where:

eGFR = estimated glomerular filtration rate (in mL/min/1.73 m^2)

SCr = serum creatinine (in mg/dL)

κ = 0.7 (females) or 0.9 (males)

α = -0.329 (females) or -0.411 (males),

min(SCr/κ or 1) = shows the minimum of SCr/κ or 1, (“calculation | Chandoo.org Excel Forums - Become Impressive in Excel”)

max(SCr/κ or 1) = shows the maximum of SCr/κ or 1, (“calculation | Chandoo.org Excel Forums - Become Formidable in Excel”)

Age in years.

As well as the 2021 version that does not include race, given as (Delgado et al., 2022):

CKD-EPI creatinine equation (2021):

$eGFR_{nonrace} = 142 \times min(Scr/\kappa, 1)^{\alpha} \times max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ *[if female]*

(“CKD-EPI Creatinine Equation (2021) | National Kidney Foundation”)

where:

Scr = serum creatinine in mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.241 (female) or -0.302 (male)

"Min(Scr/κ, 1) is the minimum of Scr/κ or 1.0" (“CKD-EPI Creatinine Equation (2021) | National Kidney Foundation”)

"Max(Scr/κ, 1) is the maximum of Scr/κ or 1.0" (“CKD-EPI Creatinine Equation (2021) | National Kidney Foundation”)

Age (years)

This equation is more correct in estimating GFR and prognosis than the 2006 modification of diet in renal disease (MDRD) study equation. In addition, the equation is used in assessing GFR in diverse populations as it also incorporates the physiological

effects of muscle mass as approximated using age, race, and gender (Inker et al., 2012; Levey et al., 2014).

Serum creatinine is captured within the laboratory data. In addition, age, race, and gender are captured within the demographic subset of the questionnaire data.

Independent Variables. A series of independent variables were explored in this study. Some are key potential predictors, while others were explored as covariates. The key independent (predictor) variables for this analysis involved in RQ1 was the exposure to acetaminophen and alcohol.

***Exposure to Therapeutic Acetaminophen*.** I defined a variable that considers the therapeutic amount of acetaminophen, "Yes" if taken up to 1.2g regularly, and "No" otherwise. To do this, I used survey questions within NHANES 2003-2004 that queried respondents whether they had drugs/over counter medication taken regularly (Yes/No). The product taken (within a list that included all acetaminophen products), currently taking product every day (Yes/No), the number of years taking product every day, the number of pills/doses taken/day, and the strength of the product.

Exposure to Social Drinking (Light-to-Moderate Amounts of Alcohol)*.** In NHANES 2003-2004, a drink was defined as a 12oz. beer, a 4oz. glass of water, or an ounce of liquor. I used the questions that asked respondents how often they drank alcohol over the past 12 months, the average number of alcoholic drinks they consumed per day in the past 12 months. I then adopted the 'dietary guidelines for Americans' that suggest drinking in moderation as having up to one drink per day for women and up to two ***drinks per day for men to define the variable on exposure to social drinking or light-to-moderate alcohol consumption.

Covariates and Additional Potential Influencers. I analyzed covariates in addition to the two key independent variables. The main covariates considered were medical conditions such as hypertension, obesity, and diabetes. Each of these variables was coded as binary categorical, denoting their presence or absence as follows: During the medical examination, three measurements of resting blood pressure were recorded for each participant captured by NHANES. Hypertension was coded as present if the averages of the last two readings of systolic blood pressure were at least 130mmHg or diastolic blood pressure was at least 80mmHg (2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline). Alternatively, if a doctor had ever told the participant they have hypertension, or they reported taking high blood pressure medication or otherwise. BMI was captured by NHANES (computed from respondents' weight and height). Obesity was defined by BMI > 30 kg/m^2. Finally, diabetes was defined from captured plasma glucose levels >126 mg/dL.

Other variables potentially influencing the outcome of RQ3 were explored, including sociodemographic such as gender, race/ethnicity, age, level of education and household income. In NHANES 2003-2004, information is available on gender coded as male/female and on race/ethnicity that were re-categorized to include: Hispanics, White (non-Hispanics), Black (non-Hispanic), and others. Age was captured as a continuous variable which includes ages from birth. This variable was re-categorized into five age groups: Age$\leq$ 20 yrs., 21$\leq$ Age $\leq$ 30, 31$\leq$ Age $\leq$ 45, 46 $\leq$ Age $\leq$ 65, and $>$ 65 yrs. Level of education for adults 20yrs+ was defined by a variable that group study participants

based on captured educational information in the following categories: “Less than 9th grade”, “9-11th grade”, “12th grade with no diploma”, “high school grad/ GED or equivalent”, “some college or AA degree”, “college graduate or above” in another category. Finally, annual household income was re-coded into ≤$25,000, $25,000-75,000 and >$75,000.

Data Analysis Plan

Data manipulation (access, exploring, re-coding) and analyses were performed using the SPSS software. The complete multistage probability design structure with right differential selection probabilities (MEC weight) and geographic clustering/stratification (survey cluster/strata) was applied to generate unbiased NPE of the United States and weighted percentages (%) for each variable, other parameters, and variance estimations. Reported descriptive statistics for this study include frequencies (counts [*n*]) for each category of the respective variables, generated NPE, weighted percentages (%), and standard errors (SE) because all the variables are categorical.

RQ1*:* Using the CKD-EPI creatinine-based eGFR prediction equation with race, is there an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amounts of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income)?

RQ2*:* Using the CKD-EPI creatinine-based eGFR prediction equation without race, is there an association between ingestion of therapeutic doses of acetaminophen

along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic characteristics (such as education and household income)?

All the required variables to answer the RQs were categorical and analyzed using multivariable logistic regression models (Go et al., 2001; Matsushita et al., 2010), also applying the complex survey design structure, generating adjusted odds ratio (AOR) and 95% confidence intervals (CI). Statistical significance was assessed at the 5% level of significance, the reason for generating 95% CI. Further, subgroup analyses for the analyses were performed based on various levels of gender, race, age, education, and income and reported to assess potential disparities in the findings.

