Examining the Impact of Behavioral Weight Loss and Increased Water Intake on Kidney Health in Adults Aged 50+ with Stage 1 or 2 Cardiovascular Kidney Metabolic (CKM) Syndrome

Shahed Sanuri

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Brenda M. Davy, Chair

Kevin P. Davy

Aubrey L. Knight

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Academic Abstract

Cardiovascular-Kidney-Metabolic (CKM) syndrome is a recently defined framework that describes the interdependent progression of cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic syndrome (MetS).[1 2] With an estimated 90% of U.S. adults meeting criteria for Stage 1 or higher CKM and a considerable proportion silently progressing to higher stages without detection, the urgency of early prevention and treatment strategies becomes critical.[3 4] Traditional approaches to these conditions are often diagnosed and treated separately, but their shared pathophysiology across the cardiovascular, renal, and metabolic processes creates a threatening cycle that calls for integrated solutions. The syndrome describes how similar underlying factors, such as inflammation, hypertension, and metabolic dysfunction, contribute to these conditions.[5] This thesis examines the effects of behavioral weight-loss intervention (hypocaloric diet and physical activity) combined with prescribed water intake on early biomarkers of kidney health in adults aged 50 years and older with Stage 1 or Stage 2 CKM, defined by excess adiposity or metabolic and chronic kidney disease risk factors, respectively. By combining weight management with hydration, this work aims to investigate a non-pharmacological approach to preventing and slowing CKM progression. It reorients the traditional pharmacological methods to disease treatment toward a more holistic approach, inspired by behavioral changes as the prescription for disease prevention. Using de-identified data from a randomized controlled trial (NCT05843318), participants (n=125; water group = 87; control group = 38) were randomized to one of three groups for a 12-week intervention trial: a hypocaloric diet with prescribed water intake (1500 mL/day; two water groups which only differed in timing of intake and were collapsed for this analysis) or a hypocaloric diet alone without prescribed water intake. The primary outcome of this study is the urinary albumin-to-creatinine ratio (uACR), a key biomarker of kidney health. The secondary outcomes are renal biomarkers and hydration status assessed using 24-hour urine samples for volume, osmolality, and specific gravity. Exploratory cardiometabolic outcomes include fasting blood glucose, blood lipid panel, blood pressure, heart rate, BMI, weight, and waist circumference. Analysis of covariance (ANCOVA) was used to evaluate group differences in outcomes. For the primary outcome, uACR did not differ significantly between the water and control groups ($p = 0.53$). Secondary renal and cardiometabolic outcomes did not demonstrate significant differences between the groups, except for hydration-related measures of urine osmolality ($p = 0.02$), specific gravity ($p = 0.01$), and 24-hour urine volume ($p = 0.01$), which improved in the water group. Both groups experienced reductions in body weight (water: -4.5 ± 3.5; control: -4.8 ± 3.0 kg), although the reductions did not differ statistically between groups ($p = 0.55$). Notable improvements were observed in CKM stage regression in both groups (water: 42.53%; control: 42.11%); however, these changes were not statistically significant between groups and warrant further research ($p = 0.85$). This research contributes to a broader vision of disease and/or syndrome prevention that prioritizes lifestyle interventions to reduce disease burden and improve quality of life.

Examining the Impact of Behavioral Weight Loss and Increased Water Intake on Kidney Health in Adults Aged 50+ with Stage 1 or 2 Cardiovascular Kidney Metabolic (CKM) Syndrome

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General Audience Abstract

Cardiovascular-Kidney-Metabolic (CKM) syndrome describes how heart disease, kidney disease, and metabolic syndrome (e.g., obesity, diabetes, hypertension) are interconnected and negatively influence one another.[1 2] Because of the high rates of obesity in the United States, it can be inferred that individuals with excess adiposity may be classified as having early-stage CKM syndrome.[2] The reality is that many of them are unaware of their condition because recognition of it by the American Heart Association is very recent.[2] Aside from the growing demand for public awareness of the syndrome, exploring simple and effective treatment strategies is important. This study examined whether lifestyle changes, such as weight loss and increased water intake, can improve early signs of kidney health and reduce the risk of CKM progression. The study used data from a 12-week randomized controlled trial of adults aged 50 and older who were assigned to either a reduced-calorie diet with more daily water intake or a reduced-calorie diet alone (without the daily water intake prescription). The goal of this research was to investigate a practical, non-pharmacological approach to improve kidney health in adults with early-stage CKM. Kidney health markers, hydration levels, and other health measures such as blood pressure, blood sugar, and body weight were also examined. The results of the study indicated that although participants successfully lost weight and increased their water intake, these actions did not lead to measurable differences between the two groups in kidney-related outcomes over the 12 weeks. The findings imply that improving early kidney biomarkers may require a longer period or more targeted interventions. The research in this study continues to support the idea that everyday behavioral changes play a crucial role in preventing disease progression. This thesis still seeks to convey the ongoing need for research on preventing CKM progression.

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Free Palestine.

