Proinflammatory Food Consumption and Chronic Kidney Disease in a Canadian Nationally Representative Sample

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A Thesis Submitted to the Faculty of Graduate Studies of
The University of Manitoba

in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

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Abstract

AIM: This study compared the consumption of proinflammatory foods, as measured by the Dietary Inflammatory Index (DII) scores, between those with late stage chronic kidney disease (CKD) and individuals without CKD and between men and women with late stage CKD, in a Canadian nationally representative sample. METHOD: The current study used data from the Canadian Health Measures Survey – Cycle 3.

RESULTS: T-tests revealed significant differences in the DII scores between individuals without CKD and those with late stage CKD, as well as between men and women with late stage CKD. A linear regression revealed that DII scores predicted eGFR in the general population. In separate regressions, DII scores predicted BMI and high cholesterol, even after controlling for other factors. CONCLUSION: This study contributes to current research on CKD and may lead to dietary prevention strategies.

Acknowledgements

I would like to sincerely thank my advisors, Dr. Ian Clara and Dr. Peter Eck for their time, insight, and research expertise. I am also grateful to my committee members, Dr. Carla Taylor and Dr. Karen Duncan, for their valuable feedback. I am indebted to my mother for her support, guidance, and understanding. Finally, I would like to thank Statistics Canada for their financial support and for granting me access to the CHMS – Cycle 3 dataset.

Table of Contents

List of Tables

List of Abbreviations

APP	Application
BMI	Body mass index
CHMS	Canadian Health Measures Survey
CKD	Chronic kidney disease
CRP	C-reactive protein
CVD	Cardiovascular disease
DII	Dietary inflammatory index
ESRD	End-stage renal disease
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
IL	Interleukin
RRT	Renal replacement therapies
TNF-α	Tumor necrosis factor-α

Proinflammatory Food Consumption and Chronic Kidney Disease in a Canadian Nationally Representative Sample

An estimated three million Canadians suffer from Chronic Kidney Disease (CKD), yet the majority of people are not aware that they have this condition (Arora et al., 2013). CKD is a progressive disease that typically begins with few or no symptoms and as the condition progresses, vague symptoms such as fatigue, difficulty sleeping, dry skin, and increased urination develop (Harvard Health Publications, 2010). CKD has been associated with a number of complications and an increased risk of mortality (Stevens, Huang, & Levey, 2010). For instance, CKD can lead to abnormal rates of bone replacement, increased cardiovascular disease risk and an altered nutrient metabolism (Legg, 2005; Thomas, Kanso, & Sedor, 2008).

As CKD progresses, the severity of symptoms increases leading to end-stage kidney disease and the requirement for more intense interventions (Levey & Coresh, 2012). Over 35,000 Canadians have end-stage kidney disease and over half of these individuals are receiving dialysis (Canadian Institute for Health Information [CIHI], 2016). The impact of late stage CKD is significant when it comes to an individual's quality of life and the healthcare system (Gemmell et al., 2016; Manns, McKenzie, Au, Gignac, Geller, & CAN-SOLVE CKD Network, 2017). Individuals with CKD tended to report a poorer quality of life and frequently suffered from depression (Legg, 2005; Seidel et al., 2014). The financial burden of CKD in Canada on the healthcare system is estimated to be tens of billions of dollars and over $200 million in disability payments each year (Manns et al., 2017).

In 2009, it was estimated that the prevalence of CKD in Canada was nearly 13%, and this figure has continued to rise, as the rates of CKD risk factors such as obesity and diabetes increase (Arora et al., 2013; CIHI, 2013). Individuals with diabetes or who were obese were

found to be at a significantly higher risk of developing CKD compared to those who did not have diabetes or who were not obese (Shen et al., 2017; Wang et al., 2008).

Another contributor to CKD is inflammation (Kovesdy & Kalantar-Zadeh, 2010). Inflammation involves a series of molecular processes that are part of the overall immune response (Kovesdy & Kalantar-Zadeh, 2010). Normally, there is a transition from the inflammatory process to the healing phase (Das & Roy, 2012). In individuals with CKD, this inflammatory process is maintained, resulting in chronic inflammation and tissue damage (Kovesdy & Kalantar-Zadeh, 2010).

There is evidence that diet can affect the overall inflammatory state in the body (Basu, Devaraj, & Jialal, 2006; Silverstein, 2009). For instance, when healthy participants consumed a portion of potato chips for 28 days, the level of free radical production increased and remained high for a further 28 days, after consumption had ceased, promoting a proinflammatory state in the body (Naruszwicz et al., 2009).

Despite these findings, there is little research that has examined the possible link between diet, inflammation and CKD. For this reason, the current study's main objective was to determine if there was an association between proinflammatory food consumption and late stage CKD. More specifically, the aims were to uncover any differences in the proinflammatory food consumption of individuals with late stage CKD and those without CKD, to reveal any differences in proinflammatory food consumption between males and females with late stage CKD, and to determine whether dietary inflammatory scores predicted the presence of late stage CKD in Canadian adults. Being able to establish a link between proinflammatory food consumption and late stage CKD would add to the current body of knowledge and possibly result in innovative dietary recommendations. Dietary recommendations that are based on reducing

inflammation in the body could ultimately lead to fewer individuals developing CKD, slow the progression of CKD among individuals already diagnosed with the condition, and reduce the financial burden of CKD on the healthcare system.

Literature Review

Chronic Kidney Disease Definition and Categorization

CKD is defined as a decrease in the glomerular filtration rate (GFR) or physical abnormalities in the kidneys that have persisted for more than 3 months (James, Hemmelgarn, & Tonelli, 2010). CKD involves a decrease in the number of functioning nephrons; these nephrons are composed of a glomerulus (the main filtration unit of the kidney) and a renal tubule and are used to remove wastes from the blood (Lewis, 2012; Schnaper, 2014). In the case of CKD, as the number of functioning nephrons decline, the remaining nephrons are forced to compensate resulting in increased pressure within the nephrons (Lewis, 2012). Eventually, this increased pressure damages the nephrons, possibly resulting in proteinuria (protein in the urine), the failure of the remaining nephrons, and death (Glassock, 2010; Koroshi, 2007; Lewis, 2012).

There are two main routes to nephron loss and ultimately, CKD (Taal, 2012). The first involves a loss of nephrons as the result of an acute injury (Taal, 2012); the second is due to increased blood flow through the kidney (referred to as hyperfiltration) (Taal, 2012; Wahba & Mak, 2007). For instance, diabetes mellitus is a common risk factor for CKD because it produces a hyperfiltration state in the kidneys leading to inflammation, increased intraglomerular pressure, and scarring of the kidneys (MacIsaac, Jerums, & Watts, 2012; Shafi & Coresh, 2010).

Another condition that may lead to CKD is metabolic syndrome and it is defined as having at least three of the following symptoms: an excess of abdominal fat, hypertriglyceridemia (elevated triglycerides), low HDL cholesterol, hypertension, and/or high fasting glucose levels (Wahba & Mak, 2007). These same authors have suggested that the insulin resistance caused by metabolic syndrome leads to chronic inflammation in the body. Individuals with CKD tend to have elevated levels of adipokines (proteins secreted by adipose tissue used in

cell signaling) such as interleukin-6 (IL-6) as well as other inflammatory markers such as C-reactive protein (CRP) (Calder et al., 2011; Wahba, & Mak, 2007).

Lastly, obesity has been linked to an increased risk of developing CKD (Wang, Chen, Song, Caballero, & Cheskin, 2008). Obesity is defined as having a body mass index (BMI) above 30 (Wahba & Mak, 2007). BMI is calculated by dividing an individual's weight in kilograms by their height in meters squared and the resulting number is compared to a classification table (World Health Organization [WHO], 2017). Individuals with a BMI under 18.5 are considered underweight, normal ranges from 18.5 to 24.9, overweight is 25 to <30 and obese is 30 and above (WHO, 2017). Wang et al. (2008) found that the likelihood of acquiring kidney disease among obese individuals was over 80% higher than among normal weight individuals. The exact process by which obesity and metabolic syndrome lead to the development of CKD remains unclear; however, hyperfiltration and increased blood flow in the kidneys are hypothesized as possible mechanisms (Wahba & Mak, 2007).

Regardless of the initial cause for the development of CKD, as the number of damaged nephrons increases, the GFR decreases because the kidneys become less efficient at filtering the blood (Schnaper, 2014). A decreased GFR leads to a reduction of excreted fluids, solutes (e.g., potassium), and wastes such as urea, often resulting in complications such as malnutrition and muscle wasting (Steiber, 2014).

Factors Affecting Glomerular Filtration Rate

The rate at which the kidneys can filter the blood is known as the glomerular filtration rate or GFR; it is measured in mL/minute/1.73 m^2 (standard body surface area) and depends on the integrity of the glomerulus structure and a sufficient blood supply (Harvard Health Publications, 2010; Lewis, 2012; Shafi & Coresh, 2010). Normal GFR is around 120

mL/minute/1.73 m^2, but this may vary depending on a number of factors (Levey et al., 2003). For example, pregnancy can increase a woman's GFR by up to 50% because hormones may cause renal vessels to dilate thereby increasing renal blood flow (Jeyabalan & Conrad, 2007; Stevens et al., 2010). During pregnancy, there is no development of structural abnormalities nor a decrease in the number of functioning nephrons and therefore this variation in GFR is not considered a sign of kidney dysfunction (Thadhani & Maynard, 2014).

Another instance of normal GFR variation occurs in elderly individuals (Glassock & Winearls, 2009). Individuals over the age of 80 can have GFRs that are up to 40% lower than their younger counterparts (Glassock & Winearls, 2009; Stevens et al., 2010). This decrease in GFR is associated with the normal aging process and is not necessarily clinically significant (Glassock & Winearls, 2009). Normal GFR can also vary throughout the day with rates slightly higher in the afternoon than during the night, and it has been suggested that this variation is due to changes in an individual's physical activity or hydration levels (Stevens et al., 2010).

While an individual's GFR cannot be directly measured, it is possible to use the quantity of a given marker such as serum creatinine to calculate an estimated GFR (eGFR) (Kawar & El Nahas, 2009; Stevens et al., 2010). Creatinine is the most frequently used marker because it can be measured and is filtered easily by the glomerulus (Stevens et al., 2010). Creatinine is produced as a consequence of normal muscle breakdown and is representative of someone's muscle mass (Stevens et al., 2010). There are several factors that can impact an individual's creatinine level however, this issue has largely been addressed with the development of equations that estimate an individual's eGFR while accounting for muscle mass differences due to gender and ethnicity (Stevens et al., 2010).

Chronic Kidney Disease Stages

CKD is categorized by a five-stage scale that was developed by the USA-based National Kidney Foundation's Kidney Disease Outcomes Quality Initiative and has been adopted internationally (Shafi & Coresh, 2010). Arora et al. (2013) and James et al. (2010) have described the stages as:

Stage 1 – normal/increased GFR (>90) with kidney damage

Stage 2 – GFR 60-89 mL/minute/1.73 m^2 with kidney damage

Stage 3 – GFR is 30-59 mL/minute/1.73 m^2

Stage 4 – GFR is 15-29 mL/minute/1.73 m^2

Stage 5 – GFR <15 mL/minute/1.73 m^2

To assess kidney damage in the early stages of kidney disease, the recommended method is assessing the level of proteinuria (National Kidney Foundation, 2013). The level of proteinuria can be determined by examining the urinary albumin-to-creatinine ratio; ratios above 2.0 mg/mmol for men or 2.8 mg/mmol for women indicate kidney damage (Levin et al., 2008). Albumin is a common protein found in the urine of individuals with CKD (National Kidney Foundation, 2013). Stages 3 through 5 are often referred to as "late stage CKD" in the literature (Arora et al., 2013; Lin et al., 2010).