Threats to Validity

Threats of validity within quantitative research are based on the determination that one can draw meaningful and helpful inferences based on scores from the instruments used during analysis (Creswell & Creswell, 2018). When assessing the research, there were three forms of validity I considered content validity (do the items measure the correct content that is intended?), predictive validity (are scores predictive of a specific measure? Is there a correlation amongst the results?), and construct validity (are the items measuring hypothetical constructs or concepts? (Creswell & Creswell, 2018). Knowing the instrument's validity helped decide whether the chosen instrument was good for this research. However, multiple threats to validity can cause concern in figuring out whether the chosen variables will affect the outcome and not another factor

(Creswell & Creswell, 2018). With, external, internal, and statistical conclusions, validity was assessed to ensure threats are minimized—the main threats to account for include internal and external threats.

Internal Validity Threats

In the case of internal validity threats, the procedures occur during research and thus affect the correct inferences from the data, which should be accounted for in the research. The analysis from this study was conducted on the chosen population from NHANES information, recommended to be of high quality. Nevertheless, various limitations were attached. Like any data set, NHANES information incorporates sampling and non-sampling errors. For example, measurement errors. The questionnaire information reflects self-reports and non-sampling errors, for example, recall bias and misinterpretation of the interview questions. MEC information has variations in most measurements and a possibility of the examiner's effect. (Creswell & Creswell, 2018)

External Validity Threats

According to Creswell and Creswell (2018), external validity threats occur when incorrect inferences are drawn based on the sample data. NCHS has carefully considered external threats such as sample bias and the Hawthorne effect for the NHANES. I avoided over-generalization of the findings beyond what was measured.

Threats to Construct Validity

How variables are measured and defined can threaten construct validity (Trochim, n.d.). Ingrasciotta and Sultana et al. (2014) highlighted several deficiencies in studies investigating analgesic use and chronic renal failure in critical reviews in the literature.

These deficiencies included an objective definition of exposure and outcome status. In this study, using the NHANES codebook, all variables associated with the definition of exposures and outcomes were found and used to operationalize the key variables involved in the RQs described in the methodology. Objective definitions from previous studies have been carefully reviewed and considered to help minimize potential errors associated with the definition of constructs.

Ethical Procedures

Ethical concerns in research are of paramount importance because they impact the research project's integrity and can affect whether the project receives credibility, social and clinical value scientific validity, fair subject selection, and receive independent review and funding. In addition, how research is conducted may also shape a community's views, positively or negatively, toward the researcher, the research project, and the topic.

Most given data set(s) is restricted for public use and requires access by the administrative data owner. Public use is also restricted until approval is granted. Permission is granted for research purposes only with applied specific terms specifying that the data set is available under the terms of a restricted license from NHANES.

The data owner already had identifiers removed before granting access to this study. In addition, any variable that is a potential identifier was removed. The data access was limited to the researcher only. Specific terms were provided on how long access was granted for this study and what is needed to ensure that all data is removed from the designated device used during analysis. Before accessing and analyzing NHANES2003-

2004 data for this study, I sought and received approval (no. 08-18-22-0154411) from the Walden University Institutional Review Board.

Summary

In this quantitative study with data-driven hypotheses, secondary data analysis was used to investigate the impact of eliminating race from the CKD-EPI creatinine-based eGFR prediction equation to assess the relationship of therapeutic doses of acetaminophen and light-to-moderate amount of alcohol to incipient renal insufficiency. The investigation required to first confirm the existence of the hypothesized relationship using the CKD-EPI creatinine-based eGFR prediction equation with race, then without race and subsequent control of factors such as diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as exploring any potential disparities based on sociodemographic characteristics.

The study utilized data from the 2003–2004 NHANE, the latest available data that included all required variables, especially analgesic pain relievers. The complete multistage probability design structure with appropriate differential selection probabilities and geographic clustering/stratification was applied to generate the United States' unbiased NPE. Binary and multivariable logistic regression models were applied to crude and adjusted odds ratios and their corresponding 95% confidence intervals to explore the hypothesized effects. The next section is the presentation of the results from the analyses.

Section 3: Presentation of the Results and Findings

Introduction

The purpose of this quantitative secondary data analysis was to investigate the impact of removing race from the CKD-EPI creatinine-based eGFR prediction equation to assess the relationship of therapeutic doses of acetaminophen and light-to-moderate amount of alcohol to incipient renal insufficiency. This investigation required first confirming the existence of the hypothesized relationship using the CKD-EPI creatinine-based eGFR prediction equation with race and without race. Later, I controlled for factors such as diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as explored any potential disparities based on sociodemographic characteristics. In this section, I present the results of the analysis of data from NHANES 2003-2004, which is the latest version of the NHAHES data set, and which contained all the variables involved in this study. I first present descriptive statistics of the analytical sample followed by results of the analysis, which answered the specific RQs of this study. The presentation of results is preceded by discussion of the underlying assumptions of the multivariable logistic regression model, which was the model used for analysis in answering the RQs.

Accessing the Data Set for Secondary Analysis

Statistical Analysis and Assumptions

This study was a secondary data analysis of the 2003-2004 NHANES data. These data were collected at one point in time from a representative sample of the U.S. noninstitutionalized population using multistage probability design sampling. As

previously alluded to in Section 2's discussion of data analysis, the complete multistage probability design structure with the right differential selection probabilities (MEC weight) and geographic clustering/stratification (survey cluster and strata) was applied to generate unbiased NPEs of the U.S. noninstitutionalized population and weighted percentages for each variable, other parameters, and variance estimations (NHANES, 2004). Reported descriptive statistics for this study include frequencies for each category of the respective variables, generated NPE, weighted percentages, and standard errors because all the variables are categorical.

To answer RQ1 and RQ2, I used multiple or multivariable (binomial) logistic regression models. This model is used when there is one nominal response, outcome, or dependent variable and multiple (two or more) measurement, explanatory, predictor, or independent variables and when there is the desire to know how the measurement/explanatory/predictor/independent variables affect the nominal outcome/dependent variable. (Go et al., 2001; McDonald, 2009; Matsushita et al., 2010).

Use of this model can help predict probabilities of the nominal outcome or dependent variable as well as help tell which of the multiple independent variables have a major effect on the dependent variable (Go et al., 2001; McDonald, 2009; Matsushita et al., 2010).