Table of Contents

Chapter 1: Introduction **1**

Chapter 2: Literature Review **4**

Chapter 3: Manuscript **27**

Chapter 4: Conclusion and Future Directions **54**

References **56**

Appendices **63**

List of Figures

Figure 1. Progression of CKM syndrome. 11

Figure 2. Conceptual diagram of CKM pathophysiology. 12

Figure 3. Kidney nephron anatomy 18

Figure 4. CONSORT flow diagram of participant enrollment, allocation, follow-up, and inclusion in the completers-only analysis 41

List of Tables

Table 1. Stages of Cardiovascular Kidney Metabolic (CKM) syndrome 5

Table 2. CKM Prevalence in U.S. Adults 7

Table 3. Research addressing CVD risk in relation to CKM syndrome 14

Table 4. ACSM cardiovascular disease risk assessment: positive and negative risk factors 15

Table 5. Protocol summary: participant testing, biological measurements, and assessments across the 12-week intervention testing period 36

Table 6. Outcome variables, clinical thresholds, and measurement methods of the examined biomarkers 39

Table 7. Variable analysis for combining the two water intervention groups 1 and 2 40

Table 8. Baseline participant characteristics 43

Table 9. Kidney and cardiometabolic health variables at baseline and 12 weeks of intervention in water vs. control groups 45

Table 10. Self-reported adherence to intervention diet and PA outcomes at baseline and week 12 47

Table 11. Changes in CKM Stage Classification over 12 Weeks 48

List of Abbreviations

ACR	Albumin-to-Creatinine Ratio
AHA	American Heart Association
ANCOVA	Analysis of Covariance
ASCVD	Atherosclerotic Cardiovascular Disease
AVP	Arginine Vasopressin
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
BUN	Blood Urea Nitrogen
CAC	Coronary Artery Calcification
CDC	Centers for Disease Control and Prevention
CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CKM	Cardiovascular Kidney Metabolic Syndrome
CMP	Complete Metabolic Panel
CVD	Cardiovascular Disease
DASH	Dietary Approaches to Stop Hypertension
DESIR	Data from an Epidemiological Study on the Insulin Resistance Syndrome
DII	Dietary Inflammation Index
eGFR	Estimated Glomerular Filtration Rate
GBM	Glomerular Basement Membrane
HbA1c	Hemoglobin A1c
HDL-C	High-Density Lipoprotein Cholesterol
HF	Heart Failure
KDIGO	Kidney Disease Improving Global Outcomes
LDL-C	Low-Density Lipoprotein Cholesterol
Lp(a)	Lipoprotein (a)
METs	Metabolic Equivalents
MetS	Metabolic Syndrome
MI	Myocardial Infarction
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
OGTT	Oral Glucose Tolerance Test
PAD	Peripheral Artery Disease
RAAS	Renin-Angiotensin-Aldosterone System
SDOH	Social Determinants of Health
SGLT2	Sodium-Glucose Co-Transporter 2
SO	Serum Osmolality
SNS	Sympathetic Nervous System
TyG-BMI	Triglyceride-Glucose Body Mass Index
uACR	Urine Albumin-to-Creatinine Ratio

Chapter 1: Introduction

MOTIVATION

The prevalence of overweight and obesity (40.3% obesity rate in 2025) has been concerningly increasing among adults in the United States.[6] What is largely unknown to most of the public is that individuals who fall in the overweight or obese BMI classification would, under the American Heart Association staging guidelines, be classified as having Stage 1 Cardiovascular-Kidney-Metabolic (CKM) syndrome.[2] If these individuals remain undiagnosed, their bodies undergo physiological changes in response to the accumulation of adipose tissue and the formation of visceral fat around their internal organs, thereby increasing cytokine release and triggering chronic, low-grade inflammation.[7] This, in turn, contributes to oxidative stress in the kidneys, forcing hyperfiltration and thereby reducing renal function.[7] These physiological alterations manifest as measurable kidney abnormalities across key clinical biomarkers. The resulting inadequately filtered blood then circulates back to the heart, increasing the risk of cardiovascular complications. The individual's body is thereby caught in a vicious cycle that elevates the risk of developing kidney disease, heart disease, and worsening metabolic dysfunction.[2 5]

These three conditions are often not recognized as components of an interconnected system that requires parallel treatment. Standard treatment approaches typically rely on pharmacologic therapies that target specific symptoms.[2 5] Such approaches do not necessarily prevent the progression of related pathophysiological symptoms because the body's compensatory responses to these abnormalities may persist.[8] Further research needs to raise awareness within healthcare systems and the broader community, promoting a more holistic approach to treatment and prevention, especially in the early stages of disease progression.[1 2] Individuals who are currently in Stage 1 CKM, caused by excess adiposity, or in Stage 2, driven by increased metabolic syndrome and chronic kidney disease risk factors, still retain a critical window of time and opportunity to address the underlying drivers of the syndrome before its progression.[9] Once individuals progress to advanced stages, the likelihood of reversibility is

significantly reduced. At this point, the approach is to shift toward disease management, with the intention of maintaining function and slowing further progression.

A common barrier for some individuals caught in this cycle stems from the social determinants of health (SDOH) that impede their well-being.[1] Some of these SDOHs are highlighted in this thesis, including limited public awareness, healthcare costs, and research gaps. Most of these barriers cannot be addressed by individuals; rather, we, as researchers and future physicians, have a duty to work toward system change in the best interests of the public and our patients. The CKM syndrome, introduced earlier in this text, is a recently defined framework, introduced in 2023, that provides a comprehensive model describing the interconnectedness of cardiovascular, kidney, and metabolic conditions through shared pathophysiological mechanisms.[1 2] Its recent introduction by the AHA helps explain the current lack of widespread awareness, but given the syndrome's severity, there is a call to action to prioritize awareness.