Management of Chronic Kidney Disease

Management of CKD involves slowing the progression of the disease and decreasing the risk of cardiovascular events; this is accomplished by controlling hypertension and dyslipidemia (high lipid levels) as well as encouraging patients to adopt a number of nutritional recommendations (James et al., 2010; Snively & Gutierrez, 2004). For example, hypertension (high blood pressure) contributes to the progression of CKD and increases the risk of kidney

failure; therefore, various pharmacological methods are employed to keep patients' blood pressure under control (James et al., 2010). CKD patients are advised to modify their lifestyle because smoking, inactivity, and poor dietary habits (e.g., excess caloric consumption) have been associated with hypertension (Thomas, 2014). Dyslipidemia (high serum lipid levels) also increases the risk of cardiovascular events, and CKD patients frequently have high triglyceride levels and low-density lipoprotein (LDL) to high-density lipoprotein (HDL) cholesterol ratios (Snively & Gutierrez, 2004). Recent kidney treatment guidelines recommend that CKD patients should maintain "LDL cholesterol level below . . . 2.60 mmol per L and a triglyceride level below . . . 2.26 mmol/L" (Snively & Gutierrez, 2004, p.1925).

As mentioned, CKD patients are commonly advised to modify their diets to slow the progression of the disease and prevent some of the complications that are associated with the condition (Legg, 2005; Thomas, 2014). Phosphate consumption is usually controlled in late stage CKD patients (e.g., reducing dairy consumption) (Waheed, Pedraza, Lenz, & Isakova, 2013). Normally, the body attempts to compensate for higher phosphate levels by producing parathyroid hormone levels that promote calcium absorption and phosphate excretion; however, in people with CKD, this mechanism is impaired (Legg, 2005). Eventually, calcium and phosphorus levels can no longer be maintained by increasing the parathyroid hormone levels culminating in an impaired process known as secondary hyperthyroidism, or the increased production of thyroid hormones (De Leo, Lee, & Braverman, 2016; Legg, 2005).

Another nutrient that is often controlled in the diets of individuals with CKD is potassium (National Kidney Foundation, 2013; Phillips & Knuchel, 2011). High potassium levels or hyperkalemia can lead to abnormal heart rates or sudden death (Legg, 2005; National Kidney Foundation, 2013; Phillips & Knuchel, 2011). Finally, it is often recommended that individuals

reduce their sodium intake to control blood pressure and fluid retention (Legg, 2005). Despite these modifications, the disease progresses and the individual is likely to experience renal failure.

When a patient goes into renal failure (also referred to as end stage renal disease), renal replacement therapies (RRT) are initiated (Beaulieu, Boudville, & Levin, 2009). While there is no set level of GFR that determines when RRT should commence, symptoms are the main consideration when transitioning to RRT (Beaulieu et al., 2009). Uraemia, a combination of metabolic and hormone abnormalities, is an important indicator that RRT should be started (Beaulieu et al., 2009); hyperpigmentation and neurological issues are both symptoms of uraemia (Young, 2010). Other indications that RRT should be initiated include difficulty maintaining blood pressure, poor nutritional status despite nutritional interventions, or impairments in cognitive function (National Kidney Foundation, 2013).

RRT involves either dialysis or a kidney transplant, with transplantation being the preferred treatment because of improved outcomes for the patient (CIHI, 2014; Phadke & Khanna, 2011; Young, 2010). In Canada, the five-year survival rate was slightly more than 40% for patients on hemodialysis and just over 50% for peritoneal patients while, over 80% of transplanted kidneys were still functioning at the 5-year point (CIHI, 2014). Unfortunately, the waiting list for renal transplantation is long, up to several years and is increasing (CIHI, 2014; The Kidney Foundation of Canada, n.d.-a). Consequently, many individuals require dialysis.

Dialysis involves removing waste from the blood and this can be accomplished through either hemodialysis or peritoneal dialysis (Phadke & Khanna, 2011). There are over 20,000 individuals currently on dialysis in Canada, and the majority are receiving hemodialysis (CIHI, 2014). Hemodialysis can occur in a medical facility or at home and involves removing wastes

from the blood via a machine that contains a semi-permeable membrane (National Institute of Diabetes and Digestive and Kidney Diseases, 2016; Phadke & Khanna, 2011). The frequency and duration per session varies, and in hospital, hemodialysis typically occurs three times per week for four hours per session; whereas at home dialysis can occur more frequently but for shorter periods (e.g., five times per week, two hours per session) or overnight for at least three nights per week (McIntyre & Burton, 2014; National Institute of Diabetes and Digestive and Kidney Diseases, 2016). In peritoneal dialysis, the removal of wastes is accomplished with the introduction of dialysis solution into the abdominal cavity and by allowing the fluid to contact the peritoneal membrane for up to 12 hours and the process occurs at home (Phadke & Khanna, 2011). During this time, an exchange of wastes and fluid occurs, followed by the removal of dialysis solution from the abdominal cavity; the number of the cycles required varies depending on the individual (Phadke & Khanna, 2011).

Patients on dialysis can suffer complications such as infections and may also experience financial burdens because of having to travel to treatment centers or, in the case of at home dialysis, increases costs as a result of significant water usage (half liter/min or more) required for the process of waste/solute exchange (Agar, Perkins, & Heaf, 2015; Kidney Foundation of Canada – Ontario Branch, n.d.; Phadke & Khanna, 2011). In addition, patients on dialysis have an increased risk of mortality compared to the general population (Robinson et al., 2013). According to the United States Renal Data Systems [USRDS], dialysis patients had only a 54% survival rate after 3 years (USRDS, 2014). Common causes of death in dialysis patients include infections and cardiac-related events (e.g., heart attacks) (Mailloux et al., 1991). For these reasons, it is important to slow the progression of CKD to prevent the need for RRT.

Chronic Kidney Disease as a Public Health Concern

According to the Kidney Foundation of Canada (2012), CKD is a serious public health concern, as there are nearly 40,000 Canadians being treated for kidney failure. The Kidney Foundation of Canada (2012) noted that almost 80% of the individuals on the organ transplant list in 2010 were waiting for a kidney and a third of these individuals died before they were able to undergo a transplant.

The estimated cost to the Canadian healthcare system, to treat kidney failure with hemodialysis is over two billion dollars a year (Manns et al., 2017). The impact of CKD on patients includes a decreased lifespan and quality of life (McFarlane, Gilbert, MacCallum, & Senior, 2013). Patients on dialysis have to contend with symptoms such as fatigue and a disrupted lifestyle because conventional hemodialysis treatment requires patients to spend several hours, three times a week, at a renal clinic (Harvard Health Publications Group, 2010; Seccareccia & Downar, 2012).

Individuals with kidney failure have a significantly higher incidence of depression than the general population (Costa & de Lima Coutinho, 2014). Lin, Lee, and Hicks (2005), conducted in-depth interviews with dialysis patients and found that hemodialysis was equated with negative concepts such as a loss of identity, concerned with being a burden to others, a loss of power/control, a loss of physical freedom, and fear of the physical effects from the dialysis itself (i.e., complications). Further, long hours spent on dialysis and declining health can have a negative effect on the employment of individuals with late stage CKD (Manns et al., 2017). Nearly 70% ofl individuals with kidney failure are unemployed, and it was estimated that over $200 million is spent annually on disability payments to Canadians who are suffering from kidney failure (Manns et al., 2017).

It is therefore essential to develop strategies that are more effective in preventing CKD. Current approaches tend to focus on public education, on reducing CKD risk factors (e.g., maintaining normal blood pressure), encouraging individuals with diabetes to keep their disease under control and avoiding long-term use of non-prescription medications that may damage kidneys (The Kidney Foundation of Canada, n.d.-b; Levey, Schoolworth, Burrows, Williams, & Stith, 2009). Anti-inflammatory drugs (e.g., ibuprofren, acetylsalicylic acid), antibiotics (e.g., amoxicillin), and other drugs (e.g., Warfarin) were found to increase the risk of renal failure particularly, at higher doses (Gutthann, Garcia Rodriquez, Raiford, Oliart, & Romeu, 1996).

Unfortunately, current CKD initiatives are often not sufficient and screening measures are not implemented early enough or fail to properly target high risk groups, leading to few public health impacts (Schoolworth et al., 2006). In Canada, the first CKD screening program that targeted at risk individuals, such as those diagnosed with diabetes, having a family history of kidney disease, and/or belonging to a high-risk group (e.g., Aboriginals) was launched by The Kidney Foundation of Canada (Galbraith et al., 2016). The See Kidney Disease (SeeKD) screening program included a medical questionnaire to identify adults who had risk factors for CKD; these individuals were given further testing (e.g., urinalysis and point-of-care creatinine testing) as well as a follow-up survey that was sent within a month of the screening (Galbraith et al., 2016). Galbraith et al. (2016) found that adults who participated in the SeeKD screening program and who were not aware that they had CKD tended to be female, had a BMI in the overweight/obese category, and had a diagnosis of diabetes, hypertension or vascular disease. These same authors noted that the prevalence of previously unidentified CKD was higher in the SeeKD program than in published population estimates, indicating the effectiveness of this type

of screening program. Early identification and initiation of treatment can help to slow the progression of the disease and reduce the risk of CKD-related complications (James et al., 2010). A number of risk factors for CKD were identified, and further research is required to understand the mechanisms involved (Khan & Pandey, 2014).

Inflammation in Chronic Kidney Disease

Inflammation has been identified as an important factor in the development of a number of chronic diseases, and it is only recently that a more comprehensive understanding of the process of tissue repair and the immune response has emerged (Galland, 2010; Punchard, Whelen, & Adcock, 2004). Acute inflammation is a normal response that protects the body from foreign material and involves a number of cells and cytokines (Allukian & Liechty, 2012). Cytokines are small proteins that have a number of key functions, particularly during the inflammatory response (e.g., IL-6) (García-García, Getino-Melián, Domínguez-Pinmental, & Navarro-González, 2014). During an acute inflammatory response, Tumor Necrosis Factor alpha (TNF-α) promotes the release of enzymes that break down bacteria and other foreign material that may have entered the body (Allukian & Liechty, 2012; Calder et al., 2011). It is necessary for the inflammatory process to end before tissue repair can begin; this occurs as a result of an increase in the production of anti-inflammatory mediators (e.g., IL-10) and the decreased production of proinflammatory mediators (e.g., TNF-α), (Das & Roy, 2012). When the inflammatory process is no longer properly controlled (e.g., the response is not shut down) or is initiated inappropriately, chronic inflammation and eventually tissue damage occurs (Calder et al., 2011). Moreover, chronic inflammation itself can lead to the production of free radicals (highly reactive intermediates) that can further damage tissues and creates a cycle of inflammation and tissue damage (Prasad, Sung, & Aggarwal, 2012).

A number of risk factors for CKD have been associated with chronic inflammation (Shankar et al., 2011). Inflammatory cytokines have been associated with renal changes including altering the permeability of the glomerulus membrane, cell death, and structural changes in individuals with diabetes (García-García et al., 2014).