All the underlying variables for this study were coded to meet the underlying requirements for multivariable logistic regression model. Typical properties of the model include, first, that the dependent variable obeys Bernoulli distribution (i.e., has two outcomes [binary categorical]). The outcome or dependent variable for this analysis was

incipient renal insufficiency, as defined and operationalized in Section 2, in terms of eGFR as nominal binary categorical with the outcome of 1 if eGFR <90mL/Minute/1.73m^2 or 0 otherwise. The other important properties of the model are that the estimation/prediction was based on maximum likelihood and did not evaluate the coefficient of determination (or R^2) as observed or is typical in linear regression. Instead, the model's fitness was assessed through a concordance (see McDonald, 2009). Apart from requiring the outcome or dependent variable to be binary categorical (following Bernoulli distribution), the observations in the data set need to be independent of each other (see McDonald, 2009), which was the case in this data set. There were no repeated measures as the NHASES data were captured at a single point in time based on the cross-sectional design and were therefore a snapshot.

The third important assumption for the model is that there is no severe multicollinearity among the explanatory variables. Multicollinearity occurs when two or more explanatory, independent or predictor variables are highly correlated to each other, such that they do not provide unique or independent information in the regression model. If the degree of correlation is high enough between variables, it can cause problems when fitting and interpreting the model. The most common way to detect multicollinearity is by using the variance inflation factor (VIF), which measures the correlation and strength of correlation between the explanatory/independent/predictor variables in the model. High VIF of above 10 is typical of multicollinearity between variables (McDonald, 2009). In this study, there was one independent, predictor or response variable (consumption of therapeutic amount of acetaminophen/light-to-moderate amount of alcohol); three

fundamental controlling factors (diabetes, hypertension, and obesity); and additional sociodemographic variables, which provided basis for stratification to assess disparities in the assessed outcomes. All these variables/factors were coded as categorical. The VIF were less than 8 supporting the conclusion that there was no violation of the multicollinearity assumption.

Also, the model assumes that there are no extreme outliers or influential observations in the data set, which was the case with these variables that were all coded as categorical variables. In general, the logistic regression model assumes that there exists a linear relationship between each explanatory variable and the logit of the response variable. Finally, the model assumes that the sample size of the data set is large enough to draw valid conclusions from the fitted logistic regression model. A rule of thumb is to have a minimum of 10 cases with the least frequent outcome for each explanatory variable (McDonald, 2009). There were 4 explanatory/controlling variables with the least frequent outcome being diabetes (6.18%) requiring at least 10*4/0.0618 = 647. With further stratification by 5 sociodemographic (gender, race, age, education, and income), bring this this to about 3,237. However, a total of 9,643 cases were included in this analysis, satisfying this requirement.

Sample Description

The general distribution of the analytical sample based on sociodemographic, predisposing factors, and exposure to a therapeutic dose of acetaminophen and light-to-moderate alcohol, as captured by NHANES 2003-2004, is depicted in Table 1. There were 9,643 participants in the study, making an NPE of 286,222,757. About half of the

study participants were between 31 and 64 years old. About 69% of the participants were White, followed by 13% Hispanic, 12% Black, and 6% Others. Female participants constituted 51% as compared to 49% males. About 58% of the participants had a high school or college education, whereas 23% were college graduates, and 18% had education less than high school. About half of the participants had an annual income between $25,000 and $74,000 (49%), 32% had an income of $75,000 or above, and 18% had an income of less than $25 per year.

Regarding BMI, 35% of participants were normal weight, followed by 28% overweight, 25% obese, and 12% underweight. For chronic conditions self-reporting, 33% had hypertension, 25% had obesity, 29% reported prediabetes, and 6% reported having diabetes. Of these 9,643, 7.8% (*n=583*) reported exposure to therapeutic dose of acetaminophen with light-to-moderate amounts of alcohol. Table 1 shows unbiased NPEs of the United States' noninstitutionalized population, corresponding weighted percentages, and standard errors for several variables.

Table 1

Sample Characteristics

Variable	*N*	National population estimate	% (*SE*)
Age (years)			
≤ 20	4,999	85,047,723	29.72 (0.58)
21-30	775	34,540,531	12.07 (0.77)
31-65	2,497	131,448,887	45.93 (0.78)
> 65	1,372	35,185,616	12.29 (0.54)
Race			
Hispanic	2,761	37,859,928	13.23 (2.48)
White	3,896	197,299,116	68.93 (3.58)
Black	2,552	35,009,218	12.23 (1.94)
Other	434	16,054,495	5.61 (0.68)
Gender			
Male	4,731	139,762,652	48.83 (0.58)
Female	4,912	146,460,105	51.17 (0.58)
Education			
Less than high school	1,402	37,878,335	18.47(1.12)
High school to college	2,470	119,704,936	58.36(1.78)
College graduate	861	47,543,211	23.18(1.52)
Income			
< $25K	2,497	49,529,365	18.41(1.41)
$25K—< $75K	4,436	130,743,492	48.60(2.40)
≥ $75K	2,084	88,736,942	32.99(2.29)
Body mass index			
Underweight	1,473	31,862,657	11.63(0.48)
Normal	3,213	95,713,884	34.94 (0.89)
Overweight	2,112	76,583,394	27.96 (0.89)
Obese	1,889	69,809,562	25.48 (0.98)
Hypertension			
No	7,132	190,619,455	66.60 (1.10)
Yes	2,511	95,603,302	33.40 (1.10)
Obesity			
No	6,798	204,159,934	74.52 (0.98)
Yes	1,889	69,809,562	25.48 (0.98)
Blood sugar level			
Normal blood sugar	2,131	68,722,131	64.69 (2.68)
Prediabetes	778	30,949,991	29.13 (2.58)
Diabetes	225	6,569,025	6.18 (0.64)
Exposure to a therapeutic dose of acetaminophen and light/moderate alcohol			
No	8,967	260,776,045	92.18 (0.50)
Yes	583	22,124,411	7.82(0.50)

Note. Data are from the National Health and Nutrition Examination Survey, 2003-2004 (National Center for Health Statistics, n.d.) The complete multistage probability design structure with the right differential selection probabilities (MEC weight) and geographic

clustering/stratification (survey cluster and strata) was applied to generate the data shown in the table.