CKM is characterized by four progressive stages, beginning with individuals who are overweight or obese (Stage 1), progressing to early CKD and metabolic syndrome (Stage 2), advancing to subclinical CVD (Stage 3), and ultimately developing into clinical CVD (Stage 4a), with the potential of end-stage CKD (Stage 4b).[1 2] Individuals who fall within this spectrum, especially in the early stages, may benefit significantly by approaching their syndrome with the intention of implementing lifestyle behavioral changes to reverse and prevent further progression. This thesis aims to examine the effects of a 12-week behavioral weight-loss intervention combined with increased water intake (1500 mL/day) on early kidney biomarkers in adults aged 50 years and older with Stage 1 or Stage 2 CKM syndrome. The primary hypothesis was that participants prescribed the combined intervention would show a reduction in urinary albumin-to-creatinine ratio (uACR) over 12 weeks compared with participants prescribed the behavioral weight-loss intervention alone. The second aim was to evaluate secondary effects on cardiometabolic outcomes. The hypothesis was that the combined intervention prescription would improve hydration markers and cardiometabolic outcomes relative to the control group.

The overarching goal of this thesis is to contribute to a broader effort that prioritizes the health of individuals who are unknowingly at risk of becoming caught in this aggressive cycle that has the potential to cause severe, irreversible heart and kidney damage. The inspiration is to be among the first research efforts to conduct an intervention trial within this population. The motivation lies in implementing a holistic approach that targets disease processes systemically by understanding the complexity and intricacy of the pathophysiology of renal, cardiovascular, and metabolic dysfunction.

Chapter 2: Literature Review

CKM SYNDROME OVERVIEW

Cardiovascular Kidney Metabolic (CKM) syndrome is a relatively new clinical and research framework that integrates the progression of cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic syndrome (MetS).[10] In October 2023, the American Heart Association (AHA) published its first major initiative to operationalize CKM and released the first formal clinical framework for the syndrome.[2] The CKM framework recognizes that the development of cardiovascular disease, kidney disease, and metabolic syndrome occurs in parallel because their progression is influenced by similar underlying causes, such as insulin resistance, chronic inflammation, and hemodynamic dysregulation. This explains why assessment should not be based on isolated disease status or on the traditional treatment of these conditions separately.[5] CKM arises from a series of interconnected pathophysiological mechanisms that simultaneously affect metabolism, kidney function, and the cardiovascular system, leading to a progressive cycle of multi-organ dysfunction.[11]

CKM Criteria

CKM is classified as a syndrome rather than a single disease because it is defined not by a single diagnosis but by a collection of related signs and biomarkers that share a common underlying pathophysiology.[12] Not only does this syndrome highlight the multiple interrelated factors affecting CKM health, but it also classifies individuals along a severity spectrum based on biomarker levels, risk factors, and measured health indicators. Diseases such as diabetes and CKD are diagnosed using specific biomarker thresholds and diagnostic testing, whereas CKM syndrome requires a multisystem assessment to identify its presence.[1 13] The severity of CKM in an individual is classified into one of four stages.[1 12 14] The AHA introduced the stages to classify CKM in accordance with its screening guidelines and to establish criteria for early detection and treatment across the spectrum.[1 2 9]

The CKM staging model follows the pathophysiological progression that triggers the emergence of the syndrome and, over time and if left untreated or unaddressed, progresses along the clinical spectrum into overt cardiovascular disease. The five stages of CKM progression are summarized in Table 1.

Table 1. *Stages of Cardiovascular Kidney Metabolic (CKM) syndrome.*

CKM Stage	Classification	Description
Stage 0	Absence of CKM health risk factors	Healthy individuals with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or CVD.
Stage 1	Excess and/or dysfunctional adiposity	Characterized by excess weight (BMI ≥ 25 kg/m2) and abdominal obesity (waist circumference ≥ 88cm for women; ≥ 102 cm for men) or by dysfunctional adiposity, defined as impaired glucose tolerance or prediabetes.
Stage 2	Metabolic risk factors and chronic kidney disease	The presence of other metabolic risk factors, moderate-to-high-risk CKD, or both. Metabolic risk factors of CKM include hypertriglyceridemia (fasting serum triglycerides ≥ 150 mg/dL) [15], hypertension (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or current use of antihypertensive medication) [16], MetS, and type 2 diabetes (fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during an OGTT, HbA1c ≥6.5% or a previous clinical diagnosis).[17]
Stage 3	Subclinical cardiovascular disease in CKM	Imaging markers of subclinical atherosclerotic disease diagnosed by CAC or subclinical HF diagnosed by elevated cardiac biomarkers.[18]
Stage 4	Clinical cardiovascular disease in CKM	Clinical CVD is classified into four categories: CAD (also referred to as coronary heart disease), cerebrovascular disease, PAD, and aortic atherosclerosis.[19] Stage 4 is segmented into Stage 4a, without kidney failure, and Stage 4b, with kidney failure.