Increased levels of inflammatory mediators and cytokines have also been observed in obese individuals (Calder et al., 2011). The increased level of proinflammatory mediators could be due to an accumulation of macrophages in the adipose tissue of obese individuals (Weisburg et al., 2003). A study by Weisburg et al. (2003) found significant differences in the distribution of macrophages within the adipose tissue of obese mice. More specifically, the authors noted that obese mice had deposits of macrophages within the adipose tissue whereas lean mice had fewer macrophages that were distributed more evenly. These authors then examined the quantity of macrophages in the adipose tissue of lean and obese humans and found that the adipose tissue of obese individuals was composed of up to 40% macrophages compared to less than 10% in lean individuals. Weisberg et al. (2003) stated this finding was significant since the majority of TNF-α production in adipose tissue is due to these macrophages. This finding could explain the link between obesity and low level chronic inflammation (Curat et al., 2006). The excess TNF-α production that accompanies obesity and is related to chronic inflammation is thought to lead to renal fibrosis (excess collagen in renal tissue) (Synder, Turner, & Turner, 2014). Renal fibrosis is the result of decreased fibrinolysis as well the development of proteins within renal cells, both of which can lead to renal damage and CKD (Hewitson, 2012; Synder et al., 2014).

Oxidative stress is another inflammatory-related mechanism that is associated with the development of CKD (Gobal, Deshmukh, Shah, & Mehta, 2011). During normal metabolic processes, the creation of highly reactive intermediates can occur (e.g., hydrogen peroxide), and

if there is an insufficient number of antioxidants to neutralize these intermediates, tissue damage and inflammation can occur (Gobal et al., 2011; Ruiz, Pergola, Agar, & Vaziri, 2013). When there are significant levels of non-neutralized reactive intermediates, the state is referred to as oxidative stress (Gobal et al., 2011). Oxidative stress was associated with the development of hypertension as well as metabolic syndrome and diabetes, all of which are risk factors for the development of CKD (García-García et al., 2014; Gobal et al., 2011; Vaziri, 2004). Smoking, another risk factor for CKD, was found to induce oxidative stress as a result of the free radicals that are present in cigarette smoke (Dietrich & Block, 2006).

Finally, inflammation was implicated in the progression of CKD (Silverstein, 2009; Vaziri et al., 2014). Silverstein (2009) noted that inflammation causes the release of cytokines that promote kidney fibrosis, resulting in further kidney damage and progression of the disease. Research in mice suggests that when oxidative stress and inflammation is controlled (e.g., by consuming a diet high in resistant starch), CKD progression is slowed (Vaziri et al., 2014). For these reasons, interventions that focus on preventing chronic inflammation may help to reduce the risk of developing CKD.

Sex Differences and Chronic Kidney Disease

A number of sex differences have been found in the development and progression of CKD (Cobo et al., 2016; Iseki, 2008). The rate of non-end stage CKD tends to be higher in women while men tend to progress faster to end-stage CKD and have higher rates of dialysis than women (Chang et al., 2016; Cobo et al., 2016; Iseki, 2008). One explanation is that testosterone may have a damaging effect, while estrogen may have a protective effect on kidneys (Cobo et al., 2016). However, the evidence is unclear because one study demonstrated that oral estrogen use may promote kidney function loss while another found that among men with

moderate CKD, a lower testosterone level was associated with an increased mortality rate (Cobo et al., 2016). Other possible explanations included differences in lifestyle factors such as dietary habits (with men tending to have poorer dietary habits than women) as well as differences in the impact of general CKD risk factors (Cobo et al., 2016). In fact, one study found that BMI had a greater effect on the progression of end-stage renal disease in men compared to women (Verhave et al., 2003). Finally, predictors of renal function decline were found to differ between men and women with urinary albumin excretion and cholesterol/HDL ratio associated with greater renal function decline in men than women, respectively (Halbesma et al., 2008). More research is clearly needed to better understand the link between sex and the progression of CKD.

Dietary Patterns and Chronic Kidney Disease

Recently, some studies have examined the impact of specific dietary patterns on the development of CKD (Dunkler et al., 2013; Khatri et al., 2014). Participants who had adhered to healthy eating guidelines (as measured by high healthy eating index scores) had lower risks of developing CKD, even among individuals with diabetes or older adults (Dunkler et al., 2013; Gopinath, Harris, Flood, Burlutsky, & Mitchell, 2013). Khatri et al. (2014) used an index that measured participants' adherence to a Mediterranean style diet (e.g., one high in vegetables, fruit, nuts and low in animal protein) to examine the effect of this diet on kidney function. Interestingly, a Mediterranean style diet was associated with decreased odds of having an unhealthy GFR (Khatri et al., 2014).

The above findings were consistent with studies that found a link between poor quality diets and an increased risk of developing kidney dysfunction (Chang et al., 2013). Chang et al. (2013) reported that individuals who consumed poor quality diets that were low in fruits and vegetables, high in animal protein and sweetened drinks (e.g., soda, juices) were more likely to

have microalbuminuria (protein in the urine), an indicator of CKD. A different study had examined dietary patterns in Americans and reported similar results; even after controlling for other factors (e.g., socioeconomic status, comorbidities) consuming a "Southern-style" diet (one high in fried foods, sugar, and sodium) was associated with higher levels of protein in the urine as well as a higher risk of mortality among individuals with CKD than those who did not consume this type of diet (Gutiérrez et al., 2014). It is important to note that these studies did not directly examine the inflammatory nature of these dietary choices. However, there are a number of studies that have linked similar eating patterns to increased levels of inflammatory markers such as CRP and IL-6 (Basu et al., 2006; Montonen et al., 2013; Shivappa et al., 2013a).

Shivappa et al. (2013a) found that consuming proinflammatory foods was associated with increased odds of having an elevated CRP level. These same authors developed and validated a 45-item dietary inflammatory index (DII); this index assigns an inflammation score to a particular food or food components, with high scores being indicative of a proinflammatory diet. Steck et al. (2014), used this index to compare three hypothetical dietary patterns based on a "typical" day's consumption of a fast food, Mediterranean, or macrobiotic diet and found that the fast food diet had a high (proinflammatory) DII score whereas, the macrobiotic and Mediterranean diets had low (anti-inflammatory) DII scores.

Recently, the DII was used to explore the effect of a proinflammatory diet on asthma, a chronic inflammatory disease (Wood, Shivappa, Berthon, Gibson, & Hebert, 2015). Wood et al., (2015) found that individuals who suffered from asthma had a higher mean DII score than those without asthma. These same authors noted that the odds ratio for every unit increase in DII score was 1.70; in other words, the odds of having asthma were 70% higher for every unit increase in inflammatory food consumption (Wood et al., 2015). Further, in a study of Swedish seniors,

researchers used an adapted 28- item version of this inflammatory index to examine the effects of diet on kidney function (Xu et al., 2015). Xu et al. (2015) found that the consumption of proinflammatory foods was associated with a decline in GFR among these seniors. It is important to note that Xu et al.'s 2015 study did not look specifically at CKD, and while age was controlled for in the statistical analysis, the issue of natural GFR decline with age versus clinically significant changes in GFR was not addressed (Glassock & Winearls, 2009; Xu et al., 2015).

Diet, Inflammation, and Chronic Kidney Disease

The mechanism between diet, inflammation, and CKD is not well characterized; the majority of studies have focused on associations between specific dietary patterns and markers of inflammation. Fassatt, Gobe, Peake, and Coombes (2010) suggested that omega-3 polyunsaturated fatty acids may be beneficial to patients with kidney disease. Experimental evidence indicated that omega-3 polyunsaturated fatty acids may positively impact kidney disease by reducing TNF-α, one protein involved in the inflammatory response, resulting in a decrease in renal fibrosis and inflammation (Fassatt et al., 2010). However, a review of the current literature found that there is a paucity of controlled clinical trials that have examined the effects of omega-3 polyunsaturated fatty acid supplementation and CKD.

There is a growing body of knowledge on the impact of dietary components and inflammation in the body (Calder et al., 2011; Naruszewicz et al., 2009). Antioxidant vitamins such as vitamin C can help to prevent oxidative stress by neutralizing reactive species and may improve the endothelium (lining of blood vessels) (Calder et al., 2011). As mentioned, oxidative stress and cardiovascular disease can play a role in the development and progression of CKD (Calder et al., 2011).

Another example is the inflammatory effect of the chronic consumption of acrylamide, a compound commonly found in carbohydrate rich fried foods such as potato chips (Naruszewicz et al., 2009). Exposure to acrylamide could result in oxidative stress and could be related to significant increases in the level of reactive intermediates, as well as a decrease in cellular antioxidants (Naruszewicz et al., 2009; Yerlikaya, Toker, & Yener, 2013). Oxidative stress has been identified as the potential link between high red meat consumption and chronic diseases such as cardiovascular disease (Cai, Gao, Peppa, He & Vlassara, 2002; Montonen et al., 2013). Conversely, whole grains may decrease inflammation due to the antioxidants contained within the grain, resulting in a decreased risk of diabetes, cardiovascular disease, and other chronic conditions (Montonen et al., 2013; Slavin, 2003). A study by Vaziri et al. (2014) involving rats found that the animals that had consumed a diet high in amylose resistant starch had decreased oxidative stress and inflammation, and they demonstrated a slower progression of CKD compared to the rats that were fed a low fiber diet. The mechanism by which the resistant starch altered the progression of CKD has not been established; however, CKD is associated with changes in the bacterial make-up of the intestinal track (Vaziri et al., 2014). These changes often lead to the build-up of toxins and damaged intestinal cells, exacerbating general inflammation (Vaziri et al., 2014). These same authors suggested that the consumption of amylose resistant starch may promote the growth of beneficial bacteria leading to a reduction in the number of toxins produced and ultimately, decreasing the inflammation that drives the progression of CKD (Vaziri et al., 2014).

In summary, increased inflammatory biomarkers were observed in individuals who consumed diets that were “unhealthy” (e.g., high fat), and evidence suggests that chronic inflammation is linked to the development and progression of CKD (Fung et al., 2001;

Silverstein, 2009; Synder et al., 2014). That being said, there is no current research, to this author's knowledge, that has explicitly examined the association between consuming a diet high in proinflammatory food components and CKD in a Canadian population. As mentioned, evidence suggests that chronic inflammation contributes to kidney damage leading to decreased GFRs; consequently, chronic inflammation is a significant factor in the development of CKD (Shankar et al., 2011).

For these reasons, this author hypothesizes that there is likely an association between the consumption of proinflammatory foods and CKD. Being able to establish an association between proinflammatory food consumption and CKD may lead to prevention strategies such as a reduction in the consumption of these types of foods.

Research Objectives and Hypotheses

The current study had several research objectives:

1. To examine the difference in the mean consumption of proinflammatory foods (represented by the mean DII score) between individuals with undiagnosed late stage CKD and those without CKD.
2. To examine the difference in the mean consumption of proinflammatory foods (represented by the mean DII score) between men and women with undiagnosed late stage CKD.
3. To examine the difference in the mean CRP levels between individuals with undiagnosed late stage CKD and those without CKD.
4. To examine the difference in the mean CRP levels in men and women with undiagnosed, late stage CKD were compared.
5. To assess whether proinflammatory food consumption (represented by the mean DII score) predicted the presence of late stage CKD.
6. To examine the link between proinflammatory food consumption (represented by the mean DII score) and CKD risk factors.
7. To determine whether proinflammatory food consumption (represented by the mean DII score) predicted eGFR in an at-risk subpopulation.

Table 1 lists the objectives and corresponding hypotheses as well as the statistical tests that were used in the current study.