In terms of NPE and weighted percentage, the prevalence of early-stage renal insufficiency (defined by eGFR <90.0 mL/minute/1.73 m^2) among those who ingested therapeutic doses of acetaminophen and light-moderate amounts of alcohol across various sociodemographic characteristics is also shown in Table 2. The results are presented based on eGFR prediction equations with and without race. Using the race-based prediction equation for eGFR, a projection of over 13.7 million U.S. noninstitutionalized individuals reported early-stage renal insufficiency (defined by eGFR <90.0 mL/minute/1.73 m^2) among those who ingested a therapeutic dose of acetaminophen and light-moderate amount of alcohol as opposed to 12.5 million when using the non-race-based prediction equation for GFR. In addition, very minor differences were seen across various sociodemographic. Table 2 includes unbiased NPEs of the U.S. noninstitutionalized population and the corresponding weighted percentages for each variable, based on eGFR prediction equations with and without race.

Table 2

Prevalence of Early-Stage Renal Insufficiency Among Those Who Ingested Therapeutic Dose of Acetaminophen and Light–Moderate Amount of Alcohol

Variable	National population estimate (NPE; %)	
	eGFR with Race	eGFR without Race
Age (years)		
≤ 20	39,814 (0.29)	-
21-30	108,367 (0.79)	108,367 (0.87)
31-65	5,842,430 (42.59)	5,353,276 (42.91)
> 65	7,726,453 (56.32)	7,012,907 (56.22)
Race		
White	11,631,043 (84.80)	10,623,756 (85.16)
Black	76,863 (5.60)	889,029 (7.14)
Hispanic	473,309 (3.45)	292,381 (2.34)
Other	843,949 (5.15)	669,384 (5.36)
Gender		

Female	7,423,136 (54.12)	6,770,527 (54.27)
Male	6,293,927 (45.88)	5,704,023 (45.73)
Education		
Less than high school.	2,418,615 (17.71)	2,238,044 (17.97)
High school to some college	7,550,729 (55.30)	7,179,875 (57.66)
College graduate	3,684,411 (26.99)	3,033,137 (24.36)
Household income (yearly)		
< $25K	2,358,258 (18.43)	2,203,811 (18.95)
$25K—< $75K	7,294,949 (57.02)	6,726,774 (57.84)
≥ $75K	3,140,275 (24.55)	2,699,922 (23.21)

Note. Data are from the National Health and Nutrition Examination Survey, 2003-2004 (National Center for Health Statistics, n.d.). The complete multistage probability design structure with the right differential selection probabilities (MEC weight) and geographic clustering/stratification (survey cluster and strata) was applied to generate data for the table. eGFR = estimated glomerular filtration rate.

[a] NPE = 13,717,064. [b] NPE = 12,474,550

Results

CKD-EPI Creatinine-Based eGFR Prediction Equation Results with Race

RQ1 was, Using the CKD-EPI creatinine-based eGFR prediction equation with race, is there an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income)? The corresponding null and alternative hypotheses were.

$H_0$1: Using the CKD-EPI creatinine-based eGFR prediction equation with race, there is no association between ingestion of therapeutic doses of acetaminophen

along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income).

H_a1: Using the CKD-EPI creatinine-based eGFR prediction equation with race, there is an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income).

Overall, when using the CKD-EPI creatinine-based eGFR prediction equation with race, results show that participants who consumed therapeutic doses of acetaminophen along with light-to-moderate alcohol are significantly associated with renal insufficiency (*Crude OR =3.22, 95%CI [2.45, 4.24]*), with a similar outcome after controlling for diabetes, hypertension, and obesity which have the potential of predisposing the kidney to acetaminophen toxicity (*Adjusted OR*= 2.65, *95%CI* [1.72, 4.09]), Table 3.

There was not a marked difference in this relationship between the various gender groups. For example, while females showed 146% increased odds (*Adjust OR=2.46, 95%CI [1.43, 4.23]*), male showed 191% increased odds (*Adjusted OR= 2.91, 95%CI [1.48, 5.73]*) of having incipient renal insufficient among those who ingested therapeutic doses of acetaminophen and light-to-moderate alcohol compared to those who did not.

Age to be problematic. Participants with age less than 30 showed 1172% increased odds (*Adjusted OR=12.72, 95%CI [1.14, 141.49]*) compared to only 115% increased odds for those 30 and above (*Adjusted OR=2.15, 95%CI [1.35, 3.43]*) of incipient renal insufficiency.

While those with lower than high school education showed only 79%increased odds, those with high school and college education showed between 183% to 197% increased odds. The results are not statistically significant for those with household income lower than 25,000 per year (*Adjusted OR = 1.76, 95%CI [0.70, 4.41]*) but higher in magnitude and statistically significant for those with income above 25 – 75K (*Adjusted OR = 2.62, 95%CI [1.51, 4.54]*) and above 75K (*Adjusted OR= 3.43, 95%CI [1.56, 7.56]*) (Table 3)

Based on the established relationships shown, I rejected the null hypothesis in general and in all cases of stratified analysis except among low-income groups (< $25K household income).

CKD-EPI Creatinine-Based eGFR Prediction Equation Results Without Race

RQ2 was, Using the CKD-EPI creatinine-based eGFR prediction equation without race, is there an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income)? The corresponding null and alternative hypotheses were.

$H_0$2: Using the CKD-EPI creatinine-based eGFR prediction equation without race, there is no association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income).

H_a2: Using the CKD-EPI creatinine-based eGFR prediction equation without race, there is an association between ingestion of therapeutic doses of acetaminophen along with light-to-moderate amount of alcohol and incipient renal insufficiency after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income).

When using the CKD-EPI creatinine-based eGFR prediction equation without race, results showed that participants who ingested therapeutic doses of acetaminophen along with light-to-moderate alcohol are significantly associated with renal insufficiency (*Crude OR=3.15, 95%CI [2.51, 3.96]*), with a similar outcome after controlling for factors such as diabetes, hypertension, and obesity which have the potential of predisposing the kidney to acetaminophen toxicity (*Adjusted OR= 2.43, 95%CI [1.88, 3.14]*), Table 3.