Abbreviations: CKM = cardiovascular-kidney-metabolic; BMI = body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease; MetS = metabolic syndrome; CAC = coronary artery calcification; CAD = coronary artery disease; OGTT = oral glucose tolerance test; HF = heart failure; PAD = peripheral artery disease. Staging criteria adapted from AHA CKM guidelines.[1 2]

The pathophysiological interactions among metabolic risk factors, CKD, and the cardiovascular system stem from excess or dysfunctional adiposity, particularly visceral adipose tissue and ectopic fat, which disrupt glomerular hemodynamics and activate the renin-angiotensin-aldosterone system (RAAS). This contributes to chronic low-grade inflammation, oxidative stress, and adipokine imbalance, leading to insulin resistance, hypertension, and dyslipidemia (among other metabolic abnormalities).[2 20] A consequence of this development is the progression of metabolic risk factors and CKD, as hemodynamic stress on the kidneys leads to renal tubular injury and a decline in glomerular filtration rate (GFR). Simultaneously, the cardiovascular system experiences arterial stiffness, left ventricular remodeling, and subclinical atherosclerosis. The cumulative progression of these effects forms a loop that advances CKM through the five stages, beginning with adiposity alone and progressing to clinical cardiovascular or kidney disease. [2 8]

CKM is assessed using multiple screening measures to determine stage classification: waist circumference, body mass index (BMI), blood pressure, lipid panel, blood glucose, kidney function tests, and coronary artery calcium measurement.[21] The American Heart Association outlines stage-specific screening considerations for adults. Stage 0 includes annual screening for Social Determinants of Health (SDOH), BMI, and waist circumference, and screening for HbA1c or fasting blood glucose every 3-5 years. Stage 1 follows the same procedure, except it recommends HbA1c or fasting blood glucose every 2-3 years. Stage 2 adds liver fibrosis screening for metabolic dysfunction-associated steatotic liver disease (MASLD) every 1-2 years using the fibrosis-4 (FIB-4) index; annual measurement of the urine albumin-to-creatinine ratio (uACR), serum creatinine, or cystatin C; and potential imaging for coronary artery calcification (CAC) or heart failure.[22] [23] Stages 3 and 4 include more frequent uACR and kidney function monitoring for individuals at higher Kidney Disease Improving Global Outcomes (KDIGO) risk, along with tailored CAC and heart failure (HF) screening.[23] The KDIGO is an international organization that develops evidence-based clinical practice guidelines for evaluating, classifying, and managing kidney disease. [24]

CKM Prevalence and Significance

Cardiovascular, kidney, and metabolic diseases were among the leading causes of death in 2024 and affected over 25% of U.S. adults between 2015 and 2020.[3 25] In a 2024 cross-sectional study by Aggarwal et al., nearly 90% of U.S. adults met criteria for Stage 1 or higher CKM (Stages 1-4), and more than 15% met criteria for the more advanced stages. Most of these individuals' statuses did not improve between 2011 and 2020, which may adversely affect their health and increase their risk factors over time if left untreated or unmanaged. An observational analysis by Kim and colleagues, published in the *American Journal of Medicine*, utilized data from adults who completed the National Health and Nutrition Examination Survey (NHANES) between 2011 and 2018 and determined that approximately 13% of adults were in Stages 3 and 4 of CKM, and with 76% at risk of progressing to those stages.[4]

Table 2. *CKM Prevalence in U.S. Adults*

CKM Stage	Prevalence (%)	Source
Stage 1 or higher	~90%	[3]
Stages 2-4	>15%	[3]
Stages 3-4	~13%	[4]
At risk of progression (to Stages 3-4)	76%	[4]

Prevalence estimates are based on U.S. adult populations and are presented as percentages.
Abbreviations: CKM = Cardiovascular-Kidney-Metabolic syndrome.

Recent CKM staging prevalence data are not yet available, but NHANES (2021-2023) data indicate that 47.7% of U.S. adults had hypertension. Prevalence increases substantially with age: 23.4% among adults aged 18-39, 52.5% among those aged 40-59, and 71.6% among adults 60 years and older.[26] During the same period, the obesity prevalence was 40.3%, the highest among adults ages 40-59.[27] In 2023, a CDC public health report estimated that more than 1 in 7 U.S. adults had CKD.[28] The magnitude of these prevalence estimates is concerning, as nearly half of U.S. adults have hypertension, and similar trends are observed for obesity and CKD.

Metabolic disorders and comorbid conditions contribute to the progression of CKM and drive high healthcare costs for patients and healthcare systems. In the United States, overweight/obesity and its comorbid conditions are estimated to cost the healthcare system $500 billion in direct costs and $1.2 trillion in indirect costs.[29] Examples of direct costs include hospitalizations, medications, treatments, and diagnostic equipment, whereas indirect costs include lost productivity, facility maintenance, and administrative expenses.[30]

As research on CKM syndrome progresses, these advances are supported by a growing understanding of the syndrome and the development of targeted treatment strategies. As more treatments become available to manage CKM and its related outcomes, healthcare systems benefit from reduced resource utilization and lower costs by avoiding the need to treat each condition separately.[2 29] Prioritizing CKM health and related outcomes can reduce disease progression and improve CKM healthcare in the U.S. by enabling early prevention and management of interacting comorbid conditions. Health systems can address CKM clinically, financially, and operationally by recognizing the need for multidisciplinary care, implementing quality-focused programs, and establishing evidence-based policies.[2 29]