Table 1

Statistical Analysis, Hypotheses and Research Objectives

Research Objective	Hypothesis	Statistical Test
To examine the difference in the mean consumption of proinflammatory foods between individuals with undiagnosed late stage CKD and those without CKD	1. Individuals with undiagnosed late stage CKD will have a significantly higher mean consumption of proinflammatory foods compared to those without CKD	Independent T-test
To examine the difference in the mean consumption of proinflammatory foods between men and women with undiagnosed, late stage CKD	2. Men with undiagnosed, late stage CKD will have a significantly higher mean consumption of proinflammatory foods compared to women	Independent T-test
To examine the difference in the mean high sensitivity C-reactive protein level of individuals with and without undiagnosed, late stage CKD	3. Individuals with undiagnosed late stage CKD will have a significantly higher mean high sensitivity C-reactive protein level compared to those without CKD	Independent T-test
To examine the difference in the mean high sensitivity C-reactive protein level of men and women with undiagnosed, late stage CKD	4. Men with undiagnosed, late stage CKD will have a significantly higher mean high sensitivity C-reactive protein level compared to women	Independent T-test
To explore the association between proinflammatory food consumption and the presence of late stage CKD	5. DII scores predict the presence of late stage CKD after controlling other factors	Logistic Regression
To explore the association between proinflammatory food consumption and CKD risk factors	6. DII scores predict BMI 7. DII scores predict high cholesterol	Linear Regression Logistic Regression
To explore the association between proinflammatory food consumption and eGFR in the general population and an at-risk subpopulation	8. DII scores predict eGFR in the general population 9. DII scores predict eGFR in individuals who reported being diagnosed with a kidney problem	Linear Regressions

The objectives of the current study were formulated to address some of the research gaps identified in the literature review. As noted previously, there is some evidence of a relationship between a low-quality diet and the development or progression of CKD, as well as a link between inflammation and CKD. However, there is a lack of research concerning the possible relationship between diet, inflammation, and late stage CKD, particularly in a Canadian population. The current study's findings may provide a possible link between these three areas of study. There is also a paucity of research surrounding sex differences and CKD. The findings of the current study may provide a possible explanation for the differences observed between sexes in undiagnosed, late stage CKD and suggest areas that future intervention research should focus on.

In the literature review, risk factors for CKD were identified, and the current study explores whether there is a link between these risk factors for CKD and the consumption of an inflammatory diet, a subject that to date has not been examined in a Canadian population. Finally, there is little research that has examined the consumption of proinflammatory foods and eGFR; the present study is the first to explore this topic in a Canadian population. Results of the current study may contribute to a better understanding of the growing issue of CKD in Canada. The next section presents information regarding the CHMS – Cycle 3 survey and describes the analysis methods that were used to meet the study's objectives.

Method

The current study used data from the Canadian Health Measures Survey (CHMS) – Cycle 3. This particular cross-sectional survey was selected as it is a nationally representative and contains variables on nutrition and laboratory test results (e.g., serum creatinine levels).

Survey Information - Target Population

The CHMS – Cycle 3 includes non-institutionalized Canadians aged 3 to 79 years old living in one of the five following regions: Atlantic, Quebec, Ontario, the Prairies, and British Columbia) (Statistics Canada, 2015a). Full-time military personnel, individuals living on reserves, in one of the territories, or in some remote locations were excluded (Statistics Canada, 2015a).

Survey Information – Data Collection

Geographical clusters were developed based on the 2011 Census and individuals within a household were assigned a probability of participating in the study depending on the targets for each age and gender group (Statistics Canada, 2015a). To minimize the issue of non-response and to encourage participation, several methods were used including contacting individuals in person when possible and informing respondents of the importance of the survey (Statistics Canada, 2015a). Participants who were not comfortable conversing in either official language were provided with an interviewer who was fluent in the participant's first language whenever possible (Statistics Canada, 2015a). Response rates were nearly 75% at the household level, nearly 90% at the individual questionnaire level, and just under 80% of individuals completed the physical testing component (Statistics Canada, 2015a).

Ethics approval was obtained from both Health Canada and Public Health Agency of Canada's research boards, and the Office of the Privacy Commissioner of Canada was consulted to ensure sufficient measures were in place to safeguard participants' privacy (Statistics Canada,

2015a). Finally, study participants were provided with a brochure and video outlining the survey process and potential risks of participation before obtaining their consent (Statistics Canada, 2015a).

To reduce the issues of bias and improve reliability, staff were provided classroom and "hands-on" training prior to data collection, and interviewers were observed on several occasions to ensure consistency (Statistics Canada, 2015a). Data collection occurred between January 9, 2012, and December 17, 2013 and household interviews were conducted in person using computer assisted interviews (Statistics Canada, 2015a). Participants were also asked to visit a mobile clinic for the collection of blood and urine samples, and to undergo a number of clinical tests (e.g., grip strength) were conducted (Statistics Canada, 2015a). More detailed information about the data collection stage are given in the *CHMS Data User Guide: Cycle 3* (Statistics Canada, 2015a).

The Current Study's Sample

The current study sample included individuals who were not pregnant, who were not aware of their CKD status, and who were between the ages of 18 and 79. Children were excluded because CKD in children typically has different etiologies than adults and pregnant women were excluded because pregnancy has been found to temporarily alter the physiology of the kidney, and current methods to calculate eGFR do not take this effect into consideration (Gulati, 2015; Vellanki, 2013). As mentioned, individuals who have been diagnosed with CKD often receive dietary recommendations to alter their intakes of various nutrients (Thomas, 2014). Consequently, these individuals may have altered their diet compared to those who have undiagnosed CKD and were not included in the main sample. This meant excluding 18% of individuals who had late stage CKD and reported having a kidney problem from all analysis with

the exception of the regression examining whether DII scores predicted eGFR in this subpopulation; therefore, just over 1,800 individuals (weighted n) met the inclusion criteria for the present study. Unless otherwise noted, to avoid repetition, the term late stage CKD will refer to individuals who have undiagnosed, late stage CKD when describing the method and results of the present study.

Study Variables

eGFR. Participants' blood was collected as part of the mobile clinic component of the CHMS – Cycle 3 and was sent to a reference lab for testing (Statistics Canada, 2015a). The chemistry component of the blood analyses included serum creatinine, and this variable was used to determine participants' estimated GFR (eGFR) (Statistics Canada, 2015a). Specifically, the eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The CKD-EPI equation[1] has been found to be more accurate at estimating GFR than the alternative equation, Modification of Diet in Renal Disease (MDRD) (Arora at al., 2013; Matsushita et al., 2012). Participants' eGFR was used to classify them as having late stage (stages 3-5) or no CKD based on the Outcomes Quality Initiative classification system described earlier. In order to identify participants who were aware that they had a kidney problem, their response to the question of whether or not a health professional had diagnosed them as having a kidney problem (yes/no) was used (Statistics Canada, 2014b).

Food Consumption. Survey participants were asked about their food consumption habits, including their meat, egg, dairy and alternatives, grain, and fruit and vegetable consumption using a food frequency questionnaire (FFQ); participants indicated how often they consumed a food (e.g., 2 times per week). Serving sizes were not noted in the CHMS

[1] $GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa,1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if of African descent]
Scr=serum creatinine in mg/dL, κ=0.7 if female or 0.9 if male (Arora, 2013)

documentation; therefore, Canada's food guide serving sizes were used. In cases where FFQ questions were not adequately specific, such as "how often do you usually eat red meat such as beef, hamburger, pork or lamb?" consumption data from Canadian Agriculture and Agri-Food Canada and other statistics were used whenever possible to determine the most commonly consumed food for calculation purposes (Statistics Canada, 2014a, pg. 78). Table 2 lists the food consumption variables that were used in the present study.

Table 2

Food Consumption Variables

Variable Name	Concept
MFC_11	Eats red meat
MFC_12	Eats liver
MFC_14	Eats beef or pork hot dogs
MFC_15	Eats sausage or bacon
MFC_19A	Eats egg/egg dishes that include the yolk
MFC_20	Eats cooked dried beans
MFC_21	Eats nuts
MDC_03A	Drinks/uses milk substitutes – rice
MDC_03B	Drinks/uses milk substitutes – soya
MDC_03C	Drinks/uses milk substitutes – almond
MDC_12A	Type of milk used – 3.25%
MDC_12B	Type of milk used – 2%
MDC_12C	Type of milk used – 1%
MDC_12D	Type of milk used – .05%
MDC_12E	Type of milk used – skim or non-fat
MDC_12F	Type of milk used - Flavored
MDC_13	Eats cottage cheese
MDC_13B	Eats processed cheese
MDC_14	Eats yogurt (excluding frozen)
MDC_15	Eats ice cream or frozen yogurt
GFV_11	Eats hot or cold cereals
GFV_12	Eats whole grain bread
GFV_13	Eats white bread
GFV_14	Eats pasta
GFV_16	Eats instant, seasoned or wild rice
GFV_17A	Eats citrus fruit
GFV_17B	Eats strawberries (during the summer)
GFV_17C	Eats strawberries (excluding summer)
GFV_17D	Eats other types of fruit
GFV_18	Eats tomatoes/tomato sauce
GFV_19	Eats lettuce or green leafy salad
GFV_20	Spinach, mustard greens, or cabbage
GFV_21	Eats fries/hash brown potatoes
GFV_22	Eats other potatoes
GFV_23	Eats other types of vegetables
GFV_24	Eats flax seeds
DFC_11	Easts regular fat dressing/mayo
DFC_12	Eats regular-fat potato chips
DFC_13	Eats margarine
DFC_14	Eats omega-3 enriched margarine
WSD_31	Drinks regular soft drinks

Table 2 continued

Food Consumption Variables

Variable Name	Concept
WSD_34	Drinks orange or grapefruit juice
WSD_35	Drinks other 100% fruit juices
WSD_38	Drinks other vegetable juices
WAQ_06	Drinks black/green/white tea
ALC_14	Drank alcohol this past week
FSF_10A	Ate lobster this past month
FSF_10B	Ate shrimp this past month
FSF_10C	Ate mussels this past month
FSF_10D	Ate scallops this past month
FSF_10E	Ate oysters this past month
FSF_10F	Ate squid/calamari this past month
FSF_10G	Ate clams this past month
FSF_10H	Ate crab this past month
FSF_10I	Ate surimi this past month
FSF_24AA	Ate fish sticks this past month
FSF_24AB	Ate tuna (in a can/pouch) this past month
FSF_24AC	Ate tuna (fresh/frozen) this past month
FSF_24AD	Ate salmon (in a can/pouch) this past month
FSF_24AE	Ate salmon (fresh/frozen) this past month
FSF_24AF	Ate smelt this past month
FSF_24AG	Ate shark this past month
FSF_24AH	Ate marlin this past month
FSF_24AI	Ate swordfish this past month
FSF_24AJ	Ate halibut this past month
FSF_24AK	Ate rainbow trout this past month
FSF_24AL	Ate Atlantic cod this past month
FSF_24AM	Ate mackerel this past month
FSF_24AN	Ate herring this past month
FSF_24AO	Ate sardines this past month
FSF_24AP	Ate sole this past month
FSF_24AQ	Ate haddock this past month
FSF_24AR	Ate tilapia this past month
FSF_25A	Ate light (flake/chunk) tuna this past month
FSF_25B	Ate white (solid) tuna this past month

Note. Derived from Statistics Canada, 2014a; Statistics Canada, 2014b

Whenever possible, the nutrients for each food were obtained from the 2015 Canadian Nutrient File, a database containing nutrient information for over 5,000 foods commonly consumed in Canada (Health Canada, 2015). Although much of the nutrient information in the

Canadian Nutrient File was based on data from the United States Department of Agriculture's National Nutrient Database for Standard Reference, it was adjusted to reflect Canadian fortification practices, as well as for foods that are only available in Canada (Health Canada, 2015). In instances where the Canadian Nutrient File did not have the item, the United States National Nutrient Database for Standard Reference was consulted. Over 1800 possible nutrient variables could be used for the calculation of participants' DII scores.