While females showed only 98% increased odds (*Adjust OR=1.98, 95%CI [1.23, 3.16]*), male showed 199% increased odds (*Adjusted OR= 2.99, 95%CI [1.77, 5.08]*) of

having incipient renal insufficient among those who ingested therapeutic doses of acetaminophen and light-to-moderate alcohol compared to those who did not.

Since race is not in the prediction equation, it was of interest to explore disparities in the outcome among racial. There was a statistically significant 113% increased odds among Whites (*Adjusted OR=2.13, 95%CI [1.48, 3.08]*), non-statistically significant 47% increased odds among Black people (*Adjusted OR=1.47, 95%CI [0.44, 4.83]*) and non-statistically significant 76% increased odds among Hispanics (*Adjusted OR=1.76, 95%CI [0.32, 9.60]*).

Participants with age less than 30 years showed 104% increased odds (*Adjusted OR=2.04, 95%CI [1.55, 2.68]*) compared to non-statistically significant 747% increased odds for those 30 years and above (*Adjusted OR=8.47, 95%CI [0.95, 75.83]*) of incipient renal insufficiency.

While those with lower than high school education showed only 83% increased odds (*Adjusted OR=1.83, 95%CI [1.00, 3.36]*), those with high school and college education showed 215 % increased odds (*Adjusted OR= 3.15, 95%CI [1.97, 5.05]*). College graduates showed a non-statistically significant 84% increased odds (*Adjusted OR= 1.84, 95%CI [0.78, 4.37]*).

Statistically significant increased odds are also shown for all income brackets: lower than 25,000 per year (*Adjusted OR = 2.48, 95%CI [1.13, 5.37]*), above 25 – 75K (*Adjusted OR = 2.28, 95%CI [1.47, 3.52]*) and above 75K (*Adjusted OR= 2.70, 95%CI [1.58, 4.62]*) (Table 3)

Based on the established relationships shown, I rejected the null hypothesis in general and in all cases of stratified analysis except among the Black people, Hispanics, those age 30 years and above, and with college degree. Table 3 shows the impact of race on the relationship of incipient renal insufficiency (eGFR < 90.0 mL/minute/1.73 m2) to therapeutic dose of acetaminophen and/or light-moderate amount of alcohol stratified by sociodemographic characteristics.

Table 3

Impact of Race on the Relationship of Incipient Renal Insufficiency to Therapeutic Dose of Acetaminophen and/or Light–Moderate Amount of Alcohol

Variable	eGFR with race		eGFR without race	
	Crude *OR*	Adjusted *OR*	Crude *OR*	Adjusted *OR*
Overall	3.22	2.65	3.15	2.43
	[2.45, 4.24]	[1.72, 4.09]	[2.51, 3.96]	[1.88, 3.14]
Gender				
Female	3.44	2.46	3.22	1.98
	[2.49, 4.76]	[1.43, 4.23]	[2.01, 5.15]	[1.23, 3.16]
Male	3.01	2.91	3.09	2.99
	[1.78, 5.10]	[1.48, 5.73]	[2.11, 4.53]	[1.77, 5.08]
Race				
White	2.65	2.04	3.00	2.13
	[2.00, 3.52]	[1.28, 3.24]	[2.35, 3.85]	[1.48, 3.08]
Black	3.31	2.51	2.30	1.47
	[1.87, 5.86]	[0.99, 6.41]	[1.05, 5.01]	[0.44, 4.83]
Hispanic	4.19	1.76	2.55	1.76
	[1.96, 9.02]	[0.37, 8.23]	[1.30, 5.00]	[0.32, 9.60]
Other	11.33	59.57	6.76	17.73
	[2.37, 54.32]	[1.50, >999]	[2.09, 21.86]	[0.97,324.65]
Age (years)				
< 30	4.50	12.72	4.81	2.04
	[0.78, 26.11]	[1.14, 141.49]	[0.83, 27.92]	[1.55, 2.68]
≥ 30	2.45	2.15	2.46	8.47
	[1.82, 3.28]	[1.35, 3.43]	[1.92, 3.15]	[0.95, 75.83]
Education				
Less than high school	4.33	1.79	3.95	1.83
	[3.09, 6.08]	[1.01, 3.16]	[2.56, 6.12]	[1.00, 3.36]
High school and some college	3.03	2.83	3.38	3.15
	[2.00, 4.57]	[1.60, 4.99]	[2.23, 5.11]	[1.97, 5.05]
College graduate	3.10	2.97	2.47	1.84
	[1.85, 5.20]	[1.17, 7.51]	[1.62, 3.77]	[0.78, 4.37]
Household income				
< $25K	3.18	1.76	3.17	2.48
	[2.00, 5.05]	[0.70, 4.41]	[1.93, 5.21]	[1.13, 5.37]
$25K—< $75K	3.49	2.62	3.32	2.28
	[(2.21, 5.52]	[1.51, 4.54]	[2.22, 4.96)	[1.47, 3.52]
≥ $75K	2.71	3.43	2.70	2.70
	[1.45, 5.06]	[1.56, 7.56]	[1.55, 4.68]	[1.58, 4.62]

Note. Data are from the National Health and Nutrition Examination Survey, 2003-2004 (National Center for Health Statistics, n.d.). Values in the table are adjusted for hypertension, obesity, and diabetes.

Summary

In this quantitative study, I used secondary data from 2003–2004 NHANES, the latest available data that included all my required variables, especially analgesic pain relievers. Since this study is a multistage probability design structure with appropriate differential selection probabilities and geographic clustering/stratification, I had to generate unbiased NPE of the United States population for the multivariable logistic regression model that allowed me to generate crude and adjusted odds ratios and their corresponding 95% confidence intervals to explore the impact of eliminating race from the CKD-EPI creatinine-based eGFR prediction equation to assess the relationship of therapeutic doses of acetaminophen and light-to-moderate amount of alcohol to incipient renal insufficiency, where I had to first confirm the existence of my hypothesized relationship using the CKD-EPI creatinine-based eGFR prediction equation with race, then without race, and then subsequently the control of factors such as diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, and then further explored any potential disparities based on sociodemographic characteristics. The observed results are comparable in magnitude, directionality and statistical significance when using CKD-EPI creatinine-based eGFR prediction equation with race (*Adjusted OR= 2.65, 95%CI [1.72, 4.09]*) as without race (*Adjusted OR= 2.43, 95%CI [1.88, 3.14]),* when assessing the hypothesized relationship of therapeutic dose of acetaminophen and light-moderate alcohol to incipient renal insufficiency.