Understanding CKM progression underscores that, aside from genetics, CKM is also influenced by risk factors organized within a comprehensive framework: the Social Determinants of Health (SDOH). [2] Annual SDOH screenings are recommended to assess external risk factors that influence individuals.[31] The SDOH framework is frequently studied for its impact on the incidence of CKM syndrome, which refers to the structural and environmental conditions that externally encompass an individual and influence their risk. SDOH introduces barriers that shape health behaviors, conditions, and outcomes at both the individual and population levels; thus, addressing these determinants is crucial for the prevention, identification, and management of CKM.[31] Dissecting the attributes of SDOH reveals that environmental, social, and structural factors, including health inequities, structural racism, access to education, neighborhood conditions, access to food, and environmental exposures, are external barriers that significantly contribute to the development and progression of CKM. [23] Often, the influence of

SDOH on the individual can be understood by how these external barriers shape behavioral factors. The presence of a barrier may lead to behaviors such as physical inactivity due to limited access to safe spaces for exercise or to community gyms; poor dietary quality due to limited access to affordable, nutritious foods; or smoking as a coping mechanism in response to chronic stress and environmental exposures.[32] This is why SDOH is a valued concept in CKM: it allows researchers and healthcare providers to examine the external influences and structural barriers that shape behavioral responses affecting an individual's health.

The NHANES analysis by Kim and colleagues found a correlation between advanced stages of CKM and several SDOH factors, including lower education levels, unemployment, and a low family income-to-poverty ratio. Mortality risk increases with progression through the stages, with the most advanced stages having the highest mortality rates. Crude mortality rates rise from 8.3-28.4 deaths per 1,000 person-years in Stages 0-2 to around 189 deaths per 1,000 person-years in advanced stages (Stages 3-4).[4]

Treatment of CKM

Treatment of CKM requires an integrated approach to address the overlap among heart disease, kidney disease, and metabolic syndrome, which demands cardiovascular support, kidney protection, and metabolic control.[2]

Cardiovascular disease is treated with medications and lifestyle modifications. Medications such as beta-blockers, ACE inhibitors (angiotensin-converting enzyme inhibitors), ARBs (angiotensin receptor blockers), and mineralocorticoid receptor antagonists reduce cardiac workload and protect the kidneys by lowering systemic blood pressure, reducing intraglomerular pressure, and improving arterial compliance. Statins help reduce the risk of cardiovascular disease by lowering blood cholesterol levels.[33 34] Cardiovascular risk reduction and management target a healthy blood pressure range consistent with current guideline-based risk reduction goals for adults with CKD, CVD, or diabetes (<120/80 mmHg) and

a healthy blood glucose concentration (fasting plasma glucose between 70-99 mg/dL), according to the AHA CVD prevention guidelines.[35]

Kidney protection treatments include SGLT2 inhibitors (sodium-glucose co-transporter-2 inhibitors), proper fluid management, and medication adjustments. These treatments not only improve glycemic control but also reduce glomerular hyperfiltration and intraglomerular pressure, thereby slowing CKD progression.[36] [34] Controlling metabolic risk factors requires maintaining healthy blood glucose levels (through diet or pharmacotherapy) and achieving weight loss. [34] Healthy blood glucose concentrations are defined as a fasting plasma glucose between 70 and 99 mg/dL, an HbA1c below 5.7%, and a 2-hour postprandial glucose under 140 mg/dL.[37]

Lifestyle changes, including nutrition, exercise, weight management, smoking cessation, and stress management (all factors that contribute to the progression of CKM syndrome), are also beneficial. Dietary patterns that promote cardiovascular and kidney health include the DASH and Mediterranean diets, both of which prioritize fruits, vegetables, whole grains, lean proteins, and healthy fats.[38] [34] Aerobic and strength-training exercises improve cardiovascular health, insulin sensitivity, and weight management, thereby reducing strain on the heart. Exercise should include at least 150 minutes per week of moderate-intensity aerobic activity, combined with resistance training at least 2 days per week, to improve cardiovascular fitness, reduce insulin resistance, and support weight management.[39] Smoking cessation improves vascular function and slows disease progression, while stress management improves blood pressure and glucose levels.[34]

PATHOPHYSIOLOGY OF CKM

Stage 0 → Stage 1

The current conceptual framework of CKM describes a metabolically healthy individual (Stage 0) with no signs of kidney or cardiovascular disease. Exposure to modifiable risk factors, such as poor diet, a

sedentary lifestyle, and challenging external influences from SDOH, may initiate underlying pathophysiological stress, independent of explicit consideration of genetic risk factors. Metabolic dysregulation is triggered by systemic inflammation, adipokine imbalance, and insulin resistance, which are exacerbated by adipose tissue dysfunction, specifically visceral fat accumulation (Stage 1).[1 2]