Participants' mean daily intakes were based on the number of servings over a seven-day period, multiplied by the amount of each nutrient (e.g., carbohydrates), in a particular item. Finally, the total amount of each nutrient consumed by the participant was obtained by summing the amount of that nutrient, in each of the foods consumed by the participant. A sample calculation for an individual's hypothetical consumption of carbohydrate was provided below (Table 3). In order to calculate participants' intakes of nutrients from the foods listed below, over 3,000 lines of syntax were written for this study.

Table 3

Simplified Sample Nutrient Calculation – Carbohydrates

Food	Mean 7 day servings	Carbohydrates per serving (g)	7 day total
White bread	**7**	17.71	123.97
Pasta	2.6	22.83	59.36
2% Milk	7	12.38	86.66

Dietary Inflammatory Index. Foods were classified as being proinflammatory based on the Dietary Inflammatory Index (DII); this index includes 45 food or food components (e.g., zinc and pepper) and was created by reviewing and scoring nearly 2,000 peer-reviewed articles that looked at the effect of various foods or food components on inflammation (Shivappa et al., 2013b). Articles involving human experimental studies were given a higher weight than articles

based on animals or cell cultures (Shivappa et al., 2013b). The weighted pro-inflammatory and anti-inflammatory articles were then divided by the total number of weighted articles followed by subtracting the anti-inflammatory results from the proinflammatory results (Shivappa et al., 2013b). This index was validated by comparing DII scores with an individual's high-sensitivity CRP value (a biomarker for inflammation); higher DII scores were found to be associated with CRP values (Shivappa et al., 2013a). The DII scores range from -8.87 (anti-inflammatory score) to 7.98 (pro-inflammatory score), with a median of 0.23 (based on the maximum and minimum DII value of each of the parameters) (Shivappa et al., 20l3b). In the current study, an individual's DII score was calculated by the procedure developed by Shivappa et al. (2013b):

1. Determining the composition of each food using the Canadian Nutrient File.
2. Deriving the inflammatory value of each food parameter by calculating the Z-score (the standard mean from the DII was subtracted from the amount of that nutrient consumed in one day).
3. Using the Z-score that was calculated in the previous step, the centered percentile of each food/component was obtained.
4. Multiplying the centered percentile by the food or food component's inflammatory effect score listed in the DII.
5. Summing the results obtained from step 4.

The following subsection lists a sample calculation for a hypothetical amount of carbohydrate (equations 1-3). However, not all of the 45 food parameters from the index were used in the current study as they were not collected in the CHMS Cycle 3 (e.g., garlic, onion, herbs) or the nutrient database did not contain information on the item (e.g., flavonols). Finally, as per van Woundenbergh et al. (2013), total fat and energy were excluded because all the

macronutrients and fatty acids were already accounted for in the DII. Twenty-eight parameters (rather than all of 45 of the original parameters) were used to determine participants' DII scores, a procedure that has been used successfully in previous research (Shivappa et al., 2013a; van Woudenbergh, 2013; Xu et al., 2015) (Table 4).

Sample DII Calculation - Carbohydrate Component of Diet.

$z = 269.99^{*} - 272.2^{**}/40.0^{**} = -0.055$ (1)

*hypothetical carbohydrate intake **from DII

Percentile score = 0.478

Centered Percentile Score. (2)

(0.478 * 2) -1 = -.044

Food Parameter Specific Score.

$(-.044)(.097^{*}) = -.004$ (3)

*from DII

(adapted from Shivappa et al., 2013b)

Table 4

Dietary Inflammatory Index Variables Used in the Present Study

Food Component
Alcohol
Vitamin A
Vitamin B_{12}
Vitamin B_6
Beta carotene
Vitamin C
Caffeine
Carbohydrate
Cholesterol
Vitamin D
Vitamin E
Fiber
Folic acid
Iron
Magnesium
MUFA
Niacin
n-3 fatty acids
n-6 fatty acids
Protein
PUFA
Riboflavin
Saturated fat
Selenium
Thiamine
Trans fat
Zinc
Green/Black Tea

Additional Variables. Factors that may influence chronic inflammation such as hypertension, BMI, high cholesterol, and diabetes were controlled for in regression analysis that examined the association between DII scores and eGFR and between DII and late stage CKD (Calder et al., 2011; Dinh, Drummond, Sobey, & Chrissobolis, 2014; Esteve, Ricart, & Fernández-Real, 2004; MacIsaac et al., 2012; Wang, Zakhari, & Jung, 2010). Determining whether or not participants had diabetes, and/or high cholesterol was based on participants'

responses to whether a doctor had diagnosed them with these conditions (yes/no) (Statistics Canada, 2014a). Hypertension was defined as having a systolic blood pressure reading above 140 mmHg and/or a diastolic blood pressure reading above 90 mmHg and the results were recoded by the researcher into a dichotomous variable (yes/no) (National Kidney Foundation, 2017). BMI was a derived variable that was subsequently used to classify participants in the standard BMI categories: underweight, normal, overweight, obese class I, obese class II, and obese class III (Statistics Canada, 2014b). The original 6 BMI categories were collapsed into 2 (underweight/normal and overweight/obese) to address the low number of participants in some of the categories, in order for demographic analysis to proceed.

A demographic factor that was controlled for was age. There is an association between advanced age and declining GFR, and current methods to calculate eGFR do not take this into account (Glassock & Winearls, 2009). There is no clear age when this effect becomes significant; however, the decline is thought to begin between 50 and 60 years of age (Glassock & Winearls, 2009). Age is also linked to increasing cholesterol levels and BMI (Cheung et al., 2009; Reas, Nygård, Svensson, Sørensen, & Sandanger, 2007).

Sex and smoking status may be risk factors in the development of CKD, while the use of lipid-lowering medications such as statins may help to prevent cardiovascular disease (CVD) (CVD is a risk factor for CKD). As a result, these variables were also controlled for in the regressions exploring the association between DII scores and kidney related variables (Fellström, 2011; Glassock & Winearls, 2009; Shinha et al., 2014; Yacoub, 2010). Evidence indicates that smoking may have an impact on BMI and therefore was included as a control variable in the regression that examined the association between DII scores and BMI (Wehby, Murray, Wilcox, & Lie, 2012). The original variable for sex was used while smoking was recoded into

daily/occasional smoker and non-smoker (Statistics Canada, 2014a). Participants were asked about their medication use and Canada's Drug Identification Number was used to help classify each drug under the Anatomical Therapeutic Chemical (ATC) system (Statistics Canada, 2015a). For further information regarding the ATC classification system used in the CHMS please refer to the *CHMS Data User Guide: Cycle Three* (Statistics Canada, 2015a). Statin use was identified by their corresponding ATC codes and grouped into one (yes/no) variable.

Demographic factors that have been associated with overall health were also accounted for during regression analyses. For instance, ethnicity can play a role in health. Aboriginal individuals tend to have higher rates of many chronic and infectious diseases compared to non-Aboriginal individuals (Mikkonen & Raphael, 2010). The derived variable identifying participants' cultural/racial group was used in the current study, and the original 13 categories were also collapsed into to two, "Caucasian" and "Other", to address the low number of participants in some of the categories.

Income is another factor that can affect health; for example, Mikkonen and Raphael (2010) noted that wealth had a significant impact on long-term health outcomes. Total reported household income was used to measure income in the present study, and the original 15 categories were collapsed into five: $0 to $19,999, $20,000 to $39,999, $40,000 to $59,999, l$60,000 to $79,999, and $80,000 and above. Another important factor is education because individuals with higher education tend to be healthier than those with lower levels of education (Mikkonen & Raphael, 2010). Participants were asked what the "highest degree, certificate, or diploma that you have obtained?" and response categories ranged from less than secondary school to post-graduate (Statistics Canada, 2014a, pg. 9).

Statistical Analysis

In order to test the hypotheses and to determine if the findings were statistically significant, statistical tests were selected based on the questions that were asked and these tests are listed in table 5. Wilcox (2009) stated that the independent t-test should be used when the dependent variable approaches a "normal bell-curve shape", and the means of two independent groups are being compared. More specifically, to determine if there was a significant difference in the means of two independent groups, independent t-tests were used in the current study to test hypotheses 1-4 (Table 5).

Table 5

Independent t-tests analyses and comparison groups

t-tests	Comparison groups
To examine the difference in the mean consumption of proinflammatory foods (hypotheses 1,2)	Individuals with late stage CKD vs Individuals without CKD
	Men with late stage CKD vs Men without CKD
	Women with late stage CKD vs Women without CKD
	Men with late stage CKD vs Women with late stage CKD
To examine the difference in the mean high sensitivity C-reactive protein level (hypotheses 3,4)	Individuals with late stage CKD vs Individuals without CKD
	Men with late stage CKD vs Men without CKD
	Women with late stage CKD vs Women without CKD
	Men with late stage CKD vs Women with late stage CKD

In order to determine if one or more independent variables predicted the dependent variables in this study, specific types of regressions were used (Table 6). Randolf and Myers

(2013) noted that linear regressions are types of correlation tests that are used in statistical analyses when the dependent variable is measured at the interval level, and logistic regressions are used when the dependent variable is measured at the dichotomous level such as yes/no categories. In both types of regressions, the independent variables may be continuous or categorical (Pallant, 2010).

Table 6

Regression Type, Hypothesis and Variables Used

Regression type	Hypothesis	Independent variables	Dependent variable
Logistic	5. DII scores predict the presence of late stage CKD after controlling other factors	Statin use, hypertension, high cholesterol, diabetes, demographics	Late stage CKD
Linear	6. DII scores predict BMI	Lifestyle factors, demographics	BMI
Logistic	7. DII scores predict high cholesterol	Lifestyle factors, demographics	High Cholesterol
Linear	8. DII scores predict eGFR in the general population	Statin use, hypertension, high cholesterol, diabetes, demographics	eGFR
Linear	9. DII scores predict eGFR in individuals who were diagnosed as having a kidney problem	Statin use, lifestyle factors, demographics	eGFR

Survey Weights and Bootstrapping. For analysis purposes and to adjust for the sampling design of the CHMS, a weighted bootstrapping analysis approach was used. Survey weights are designed to make the survey representative of the Canadian population and to make adjustments for non-responses (Statistics Canada, 2015a). Therefore, each survey participant is weighted to represent a certain number of people in the Canadian population (Statistics Canada, 2015a). For

example, if a case was given a weight of 2, it would represent two cases in the dataset (Johnson, 2008). In order to properly estimate the variance, a bootstrap method is required. For the CHMS, this process involved re-sampling with replacement 500 times and the "variability among the 500 estimates gives the variance estimate" (Statistics Canada, 2015a, pg. 51). The 500 bootstrap weights are provided with the dataset.

Statistical Software. Variable recoding, participants' DII scores and eGFR calculations, and t-test analyses were conducted using SPSS ver. 22. The researcher learned how to code syntax in STATA ver.13 in order to perform analyses that required bootstrapping (i.e., regressions, crosstabs).