Section 4: Application to Professional Practice and Implications for Social Change

Introduction

In conducting this quantitative secondary data analysis, I sought to investigate the impact of dropping race from the CKD-EPI creatinine-based eGFR prediction equation to assess the relationship of therapeutic doses of acetaminophen and light-to-moderate alcohol to incipient renal insufficiency. This investigation required first that I confirm the existence of the hypothesized relationship using the CKD-EPI creatinine-based eGFR prediction equation with race and without race. I later controlled factors such as diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, as well as sociodemographic (such as education and household income) by stratification(National Kidney Foundation, 2021)

Interpretation of the Findings

Previously, laboratories included race as one of the factors in calculating eGFR (National Kidney Foundation, 2021). The inclusion of race has been a topic of debate for years. Research shows that, on average, Black people have higher creatinine levels in the body than other members of other racial groups (Hsu et al., 2021; Inker et al., 2021). As a result, the National Kidney Foundation reassessed the use of race in eGFR calculations. Last year, the organization recommended adopting the new eGFR CKD-EPI creatinine equation. (National Kidney Foundation, 2021)

In this study, I assessed the relationship between the consumption of a therapeutic dose of acetaminophen with light-moderate amount alcohol and incipient renal insufficiency using both CKD-EPI creatinine-based eGFR with and without race.

Research shows that the usage of widely available acetaminophen with light-moderate use of alcohol has toxic effects on the kidneys (Ndetan et al., 2018, 2020). My goal was to explore whether in inclusion or exclusion of race in the definition of kidney function influenced the relationship under investigation. The results reported in Section 3 show that, when using the CKD-EPI creatinine-based eGFR prediction equation with race, there was 222% increased odds (Crude *OR* = 3.22) as compared to 215% increased odds when using the prediction equation without race (Crude *OR* = 3.15). After adjusting for diabetes, hypertension, and obesity, the corresponding models showed 165% and 143% increased odds, respectively (Adjusted *OR* = 2.65 with race and Adjusted *OR* = 2.43 without race). There is only a very slight difference in magnitude with no difference in directionality and statistical significance in the hypothesized relationship when assessed using the CKD-EPI creatinine-based eGFR prediction equation with or without race both in the crude and adjusted models. The result is like that reported by Ndetan and colleagues in 2020 in their analysis, which used a race based eGFR equation. In general, controlling for those chronic conditions, which tend to predispose the kidney to acetaminophen toxicity, reduced the magnitude of the hypothesized effect, both in the model that included race in the definition of kidney function as well as the one that did not include race.

The National Kidney Foundation (2021) recommended using the CKD-EPI creatinine-based eGFR prediction equation without race in every United States laboratory to avoid racial discrimination. This recommendation affects the public health burden of kidney disease and patient care in the United States. This study did not show differences

in results with and without the race equation in both the crude and adjusted models. Even stratification by sociodemographic did not show a profound impact by gender and income. However, when the CKD-EPI creatinine-based eGFR prediction equation did not include race, the outcome was further stratified by race and showed a slight disparity with increased magnitudes with statistical significance amongst Whites compared to Black people and Hispanics. There was a statistically significant increased odds (by 113%) among Whites but non-statistically significant increased odds among Black people (by 47%) and among Hispanics (by 76%). There were some age disparities, but these could not be delineated based on whether the prediction equations included race or not. In general, those in the middle-aged group as well as high school to graduate education seemed to show higher magnitude of the effect measures. In their 2020 study, Ndetan and colleagues also noted that early-stage renal dysfunction, as determined by self-report (being told by a doctor) and serum creatinine, may occur among those who concomitantly ingested therapeutic doses of acetaminophen and light-moderate alcohol, with risk more profound among women, Blacks and Hispanics, individuals below legal drinking age of 21, and individuals with household income below $25K. Although my study supported these findings as well, it used a different definition for the outcome, or dependent, variable. Ndetan's focus for stratification was based on self-report as being told by the doctor as well as measured serum creatinine that is based on eGFR. The results of my study confirm existence of such disparities only when using the race-based eGFR equation among females and age, though with a different age categorization (< 30 years for mine as opposed to < 21 years for theirs) and household income. My analysis with

non-race-based eGFR did not seem to confirm disparities based on race, among individuals aged 30 years and above and with college degrees.

The study results suggest, with and without race, there is a substantial risk of developing insufficiency among people who use acetaminophen along with light-moderate use of alcohol. When looking at other racial groups, I found the highest odds ratio with wide confidence intervals that came with a low sample size of the population but also signifies that people of other races are at risk of renal insufficiency. In addition, the study showed that people with higher incomes, high school education, and some college had higher association rates. As discussed in Section 3, high alcohol intake could be due to social status. This study's main strength is that it compares the eGFR equation, including and excluding race.

The entire premise of my study was based on both TRA and TPB (as the theoretical framework) which describe how one's health behavior is based on their intent, which is in turn informed by one's attitude towards the behavior and subjective norms, such as social and environmental surroundings, and one's perceived control over their behavior (Fishbein & Ajzen, 2009). This study looked at two attitudes: the intake of acetaminophen in therapeutic amount and the intake of alcohol in light-to-moderate amount. The behavior of concern is the potential concomitant consumption of both. Given readily availability of acetaminophen especially over the counter (Consumer Healthcare Products Association, 2020; Food and Drug Administration, 2020) and the high prevalence of prevalence of alcohol especially among social drinkers (National Institutes for Health, 2020), the potential of concomitant consumption is high, especially

among those who do not have the ability to safe medicate (Ndetan et al 2018). The concern here is that this behavior stemming from those attitudes is potentially harmful to the kidney based on the findings (observed statistically significant associations) of this study. I posit that health care providers and public health professionals can help with prevention campaign among their patients and members of the public by educating them about potential adverse health effect of this modifiable risk behavior thereby creating health literacy. Such health literacy has the potential of creating, in return, self-efficacy which may result in future reasoned actions and positively planned behaviors associated with their social norms. (Kennedy et at, 2017). Sociodemographic characteristics tend to play a role in perceived self-efficacy related to health habits and warrant controlling for in investigations that assess the relationship between specific health behavior and health outcome.