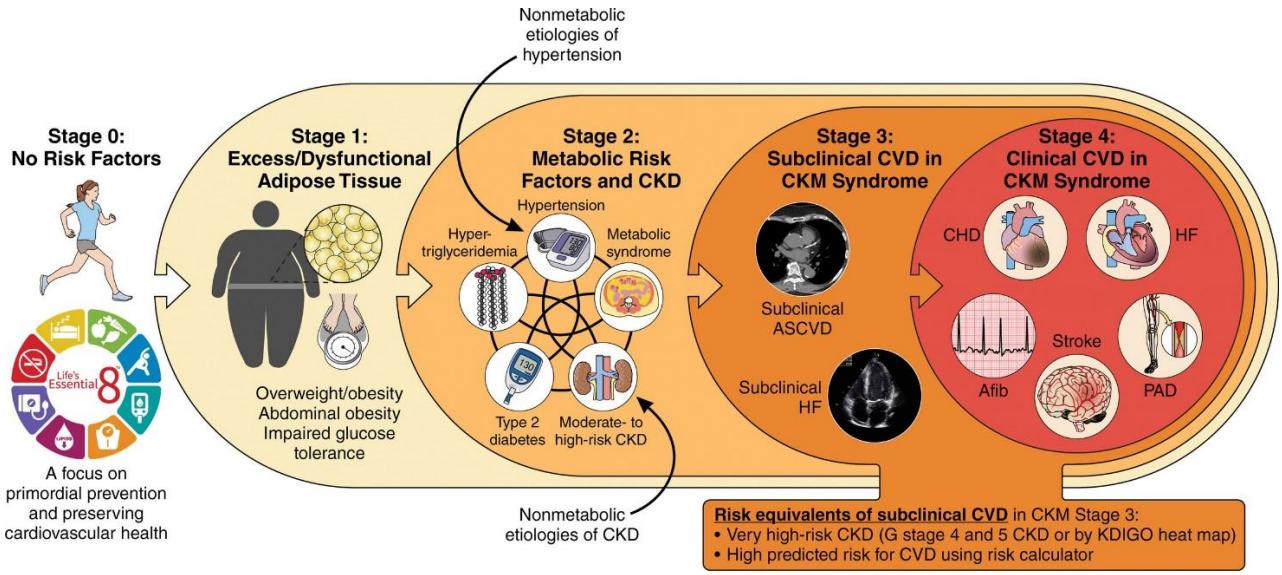

Figure 1. *Progression of CKM syndrome.*

Stage 1 → Stage 2

As illustrated in Figure 1, this process activates the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, causing hemodynamic stress on the kidneys and vessels. This stress eventually manifests as hypertension, hyperglycemia, hypertriglyceridemia, and albuminuria, all of which contribute to renal injury. These changes increase the albumin-to-creatinine ratio and decrease eGFR, which serve as diagnostic indicators of kidney damage. The onset of CKD is driven by glomerular hyperfiltration and tubular inflammation, while cardiovascular impairments arise from arterial stiffness and endothelial dysfunction (Stage 2). [1 2]

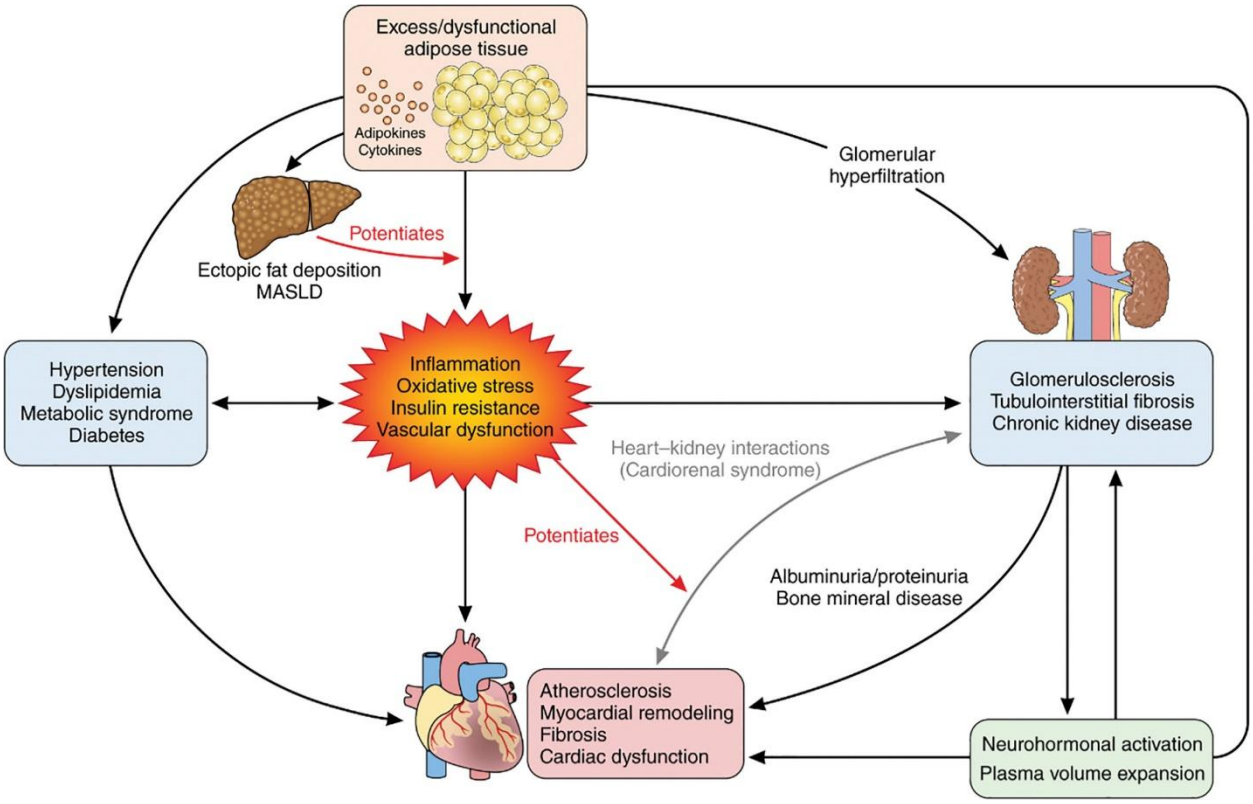

Figure 2. *Conceptual diagram of CKM pathophysiology.*

Stage 2 → Stage 3

Figure 2 (synopsis) illustrates the coexistence of kidney injury mechanisms and cardiovascular strain. This progressive organ damage, including left ventricular hypertrophy, coronary artery calcification, and elevated cardiac biomarkers (NT-proBNP, troponins), results in subclinical cardiovascular changes. (Stage 3). [1]