In summary, the current study included adult participants of the CHMS – Cycle 3 who either did not have CKD or had undiagnosed, late stage CKD. Participants' self-reported food consumption habits and nutrient information from the Canadian Nutrient File were used to calculate the overall DII score for each participant. This variable was used in subsequent statistical analysis to compare degree of inflammatory food consumption between groups. This variable was also used in separate regression analyses to determine whether it predicted late stage CKD, high cholesterol, BMI, and eGFR, after controlling for factors that may contribute to the development of CKD and/or overall health. The following section presents the demographic profiles of individuals with late stage CKD and those without CKD and the results of the statistics analyses.

Results

There was nearly an equal number of male and female participants in the CHMS who did not have CKD (Table 7). Most of these participants were between the ages of 18 and 65, had completed post-secondary education, had a household income of $60,000/year or greater and were Caucasian. Nearly half of the participants without CKD had a BMI in the underweight/normal category, while the majority had not been diagnosed with diabetes, hypertension or high cholesterol at the time of the survey.

Over 4.6% of Canadians in the CHMS were not aware that they suffered from late stage CKD. This group of participants tended to be female, were older and had less education than individuals who did not have CKD, were Caucasian, and had a yearly household income below $60,000 (Table 7). Over half of participants with late stage CKD had a BMI in the overweight or obese categories, and had higher rates of diabetes and hypertension compared to the no CKD group. With the exception of sex, there were significant differences in all of the demographic categories mentioned between the no CKD and late stage CKD groups. Among individuals with late stage CKD, men tended to be younger and had been diagnosed with diabetes compared to women however, none of these differences were statistically significant (Table 8).

Table 7

Demographic Information for Individuals with Late Stage CKD and Without CKD

Characteristic	Weighted Prevalence (percent)		χ^2
	No CKD[a]	Late stage CKD[b]	
Sex			2.50
Males	52.13	43.30	
Females	47.87	56.87	
Age (Years)			717.60**
18-65	96.24	81.98	
66-79	3.76	18.02	
Education Level			19.32**
Less than secondary	10.09	25.30	
Secondary	22.74	17.44	
Post-secondary	67.18	57.26	
Yearly Household Income ($)			12.43*
0-19,999	6.26	12.94	
20,000-39,999	17.17	19.15	
40,000-59,999	20.22	27.20	
60,000-79,999	13.53	13.94	
80,000 and over	42.81	26.77	
Ethnicity			13.87**
Caucasian	74.78	92.64	
Other	25.22	7.36	
BMI Category			8.5*
Underweight/Normal	45.79	35.97	
Overweight	33.58	30.04	
Obese	20.64	33.99	
Diagnosed with Diabetes			46.86**
Yes	5.68	24.59	
No	94.32	75.41	
Diagnosed with Hypertension			
Yes	7.24	18.26	13.60**
No	92.76	81.74	
Diagnosed with High Cholesterol*			16.11**
Yes	28.29	49.73	
No	71.71	50.27	

Note. *p < .05 **p < .001 [a]No CKD = GFR in the normal range [b]late stage CKD=stages 3-5

Table 8

Demographic Information for Males and Females with Late Stage CKD

	Weighted Prevalence (%)	
	Males	Females
Age (Years)		
18-65	25.3	12.46
66-79	74.7	87.54
Education Level*	-	-
Yearly Household Income ($)*	-	-
Ethnicity*	-	-
BMI Category		
Underweight/Normal	39.79	33.11
Overweight	22.02	36.05
Obese	39.18	30.85
Diagnosed with Diabetes		
Yes	32.67	18.42
No	67.33	81.58
Diagnosed with Hypertension*	-	-
Diagnosed with High Cholesterol		
Yes	49.58	49.73
No	50.52	50.15

Note. *Sample sizes were too small to be released

C-Reactive Protein Levels and Dietary Inflammatory Index Scores

As hypothesized, individuals with late stage CKD had significantly higher mean C-reactive protein (CRP) levels and DII scores compared to individuals without CKD (Tables 9, 10). Women who did not have CKD, had a lower mean CRP level and a lower DII score compared to women who had late stage CKD (Tables 9, 10).

Table 9

T-test Results Comparing CRP Levels

Variable	*M*	*SD*	*t*
CKD Status			-193.45*
Individuals without CKD[a]	2.37	2.67	
Individuals with late stage CKD[b]	2.99	2.54	
Women			-112.09*
Without CKD	2.48	2.77	
With late stage CKD	3.00	2.72	
Men			-163.35*
Without CKD	2.25	2.56	
With late stage CKD	2.98	2.26	
Sex			-4.39*
Men with late stage CKD	2.98	2.26	
Women with late stage CKD	3.00	2.76	

Note. *p < .001 [a]No CKD = GFR in the normal range [b]late stage CKD=stages 3-5

Table 10

T-test results comparing DII scores

Variable	*M*	*SD*	*T*
CKD Status			-67.42*
Individuals without CKD[a]	0.66	2.14	
Individuals with late stage CKD[b]	.84	2.00	
Women			-28.91*
Without CKD	0.48	2.05	
With late stage CKD	0.58	2.15	
Males			-98.50*
Without CKD	0.83	2.21	
With late stage CKD	1.16	1.73	
Sex			120.38*
Men with late stage CKD	1.16	1.73	
Women with late stage CKD	0.58	2.15	

Note. *$p < .001$ [a]No CKD = GFR in the normal range [b]late stage CKD=stages 3-5

Similar findings were observed in men. Men who did not have CKD had significantly lower mean CRP levels and DII scores, compared to men with late stage CKD (Tables 9, 10). As hypothesized, men with late stage CKD also had significantly higher mean DII scores compared

to women with late stage CKD. In contrast, women with late stage CKD had slightly significant higher mean CRP levels compared to men.

In the general population, DII scores did predict eGFR after controlling for other factors and over half of the variance was explained by the model (Table 11). Separate linear regressions revealed that DII scores did not predict late stage CKD or eGFR in participants who reported a diagnosis of kidney issues after controlling for other factors.

Regression analysis revealed that DII scores did predict high cholesterol and BMI, even after controlling for other factors (Table 12, 13). That is, for every one-unit increase in the DII score, there was a 13% increased odds of having high cholesterol and a .21 unit increase in BMI, respectively.

Table 11

Unstandardized Coefficients and 95% Confidence Intervals for Predictor Variables of eGFR

Variable		B	SE (B)	95% CI
DII score		-0.57*	0.22	[-1.056, -0.08]
Education		-0.35	0.74	[-1.97, 1.28]
Total household income		-1.13*	0.37	[-1.95, -0.32]
Sex		0.77	1.34	[-2.19, 3.73]
Age		-0.85***	0.03	[-0.90, -0.79]
Ethnicity		6.93***	1.26	[4.16, 9.69]
BMI		-0.01	0.08	[-0.18, 0.16]
Statins		-1.50	1.70	[-5.26, 2.26]
Diabetes		-1.80	2.00	[-6.18, 2.58]
Constant		133.09***	3.47	[125.46, 140,73]
R^2	0.55			
F	104.77**			

*Note. *p < .05 **p < .01 *** p < .001*

Table 12

Odds ratios and 95% Confidence Intervals for Predictor Variables of High Cholesterol

Variable		OR	95% CI
DII score		1.13*	[1.03, 1.25]
Education		1.00	[0.80, 1.25]
Total household income		1.04	[0.88, 1.24]
Sex		0.77	[0.56, 1.08]
Age		1.05***	[1.03, 1.06]
Ethnicity		1.14	[0.56, 2.34]
Constant		0.03**	[0.01, 0.31]
F	9.58**		

*Note. *p < .05 **p < .01 *** p < .001*

Table 13

Unstandardized Coefficients and 95% Confidence Intervals for Predictor Variables of BMI

Variable		B	B (SE)	95% CI
DII score		0.21*	0.09	[0.02, 0.41]
Education		-0.58	0.27	[-1.16, 0.01]
Total household income		-0.08	0.17	[-0.45, 0.30]
Sex		-0.55	0.41	[-1.46, 0.35]
Age		0.04**	0.01	[0.02, 0.07]
Smoking		-0.61	0.46	[-1.62, 0.41]
Ethnicity		-1.66*	0.71	[-3.23, -0.11]
Constant		30.07***	1.16	[27.50, 32.61]
R^2	0.04			
F	7.90*			

*Note. *p < .05 **p < .01 *** p < .001*

Table 14 summarizes the results and indicates whether or not the hypotheses of the current study were supported.

Table 14

Summary of the Current Hypotheses and Results

Hypothesis	Results Support Hypothesis
1. Individuals with undiagnosed late stage CKD will have a significantly higher mean consumption of proinflammatory compared to those without CKD	Yes, individuals with late stage CKD had significantly higher mean DII Scores (higher proinflammatory food consumption)
2. Males with undiagnosed, late stage CKD will have a significantly higher mean consumption of proinflammatory compared to females	Yes, males with late stage CKD had significantly higher mean DII Scores (higher proinflammatory food consumption)
3. Individuals with undiagnosed CKD will have a significantly higher mean high sensitivity C-reactive protein level compared to those without CKD	Yes, individuals with late stage CKD had significantly higher mean CRP scores
4. Males with undiagnosed, late stage CKD will have a significantly higher mean high sensitivity C-reactive protein level compared to females	No, females had significantly higher mean CRP levels
5. DII scores predict the presence of late stage CKD after controlling other factors	No
6. DII scores predict BMI	Yes. As DII scores increased, BMI also increased
7. DII scores predict high cholesterol	Yes. As DII scores increased, the risk of high cholesterol also increased
8. DII scores predict eGFR in the general population	Yes. As DII scores increased, eGFR decreased
9. DII scores predict eGFR in individuals who reported being diagnosed with a kidney problem	No

In the following section, a discussion on the participant profile in the current study is compared to profiles reported in other CKD studies. Noteworthy differences between participants with late stage CKD and those without CKD and the possible implications of these differences, are highlighted. The current study's findings and contribution to the current body of

knowledge on inflammation and CKD is explored. The variation in the findings between the sexes who had late stage CKD are also discussed.

Discussion

The overall objective of the present study was to examine proinflammatory food consumption in Canadians with late stage CKD, as well as the relationship between proinflammatory food consumption and GFR. In this current study, the CHMS-Cycle 3 revealed that over 4.6% of the Canadian population or 660,000 individuals had late stage CKD. This prevalence rate is lower than the global mean CKD prevalence rate of 10.6% (Hill et al., 2016). Two possible reasons for the lower prevalence rate in Canada compared to the global mean prevalence rate are the exclusion of Aboriginals who live on reserve and of individuals who live in long-term care facilities. It is possible that if Aboriginal people who live on reserves had been included in the CHMS, the prevalence rate may have been even higher, since a third of Aboriginals in Canada live on reserve, and the rate of late stage CKD is twice as high when compared to non-Aboriginal Canadians (Statistics Canada, 2015b; Yeates & Tonelli, 2010). Late stage CKD rates are also high among those who live in long-term facilities (Bailey, Higa, Reardon, & Bailey, 2010; Dharmarajan, Banik, Kanagala, Scarpa, & Norkis, 2010). Other studies found that almost half of individuals in long-term care facilities had late stage CKD (Dhamarajan el at., 2010; McClellan et al., 2010). However, individuals in long-term care facilities were also excluded from participating in the CHMS- Cycle 3 (Statistics Canada, 2015a). Their inclusion may have resulted in a slight increase in the prevalence rate of late stage CKD in Canada than what was observed.