Race was a fundamental feature of this study. One's ethnic/racial group membership is integral to one's identity and serves as a relevant source of psychological well-being and a lens through which others perceive them (Rivas-Drake et al., 2014). The kidney function prediction equation remained predominant because many members of the medical community conceived people of African American descent as being muscular, which intends to affect the role of creatinine in kidney filtration (Delgado et al., 2022). The scientific basis of this claim is currently being scrutinized (Delgado et al., 2022). Social norms, broadly defined as the shared ideals and standards that guide or regulate the behaviors of members of a group (Cialdini & Trost, 1998), increasingly affect an individual's intergroup behavior and explicit attitudes (Nesdale, 2004; Rutland, 2004). It

is theorized to work harmoniously with social identity to help individuals formulate strong group identities and understand proper intragroup and intergroup behaviors (Nesdale, 2011).

Although I did not find significant differences in the fundamental relationships under investigation by using race-based eGFR as compared to using a non-race-based eGFR in defining renal function, I glimpsed the impact of race in the hypothesized relationship as reported by Ndetan and colleagues in 2020. Their study reported a profound effect of therapeutic amount of acetaminophen and light-moderate alcohol on early-stage kidney disease among minority racial groups compared to their white counterparts. However, these effects using a definition of kidney function based self-reports and serum creatinine and not eGFR as in the present study.

Age further complicates how social norms such as race affect the fundamental relationship under investigation here. While there seemed to be no convergence in alcohol use across a life course (age) with race as reported by Caetano and Kaskutas (1995), the interplay with acetaminophen and how it affects the kidney seemed to be suggestive in my analysis when defining eGFR different with and without races and should warrants further investigation. Further, the intersection of race and gender in trajectories of alcohol and acetaminophen may shed light on the observed disparities in this relationship. While social norms regarding substance use are changing for women (Goodwin et al., 2009; Keyes et al., 2008a, 2010), drinking remains less acceptable compared to men (Ahern et al., 2008; Keyes et al., 2011). The evidence suggests that Whites are more susceptible to influence from social norms about alcohol, with more

positive attitudes toward drinking than Black people (Keyes et al., 2012). In general, at equal levels of alcohol consumption relative to their White counterparts, Black women are reported to have higher rates of alcohol-related problems. Among those with low levels of heavy drinking, Black men have higher rates of alcohol-related problems (Witbrodt et al., 2014). The result of my study, which is in congruent with that by Ndetan and colleagues (date?) seems to suggest that the effect of acetaminophen and alcohol may be stronger among females than may but reverses when adjusting for predisposing factors.

Finally, although it has been hypothesized that socioeconomic indicators could fully account for racial/ethnic differences in age-related variation (Watt, 2008), the exact extent of how it plays in this relationship still is a dilemma. According to little available evidence, while income is positively associated with alcohol use in general (Keyes & Hasin, 2008), among those in poverty, Black men have higher rates of heavy drinking compared to their White counterparts (Ford et al., 2007; Gilman et al., 2008). In this study, the fundamental relationship under investigation was statistically significant among those in higher income group but with no college degrees which is further complicated to rationalize.

Limitations of the Study

The main limitation of the study is that it was a secondary data analysis, which meant that the data were not specifically collected for this specific research purpose. As such not all the desired variables are captured and even those captured may not be perfect

delineated for this purpose. For example, first, the study uses data captured in the 2003-2004 NHANES which is an exceedingly long time ago and population dynamics then may not be representative of current realities, thus questioning the applicability of the findings of this study. However, that is the only version of publicly available data that contained the all the variables inherent in this analysis. Second, this study used 2009 CKD-EPI prediction equation for eGFR to define renal insufficiency which is the dependent and key variable for the investigation. However, this creatinine-based equation has long been touted as being limited in accuracy as compared to a 2012 version which is based on creatinine and cystatin-C (Inker et al., 2012; Levey et al., 2014; Ndetan et al., 2020. Creatinine alone is heavily affected by muscle mass and thus its influence on GFR (Inker et al., 2012; Levey et al., 2014; Ndetan et al., 2020). On the other hand, Cystatin-C is a no glycosylated protein whose complete catabolism occurs in the proximal renal tubule and is not returned to the blood (Tittarelli et al., 2017). The level of cystatin-C is not affected by muscle mass, age, race, gender, and protein intake (Inker et al., 2012; Levey et al., 2014). Furthermore, the production of cystatin-C is independent of nutrition factors, renal conditions, and increased protein catabolism. Thus, incorporating this factor in the prediction equation of eGFR results in an equation with multiple endogenous filtration markers providing a much accurate/precise definition for renal function compared to the one used with just a single filtration marker (Inker et al., 2012; Levey et al., 2014; Ndetan et al., 2020). However, cystatin-C was not captured in NHANES 2003-2004 used for this analysis. Although it was captured in earlier versions, specifically, in NHANES 1999-2002 and 2001-2002, the data had been recalled for recalibration at the

time of this current analysis and was not publicly available. As such, the observed results may not be as strong due to the use of a less accurate measure for renal function. Third, there is always the frequently parroted issue of recall bias that is inherent in every survey design. NHANES used a multiple of approaches to capture data on of which is questionnaire that was the primary means of capturing data on the key exposure variables for this study, namely, the ingestion of acetaminophen and the consumption of alcohol. Where self-reported which could suffer from recall bias. Fourth, the analytical approach used lots of sub setting based on exposure combinations to define therapeutic dose of acetaminophen and light-moderate alcohol, including the additional predisposing factors and sociodemographic. A good proportion of the sampled population with renal insufficiency did not report some of these variables. This and the corresponding sub setting tend to result in lots of missing data, resulting in small samples and potentially low-powered analyses. As such it was not possible to further assess the roles of small groups based on sociodemographic.