Stage 3 → Stage 4a and 4b

Over time, this process may lead to clinical cardiovascular disease, including heart failure, myocardial infarction, stroke, and atherosclerosis (Stage 4a), which may subsequently cause overt CKD or kidney failure (Stage 4b). Cardiac output and renal function decline substantially, increasing the risk of hospitalization, disability, and mortality. This cycle underscores the critical need for stage-specific

screening and interventions to disrupt or delay disease progression and reduce severe morbidity and mortality through early identification and management. [1 2]

Cardiovascular Disease

Many cardiovascular risk factors are modifiable, especially among individuals with CKM. The correlation between CKD biomarkers and metabolic risk factors substantially influences CVD risk and mortality.[11] Traditional CVD risk factors should be examined alongside novel nontraditional risk factors and biomarkers, including apolipoprotein B (ApoB), lipoprotein(a) (Lp(a)), high-sensitivity cardiac troponin, B-type natriuretic peptide (BNP), estimated glomerular filtration rate (eGFR), and albuminuria. [40] The PREVENT assessment evaluates ASCVD and HF and determines CVD risk by incorporating CKM biomarker assessments alongside traditional CVD risk factors, including BMI and eGFR. Early CVD prevention begins at birth and continues throughout the lifespan; the PREVENT equation for estimating formal risk is applied starting at age 30.[41] CVD risk factors are traditionally grouped into two categories: conditions and behaviors. Conditions that increase CVD risk include high blood pressure, high cholesterol, diabetes, and obesity; behaviors that influence CVD risk include nutrition, physical activity, alcohol use, and smoking. [42]

Researchers have identified links among metabolic and renal biomarkers, behavioral risk factors, and cardiovascular dysfunction. These findings establish a relationship between biomarkers that drive CVD progression and the key determinants of CKM development. The studies in Table 3 highlight this relationship by demonstrating how CVD-related biomarkers interact with CKM progression. This further strengthens understanding of the shared pathophysiology between these conditions.

Table 3. *Research addressing CVD risk in relation to CKM syndrome*

Study	Focus	Key Findings	Relevance to CKM
Li et al.	Nationwide prospective cohort; CKM stage 0-3	The cohort study reported a 6.5% increase in the risk of developing CVD with each 10-unit increase in TyG-BMI (95% CI: 1.041-1.090); a positive linear relationship was confirmed ($P < 0.001$).	TyG-BMI may serve as a predictive biomarker for early CVD risk in CKM stages 0–3.
Khan et al.	AHA Scientific Statement on CVD risk	The statement expanded CVD risk assessment to include CKD and MetS biomarkers: eGFR, albuminuria, fasting glucose, and triglycerides. It identified novel risk factors: ↑ Apolipoprotein B, ↑ Lipoprotein A, ↑ high-sensitivity troponin, and ↑ B-type natriuretic peptide.	Integrates non-traditional biomarkers into CKM-related CVD risk prediction.
Fryar et al.	NHANES 1999-2010	High blood pressure, high cholesterol, diabetes, and obesity are risk factors for cardiovascular disease (CVD); uncontrolled hypertension is associated with left ventricular hypertrophy, arterial stiffness, and endothelial dysfunction – all of which contribute to CKM.	Defines the overlap between CKM stage progression and uncontrolled traditional CVD risk factors.
Kaminsky et al.	Review of lifestyle and CVD	Physical inactivity ↑ CVD risk; Mediterranean diet ↓ LDL, glucose, BP, weight; smoking ↑ MI/mortality; vaping is linked to endothelial dysfunction; poor sleep is linked to diabetes, hypertension, CHD, stroke, MetS.	Highlights how behavioral risk factors are modifiable through lifestyle changes that influence CKM progression.

This table summarizes research publications on cardiovascular disease risk. The relevance of these studies to CKM syndrome is also highlighted in the table. Each article examines biomarkers, clinical conditions, or behavioral factors that influence CVD risk and CKD progression. Abbreviations: TyG-BMI = triglyceride-glucose body mass index; eGFR = estimated glomerular filtration rate; MetS = metabolic syndrome; BP = blood pressure; MI = myocardial infarction; CHD = coronary heart disease; NHANES = National Health and Nutrition Examination Survey. [40 43 44] [45]

The ACSM cardiovascular risk assessment considers eight positive risk factors and one negative risk factor that, if applicable, offsets one of the positive risk factors. [46] Cardiovascular risk assessment is determined using the following factors:

Table 4. *ACSM cardiovascular disease risk assessment: positive and negative risk factors*