A significant number of individuals with late stage CKD in the present study were found to have comorbid conditions such as diabetes, hypertension and high cholesterol. This figure is likely to increase as the rates of diabetes, hypertension and other CKD risk factors continue to rise (Arora et al., 2013). CKD has a negative impact on an individual's quality of life and

increases their risk of mortality (McFarlane et al., 2013). Research suggests that modifying lifestyle factors such as diet may help to slow the progression of CKD and reduce the likelihood of mortality that is associated with late stage CKD (Huang et al., 2013; Ricardo et al., 2015).

Participant Profile

Participants in the current study who had late stage CKD tended to be older and had a higher BMI as well as higher rates of other chronic conditions (e.g., hypertension, diabetes) than those who did not have CKD. These results are consistent with previous research that examined the prevalence rate of CKD in Canada and are similar to studies in other countries such as the United States of America and the United Kingdom, (Arora et al., 2013; Murphey et al., 2016; Stevens et al., 2007).

In the current study, the higher proportion of individuals over 66 years of age in the late stage CKD group was in keeping with studies that have reported an association between age and higher rates of CKD (Hill et al., 2016; Glassock & Winearls, 2009). As noted earlier, a slight decline in GFR occurs as part of the aging process but it is not indicative of disease whereas, late stage CKD involves a significant decline in renal function (Glassock & Winerals, 2009; Young, 2010). The higher rate of late stage CKD in older adults, is likely a result of the higher number CKD risk factors observed in this age group, rather than as result of the aging process (McMahon, Preis, Hwang, & Fox, 2014; Prakash & O'Hare, 2009).

McMahon et al. (2014) found that individuals who had chronic conditions (e.g., hypertension, diabetes) and were obese, were more likely to develop CKD than those without chronic conditions. In addition, Prasad et al. (2012) suggested that chronic diseases (e.g., cardiovascular disease, type 2 diabetes) tend to develop in older adults, as a result of the cumulative effects of a poor lifestyle (e.g., smoking, consuming a high fat diet etc.). It is not

surprising then, that individuals with CKD tend to have multiple health conditions, in addition to their CKD diagnosis (Fraser et al., 2015; Keith, Nichols, Gullion, Betz Brown, & Smith, 2004). Keith et al. (2004) conducted a longitudinal study with over 11,000 Americans and found that over half of the study's participants with CKD had comorbidities (e.g., hypertension, diabetes) at baseline compared to just over a quarter of the non-CKD control group (Keith et al., 2004). Finally, Fraser et al. (2015) reported that nearly 70% of participants with stage 3 CKD, in the *Renal Risk in Derby Study* had two or more comorbid conditions. Comorbidity in CKD increased the risk of death even when compared to individuals who had the same comorbidities but did not have CKD (Fraser et al., 2015; Tonelli et al., 2006). For these reasons, future public health interventions should place a greater focus on controlling hypertension and other chronic diseases that are risk factors for CKD.

Sex Differences and Chronic Kidney Disease

In the current study, the slightly higher rate of late stage CKD among women was consistent with a number of other studies (Arora et al., 2013; Goldberg & Krause, 2016; Hill et al., 2016; Murphey et al., 2016). A recent meta-analysis found that women had a higher rate of late stage CKD compared to men in three-quarters of the studies that reported prevalence by s (Hill et al., 2016). Studies that have examined the progression of CKD to end stage renal disease (ESRD) (identified by the use of RRTs), frequently reported a slower rate of progression in women (Cobo et al., 2016; Iseki, 2008). It was not possible to determine the rate of ESRD in the present study because information on dialysis and other ERSD treatments was not collected; therefore, further research on this topic is warranted.

A noteworthy finding was that men with late stage CKD had mean DII (i.e., proinflammatory food consumption) scores that were higher than women with late stage CKD.

This result is similar to previous research in both non-CKD and CKD populations, where men were found to have worse diets compared to women (Cobo et al., 2016; Imamura et al., 2015; Von Bothmer & Fridlund, 2005); men typically tended to have a higher meat consumption and have a more energy dense diet compared to women (Goldberg & Krause, 2016; Leblanc, Bégin, Corneau, Dodin, & Lemieux, 2014). Evidence indicated that there was a link between a poor diet (high animal protein consumption, low fruit/vegetable consumption, etc.), increased albumin (protein) excretion, and declines in GFR (Hariharan, Vellanki, & Kramer 2015).

In contrast, other research suggested that antioxidants, such as those found in fruits and vegetables, could help to slow the progression of CKD, into renal failure and even improve renal function (as measured by creatinine clearance) (Jun et al., 2012). The findings of the current study provide further weight to the hypothesis that diet is an important factor in CKD, progression in men and women. Further research that explores the long-term effect of proinflammatory food consumption on CKD progression, in both sexes is needed.

Socioeconomic Status, Chronic Kidney Disease, Diet

Another important factor in the development and progression of CKD is socioeconomic status. As mentioned, there were significant differences between socioeconomic factors such as education and income between the groups without CKD and those with late stage CKD. Previous research has linked socioeconomic factors to dietary habits and health (Dynesen, Haraldóttir, Holm, & Astrup, 2003). A recent meta-analysis reported an association between low socioeconomic status and CKD indicators such as low GFR, presence of albuminuria and even renal failure (Vart, Gansevoort, Joosten, Bültmann, & Reinjneveld, 2015). Individuals with a low socioeconomic status have a greater difficulty not only affording healthy foods but also accessing them when compared to individuals with a higher socioeconomic status (Suarez et al.,

2015). Suarez et al. (2015), reported that limited access to grocery stores was associated with higher blood pressure levels and increased odds of CKD among Americans. Unfortunately, it was not possible to examine whether participants in the present study lived in areas where nutritious foods were affordable and accessible. Further, Mikkonen and Raphael (2010) listed socioeconomic factors (e.g., income, education) along with food insecurity, the inability to obtain sufficient and/or nutritious food, as major determinants of health in Canada, which may make the results of the Suarez et al. (2015) study applicable to a Canadian population.

C-Reactive Protein Levels

CRP is a biomarker that is commonly used to measure the level of inflammation in the body, and an elevated CRP level is associated with inflammatory diseases including CKD (Ansar & Ghosh, 2016). As expected, the mean CRP levels were higher among individuals with late stage CKD than those without CKD. This finding may reflect the lower levels of antioxidants consumption, presence of comorbid diseases (especially other inflammatory conditions such as diabetes and cardiovascular disease) and "[the] decreased clearance of proinflammatory cytokines [resulting from] decreases in renal function", that are often present in individuals with late stage CKD (Krovesdy & Kalantar-Zadeh, 2010, p. 185; Silverstein, 2009).

Findings of higher CRP levels in participants with late stage CKD may also be related to the higher overweight and obese BMI rates observed in this group. As discussed earlier, obesity is thought to promote inflammation in the body through the production of the proinflammatory cytokine TNF-α (Dandona, Aljada, & Bandyopadhyay, 2004). Hotamisligil, Shargill, and Spiegelman (1993) provided the first evidence of a link between TNF-α and insulin resistance, with the demonstration that a decrease in TNF-α in obese mice decreased insulin resistance. More recently, research in humans found a similar association between obesity, insulin resistance

and decreased TNF-α levels after weight-loss (Dandona et al., 2004). This effect is likely related to the anti-inflammatory activities of insulin (Dandona, Chaudhuri, Mohanty, & Ghanim, 2007). Insulin prevents the production of reactive intermediates that may damage tissues and may also decrease CRP levels (Dandona et al., 2007).

Mean CRP levels were also higher among females compared to males with late stage CKD. Evidence suggests that women tend to have higher CRP levels compared to men, even when they do not have late stage CKD (Khera at al., 2005; Kubo et al., 2016; Lakoski et al., 2006; Oliveira, Rodríguez-Artalejo, & Lopez, 2009). Further, unlike in men, CRP levels in women tend to be higher irrespective of their dietary habits, particularly fruit and vegetable consumption (Brighenti et al., 2005). A review of the literature failed to provide a definitive explanation for this phenomenon. That said, Cartier et al. (2009) suggested that the higher levels of adipose tissue in women compared to men could explain the differences in CRP levels. In the present study, women with late stage CKD did have higher BMIs than men but this difference was not statistically significant, and adipose specific measurements were not available in the CHMS. Even though inflammation has been implicated in the development of CKD (Gobal et al., 2011), additional research that examines the mechanisms behind the sex differences and CRP levels, particularly in individuals with late stage CKD, is needed. Such research may lead to sex specific interventions that reduce inflammation and therefore, the risk of developing CKD.

Proinflammatory Food Consumption and Chronic Kidney Disease

As expected, proinflammatory food consumption as measured by the DII was higher among individuals with late stage CKD than those without CKD. These results are similar to recent studies that examined DII scores of individuals with other inflammation-related diseases (Ramallal et al., 2015; Wood et al., 2014). Wood et al. (2014) reported, that asthmatics in their

study had a significantly higher DII score than the non-asthmatic control group. Cardiovascular disease, another inflammation-related condition, was related to proinflammatory DII scores (Ramallal et al., 2015); as such, the current study's findings provide further evidence of a possible link between proinflammatory diets and inflammation-related diseases such as CKD.

A weighted, non-bootstrapped logistic regression revealed that DII scores did predict the presence of late stage CKD; however, these results were not significant after bootstrapping. This finding may be related to the proportional weighting used in STATA's bootstrapping method. As mentioned, to ensure that the survey is representative of the Canadian population, each participant's responses are assigned a weight based on the number of people their responses represented (Statistics Canada, 2015a). However in STATA, a proportional weight is applied when bootstrapping, to address the likelihood (or probability) that the participant will be included in the survey (Heeringa, West, & Berglund, 2010; STATA, 2013). This proportion can be problematic in smaller samples because it essentially reduces the sample size even further (Heeringa et al., 2010). The significant differences in the mean consumption of proinflammatory food between individuals with late stage CKD compared to those without CKD and the significant weighted, non-bootstrapped logistic regression that predicted late stage CKD are indications that a larger sample size was likely required.

Proinflammatory Food Consumption and Chronic Kidney Disease Risk Factors

In the present study, proinflammatory food consumption predicted an increase in BMI as well as the presence of high cholesterol. Research indicates that BMI is associated with the development of CKD (Nomura, Kato, & Kitamura, 2009; Yamagata et al., 2007). Additionally, a higher BMI was associated with a greater decline in GFR, increased risk of stage 4-5 CKD in women, and a higher mortality rate in some individuals with CKD (Harrington et al., 2017; Lu, Kalantar-Zadeh, Ma, Quarles, & Kovesdy, 2014; Yamagata et al., 2007).

Evidence suggests that high cholesterol is also a risk factor for the development of CKD and that both BMI and cholesterol are risk factors for coronary heart disease in individuals with CKD (Munter, He, Astor, Folsom, & Coresh, 2004; Yamagata et al., 2007). This evidence is significant because individuals with CKD are at a greater risk of cardiovascular related deaths (Tonelli et al., 2006). The present study's findings suggest that DII scores may have an indirect impact on the development, progression and mortality risk in individuals with CKD.