Recommendations

Practice and Behavioral Considerations

An eGFR is an estimation of the approximate percentage of kidney function patients, and there are normal for Black individuals and non-Black individuals. (“Find local offices and events - National Kidney Foundation”) According to prevailing research studies, the eGFR should be higher in Black people than non-Black people due to their body mass and its application in the diagnoses, treatment, and care of patients compared to race and non-race individuals in the community.

I had to generate unbiased NPE of the United States population for the binary and multivariable logistic regression models which allowed me to apply crude and adjusted odds ratios and their corresponding 95% confidence intervals to explore the hypothesized effects of the analysis in my investigation of the impact of eliminating race from the CKD-EPI creatinine-based eGFR prediction equation to assess the relationship of therapeutic doses of acetaminophen and light-to-moderate amount of alcohol to incipient renal insufficiency, where one had to first confirm the existence of hypothesized relationship using the CKD-EPI creatinine-based eGFR prediction equation with race, then without race, and then subsequently the control of factors such as diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity, and then further explored any potential disparities based on sociodemographic characteristics.

The principles for research involving people and how they are put into effect are likely to have several consequences that can be further researched for those in practice, care, and treatment of persons concerning their race and gender (and impact assessment professionals). For this study, it is important for practitioners to realize that the impact of race and the effect on care and treatment cannot be presumed, denied, or overlooked and people of different races will be unlikely to accept the presumption that a researcher or practitioner has a right to apply research values or collect data in care and treatment.

The continued care and treatment of people of all races will depend on the practitioner being genuine on the implications of race in treating the patient and in the practitioner showing meaningful engagement and understanding of those values about

race and non-race eGFR. This will mean that the use of race and non-race in the eGFR would have to be considered or not in their practice and treatment.

The finding in this study of early changes in the kidney due to acetaminophen will begin to alert physicians to this complication and so stimulate them to begin questioning patients about acetaminophen intake any time they come across patients with unexplained slightly abnormal kidney function tests, which would enable them to recommend cessation of acetaminophen ingestion and so prevent the development of frank clinical or severe renal disease such as acute/chronic renal disease or end stage renal disease

Further Research

Given the limitations outlined above inherent in secondary data analyses, future large-scale epidemiological studies to investigate this issue in greater depth are warranted. It is important to continue exploring the relationship using a more accurate definition for kidney function that may incorporate multiple endogenous filtration markers such as the creatinine- and cystatin-C-based eGFR prediction equation including versions that have traditionally included race and versions that exclude race as outcome of the broader debate of the impact of race in kidney function.

Other important considerations for future studies including methodological issues that relate to the definition of exposures to therapeutic acetaminophen and light/moderate alcohol. What is the minimum duration, dose, and frequency of exposure to these factors alone, and concomitantly that may be associated with renal insufficiency? Other questions that may warrant investigation include:

In hospital-based case-control studies of acetaminophen-induced renal toxicity, should subjects with elevated liver enzymes be excluded from the control group, and if so at what levels of the liver enzymes? Is any observed interaction between exposure to therapeutic doses of acetaminophen and ingestion of lesser amounts of alcohol as occurs in social drinking additive or multiplicative? What is the significance of the frequent observation that blood urea nitrogen and serum creatinine are slightly elevated above normal? Physicians tend to ignore these slight elevations when obvious causes have been ruled out. Could they be related to undiagnosed causes such as acetaminophen and/or alcohol ingestion?

Implications for Professional Practices and Social Change

This study spurs on from the question on the consideration of race in the prediction of renal function based on eGFR and explored its application/implication in a previously hypothesized and examined relationship of incipient renal insufficiency to therapeutic amount of acetaminophen and light-moderate alcohol consumption. While the analysis here confirms previous findings on the hypothesized relationship, it did not find a strong impact of including or eliminating race from the eGFR prediction equation applied in the definition of incipient renal insufficiency. Including race in prediction equations for kidney function has generated some controversy, and a call for its elimination was made on grounds that it may influence the diagnosis, treatment, care, and inequality of care to nonwhite and white individuals in the community. I posit that while general disparities exist based on race, this analysis, given its documented limitations, did not find a strong basis for that in the hypothesized relationship under investigation here.

i.e., posit that, the continued care and treatment of people of all races will depend on the practitioner being genuine on the implications of race in treating the patient and in the practitioner showing a meaningful understanding of values, beliefs, and experiences of various racial groups while encouraging further investigation on the race of race in eGFR and other kidney function prediction equations.

Assessing the inclusion of race in estimating GFR as part of a larger conversation in addressing racial disparities in kidney health can help erase the mistaken age-old belief held by the medical community that levels of creatinine, a waste product of muscle metabolism, are higher in Black people. This misinformation can potentially make some Black people's kidneys appear healthier than they were, thus delaying life-saving transplants. In terms of regulations, this study would guide the government and public health professionals on how to restructure their policy after reviewing the relationship of acetaminophen and alcohol to incipient renal insufficiency on the role of race in estimating GFR.

Conclusion

This study of the impact of eliminating race from the CKD-EPI creatinine-based eGFR prediction equation to assess the relationship of therapeutic doses of acetaminophen and light-to-moderate amount of alcohol to incipient renal insufficiency was first to confirm the existence of the hypothesized relationship using the CKD-EPI creatinine-based eGFR prediction equation with race, assess the implication of eliminating race and a subsequent control of other factors such as diabetes, hypertension, and obesity. which predispose the kidney to acetaminophen toxicity, and then explored

any potential disparities based on sociodemographic characteristics. The results showed that there is a statistically significant relationship between consuming therapeutic dose of acetaminophen and light-moderate alcohol to incipient renal insufficiency, even after controlling for diabetes, hypertension, and obesity, which predispose the kidney to acetaminophen toxicity as previously hypothesized and seemed to be the case when renal insufficiency (the outcome of interest) was defined based on a creatinine-based eGFR prediction equation with and without race as a variable.

Thus, while the debate of the impact of race as a potential discriminant in the prediction of kidney function is ongoing, it does not seem to impact the hypothesized relationship of therapeutic dose of acetaminophen and light-moderate alcohol to incipient renal insufficiency. The relationship previously observed is ordered-preserved. However, given potential limitations of secondary data analyses, future large-scale epidemiological studies to investigate this issue in greater depth are warranted. Regardless, public health professionals can continue to design interventions targeting harm reduction in all racial groups.

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