Dietary Inflammatory Index Scores and Estimated Glomerular Filtration Rate

DII scores predicted eGFR in the general population, even after controlling for other factors. This finding is similar to Lin, Fung, Hu, and Curhan's 2011 study that reported a link between consumption of a Western diet and an increased risk of rapid GFR decline whereas, a diet rich in vegetables and fruits was associated with a decreased risk of rapid GFR decline. The present study's findings provide further evidence of a link between diet and kidney function. Xu et al. (2015) suggested that diet may impact the level of inflammation in the body, and thus could affect kidney function. Of the socioeconomic factors that were controlled for in this regression, only household income was significant. As mentioned, income is a major determinant of health in Canada and was linked to other health determinants such as food security (Mikkonen & Raphael, 2010). Research using the Family Food Expenditure Survey found that lower income families in Canada, tended to buy foods that were less nutritious (i.e., higher in fat, salt) and purchased less fresh fruit and vegetables than families who had higher incomes (Milway, Chan, Stapleton, & Cook, 2010). As discussed, socioeconomic status can impact whether or not someone has convenient access to sufficient, nutritious food and diet can impact chronic health conditions (Mikkonen & Raphael, 2010). Results of the present study suggest that public health interventions should include measures to ensure that low income families are able access to

healthy foods, like fresh fruits and vegetables, in order to reduce the risk of developing chronic conditions such as CKD.

In this study, a weighted non-bootstrapped linear regression showed that DII scores predicted eGFR in individuals who reported being diagnosed by a health professional as having kidney dysfunction or disease; however, this finding was nonsignificant after bootstrapping. With respect to the results for DII scores and late stage CKD, this result finding is likely the result of proportional weighting and a small sample size, an indication that a larger sample was required.

Current evidence-based dietary recommendations for people with kidney issues such as CKD tend to focus on reducing protein consumption (particularly animal-based protein sources), controlling dairy consumption (in advanced CKD), restricting sodium intake, limiting phosphate intake (found in animal protein, carbonated drinks, chocolate, legumes etc.) and supplementing nutrients as needed (e.g., B_{12}, iron) (Chan, Kelly, & Tapsell, 2016; National Kidney Foundation, 2013). However, diet quality is not clearly emphasized despite the growing body of literature that suggests it is an important consideration (Rouhani et al., 2016). As noted by Kant (1996), the consumption of a particular nutrient, food or food component does not occur in isolation therefore, to focus on the effect of that a nutrient, food or food component on a specific health outcome, without sufficiently considering the wider diet, may result in an incomplete picture (Kant, 1996). The DII was designed to produce a score that categorized an individual's overall diet on a continuum from anti-inflammatory to pro-inflammatory, providing researchers another method to assess diet quality (Cavicchia et al., 2009).

In summary, the present study is the first to this author's knowledge that examined diet quality in terms of its potential inflammatory effect in individuals with late stage CKD. As

mentioned, evidence suggests that inflammation influences the progression of CKD (Silverstein, 2009). Future research should examine whether adherence to a low-inflammatory diet, as measured by the DII, addresses some of the nutrition-related health concerns associated with late stage CKD such as insufficient vitamin intake (e.g., anemia) and excess mineral consumption (e.g., hyperkalemia) (Chan et al., 2016). This research could lead to improved dietary interventions that are more successful at reducing CKD progression and mortality while ensuring individuals with CKD maintain an adequate nutritional status.

Significance of the Current Study

This study added to the existing body of knowledge on CKD and nutrition by exploring a possible link between proinflammatory food consumption and late stage CKD in a nationally representative sample, a subject that to this author's knowledge has not been examined in a Canadian population. Further, this is study is only one of two studies to date, that used the DII to examine proinflammatory consumption in relation to kidney function. This study also explored sex differences in late stage CKD and is one of few studies that has looked at this topic in a Canadian population. This research supports the findings of studies that examined the relationship between inflammation, diet, and CKD. Finally, this study could ultimately lead to novel nutritional interventions that are aimed specifically at preventing CKD.

Conclusion and Implications

The objectives of the present study were to examine the mean consumption of proinflammatory foods and CRP levels between individuals with late stage CKD and those without CKD. The present study provides further evidence that diet is an important factor in the link between inflammation and CKD. An "unhealthy" diet (e.g., low in fruit and vegetable consumption or high in fried foods) can influence CKD progression (Hariharan et al., 2015; Turner-McGrievy et al., 2015). In addition, an unhealthy diet tends to have a high or pro-inflammatory DII score, tends to be low in antioxidants, promotes the generation of reactive intermediates and leads to oxidative stress (Fernández-Sánchez et al., 2011; Hodge et al., 2016; Seaman, 2002; Steck et al., 2014; Turner-McGrievy et al., 2015). As mentioned, oxidative stress is involved in CKD risk factors (e.g., BMI), the progression of CKD, and lifestyle choices such as smoking that lead to CKD (Curat et al., 2006; Orth, 2003; Synder et al., 2014; Tucker, Scanlan, & Dalbo, 2015). For these reasons, the present study lends further weight to the idea that there could be an interconnection between diet, oxidative stress, and CKD and makes the case for further research into this area.

The present study also aimed to explore the link between proinflammatory food consumption (represented by the mean DII score) and CKD risk factors. DII scores predicted BMI and the presence of hypertension, two risk factors for CKD (James et al., 2010; Wang et al. 2008). Unsurprisingly, there is mounting evidence that a high BMI and hypertension are associated with lower diet quality and the current study's findings support this link (Livingston & McNaughton, 2016; Newby et al., 2003; Sundararajan, Campbell, Choi, & Sarma, 2014).

Participants in the current study who did not have CKD, had lower mean DII scores and therefore, consumed a diet that was less inflammatory than the mean score of participants who had late stage CKD. A review by Wirt and Collins (2009) found that the consumption of a high

quality, diet as measured by either the Healthy Eating Index or adherence to national recommendations, was associated with a lower risk of diseases such as CVD and mortality. More recently, anti-inflammatory (i.e., low) scores on the DII were associated with better scores on other measures of diet quality (Wirth et al., 2016). Although causation cannot be inferred from the current study's results, it does provide further evidence that the DII is a valuable measure of diet quality. More specifically, a diet that is high in fruit and vegetables and lower in meat consumption was associated with a lower DII score and decreased odds of having an unhealthy eGFR (Steck, 2014). A low DII score is similar to the Canada's Food Guide recommendations that emphasize the consumption of fruit and vegetables, fish, meat alternatives and limit the intake of fat and salt (Health Canada, 2011; Khatri et al. 2014). The current study's finding, that eGFR decreases as DII scores increases even after controlling for factors that are associated with eGFR, suggests that current healthy eating recommendations for the general population are beneficial and that new healthy eating guidelines are not required. That said, more should be done to promote the consumption of an anti-inflammatory diet (as measured by the DII). For example, the scoring algorithm could be incorporated into current diet assessment tools or developed as a standalone application (APP) for use by the public.

Another objective of the current study was to examine the difference in the mean consumption of proinflammatory foods between males and females with undiagnosed late stage CKD. Findings in this study demonstrated that males consumed a more inflammatory diet than females, providing a possible explanation for males' faster CKD progression as observed in some studies (Chang et al., 2016; Cobo et al., 2016).

Finally, the current study highlights the importance of food literacy, food security and socioeconomic status in CKD. Having a low socioeconomic status creates barriers such as

accessing healthy and affordable food and supermarkets (Suarez et al., 2015). As discussed, food security is major determinant of health in Canada and is associated with increased odds of developing CKD (Mikkonen & Raphael, 2010; Suarez et al., 2015). Consistent with previous research, the present study noted that individuals with late stage CKD tended to have a lower socioeconomic status (i.e., less education and household income) than individuals without CKD (Nicholas, Kalantar-Zadeh, & Norris, 2015; Suarez et al., 2015). Although attempts have been made to address food insecurity, awareness of another related issue, food literacy (i.e., skills and knowledge needed to prepare foods that promote health) and its impact on health has not been emphasized (Cullen, Hatch, Martin, Higgins, & Sheppard, 2015; Howard & Brichta, 2013). Cullen et al. (2015), stated that both food security and food literacy contribute to an individual's health. Food illiteracy is not exclusive to those with a lower socioeconomic status; however, it can present an additional barrier to preparing a healthy diet (Howard & Brichta, 2013). Howard and Brichta (2013) established a connection between food literacy and diet quality; therefore, it is possible that having poor food literacy could impact the amount of proinflammatory foods that are consumed. There is a paucity of research examining the effect of food security and literacy on CKD, particularly in Canada. Research is also needed to better understand the relationship between food security, food literacy and proinflammatory food consumption.

In the future, health strategies aimed at reducing the incidence of CKD and its progression should consider the possible the link between inflammation and diet. The promotion of "healthy" diets such as the Mediterranean diet, could help to decrease the consumption of proinflammatory food. That said, additional research is needed to determine the effect of consuming an anti-inflammatory diet, as measured by the DII, on CKD.

Limitations and Future Research

There are several limitations to the current study. First, survey participants were not asked about their onion, garlic, spice, and herb consumption nor were they asked about serving sizes; therefore, it is possible that their diets were slightly more or less inflammatory than could be assessed. An in-depth analysis of participants' diet would have needed to be collected in order to provide this additional information. Moreover, consumption data in the CHMS – cycle 3 were collected via self-reports therefore, participants' recall of their food intake may not be entirely accurate. Second, the survey's cross-sectional design means that causation cannot be inferred; in other words, a more controlled study (e.g., an animal study) would be required to show that the consumption of proinflammatory foods causes CKD. Third, it is possible that genetics may play some role in the interaction between diet, inflammation, and CKD, and this potential effect could not be examined in the CHMS – Cycle 3.

Finally, only individuals living off reserve and in one of the 5 regions of Canada were surveyed; therefore, the results may not be fully representative of individuals living on-reserve or in one of the three territories. Individuals living on reserve or in Northern regions tend to have different dietary habits than those living off reserve or in the Southern regions (Council of Canadian Academies, 2014). For instance, traditional foods (e.g., caribou) made up to 30% of the diet of Aboriginals living in Northern regions (Council of Canadian Academies, 2014). Aboriginals are more likely to have end-stage renal disease (ESRD); among those with ESRD, Aboriginals are typically younger and have higher rates of obesity and diabetes and live in remote locations than those of other ethnic backgrounds (CIHI, 2013). It is important that future research includes Aboriginals living on reserve or in remote locations, to better understand the impact that proinflammatory food consumption may have in the development and progression of CKD in this population.

The present study identified several areas that warrant further research. Sex differences in late stage CKD and inflammation are not well characterized. The impact that a proinflammatory diet could have on CRP levels and other inflammatory biomarkers and CKD progression in men and women needs to be explored. A better understanding of the interaction between sex, inflammation, and a proinflammatory diet could lead to sex-specific dietary recommendations.

Another area that needs additional research is diet quality and CKD. In particular, how dietary recommendations that focus on diet quality (as measured by indices such as the DII), impact CKD. In addition, exploring the inflammatory nature of current dietary recommendations for individuals who have ESRD would also be useful. Dietary interventions that better balance the nutritional needs and physiological issues of individuals with CKD would be beneficial.

It may also be useful to examine how scores on the DII relate to established healthy eating indices, such as Diet Quality or the Health Diet Indicator; research indicates that a "good score" on these established health eating indices was associated with decreased risk of mortality and illness (e.g., cancer) (Wirt & Collins, 2009).

Research that examines the intersection of both food literacy and food security on CKD is also needed. Evidence-based public health programs that improve food literacy and security for individuals with CKD could not only improve CKD outcomes, but also reduce the financial burden of CKD on the healthcare system. Future studies on CKD, inflammation and proinflammatory food consumption should include biomarkers of oxidative stress to better understand the effect proinflammatory food consumption in individuals with CKD. Finally, the development of a survey that includes both individuals who are at a high risk of developing CKD and individuals who have any stage of CKD and comprises a wide range of demographic,

lifestyle, food security, food literacy, and diet-related variables, would be beneficial to researchers and would help to advance the current understanding of the impact diet has on CKD.

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