Positive risk factors			
Age	Men ≥ 45 years Women ≥ 55 years	BMI/ waist circumference	BMI ≥ 30 kg/m^2, *or* Men waist girth >102cm Women waist girth >88cm
Family history	Myocardial infarction, coronary revascularization, or sudden death before 55 years in father or male first-degree relative, or before 65 years in mother or female first-degree relative	Blood pressure	Systolic blood pressure ≥ 130 mmHg and/or diastolic ≥ 80 mmHg on ≥2 readings on ≥2 occasions, *or* Antihypertensive medication
Blood glucose	Fasting plasma glucose ≥ 100 mg/dL, *or* 2-hour plasma glucose values in oral glucose tolerance test (OGTT) ≥ 140 mg/dL, *or* HbA1C ≥ 5.7%	Lipids	LDL-C ≥ 130mg/dL, *or* Men HDL-C < 40 mg/dL Women HDL-C < 50 mg/dL, *or* Non-HDL-C <130 mg/dL, *or* Lipid-lowering medication, *or* If total serum cholesterol is only available ≥ 200 mg/dL
Physical inactivity	<500-1000 MET-min of moderate-to-vigorous physical activity or 75-150 min/week of moderate-to-vigorous physical activity	Cigarette smoking	Current smoker or quit within the previous 6 months, or exposure to environmental tobacco smoke
***Negative risk factors**			
HDL-C	≥60 mg/dL		

Positive risk factors include age, family history, cigarette smoking, physical inactivity, obesity, hypertension, dyslipidemia, and impaired blood glucose. *A negative risk factor, high HDL-C (≥60 mg/dL), offsets one positive risk factor when presented *from ACSM's Guidelines for Exercise Testing and Prescription (10th ed., 2021).*

Chronic Kidney Disease

Cardiorenal syndrome describes the bidirectional relationship between cardiac and renal dysfunction, in which impairment of one organ affects the function of the other. Kidney dysfunction often mediates the link between metabolic risk factors and heart failure. The CKM framework integrates these conditions by linking heart disease, kidney disease, and metabolic syndrome. CKM diagnostic criteria assess kidney function using eGFR and albuminuria, both of which are strong indicators of adverse cardiovascular events.[2] Increased albuminuria (normal <30 mg/day, increased 30-300 mg/day, and severely increased >300 mg/day), increased albumin-to-creatinine ratio (30-300 mg/g or >300 mg/g), and decreased eGFR (normal >90 mL/min/1.73 m2, mild 60-89 mL/min/1.73 m2, moderate 30-59 mL/min/1.73 m2, severe 15-

29 mL/min/1.73 m2, and kidney failure <15 mL/min/1.73 m2) stratify kidney failure risk from low to high.[1]

Albuminuria, the presence of albumin in the urine, can indicate damage to the glomerular basement membrane (GBM) and podocytes. Damage to the kidney's filtering units allows albumin to leak into the urine, triggering inflammatory and fibrotic responses in the tubules and potentially worsening kidney damage. [47] [2] In CKM, albuminuria levels indicate the stage of syndrome progression. The albumin-to-creatinine ratio (uACR) measures the albumin level in urine relative to creatinine and is a reliable indicator of albuminuria and an early marker of kidney dysfunction. Elevated uACR indicates subclinical glomerular dysfunction, which predicts progression to chronic kidney disease and increased cardiovascular risk. Elevated uACR further promotes inflammatory and fibrotic responses linked to albuminuria. [2].

The estimated glomerular filtration rate (eGFR) is calculated using an equation that incorporates serum creatinine, age, sex, and race to assess the kidneys' ability to filter waste from the blood. A decreased eGFR indicates reduced kidney function; chronic kidney disease is diagnosed when eGFR is below 60 mL/min/1.73 m2 for more than three months. [48] [49] In the early stages of CKM, glomerular hyperfiltration may occur due to increased metabolic demand. When persistent, this hyperfiltration induces mechanical stress that accelerates glomerulosclerosis, progressively lowering eGFR and contributing to renal dysfunction.[34]

The presence of albuminuria in the earliest stages of kidney disease is a strong risk factor for CVD, as kidney dysfunction amplifies metabolic risk factors such as hypertension and hyperglycemia. These risk factors are essential to consider because they contribute to early organ dysfunction and are key determinants of cardiovascular injury. Their progression over time directly influences CKM stage advancement and increases the risk of cardiovascular and renal issues. [1]

Kidney Physiology

Given that this thesis focuses on the early stages of CKM, which are largely driven by kidney function, it is important to examine renal physiology in greater detail to better understand the kidneys' role in CKM and the rationale for hydration as an intervention in the clinical trial.

The renal system consists of the kidneys, ureters, and urethra, and its primary function is to filter blood by excreting toxins, metabolic waste products, and excess ions while retaining essential substances that return to systemic circulation. [50] The nephron is the functional unit of the kidney. Blood flows to the kidneys and passes through the glomerulus, where filtration occurs. GFR, or glomerular filtration rate, is the volume of fluid filtered per minute and is influenced by multiple factors: hydration status, high dietary protein intake, sodium intake, and physical inactivity.[51]

As blood passes through the nephron, the filtrate undergoes regulatory processes that control water reabsorption, sodium balance, and acid-base homeostasis, all of which are critical for hydration status. In the collecting duct, vasopressin regulates water reabsorption.[51] Elevated vasopressin levels occur in response to low water intake and increase renal stress by promoting hyperfiltration and tubular strain.[51]

Even minor renal alterations can cause dysfunction and extend to the heart by increasing volume overload, activating RAAS, and elevating blood pressure to meet renal demands, thereby stressing the heart.[50] Early kidney dysfunction, if left untreated, can lead to the silent progression of CVD, underscoring the importance of early identification and intervention to prevent further disease advancement and adverse outcomes.

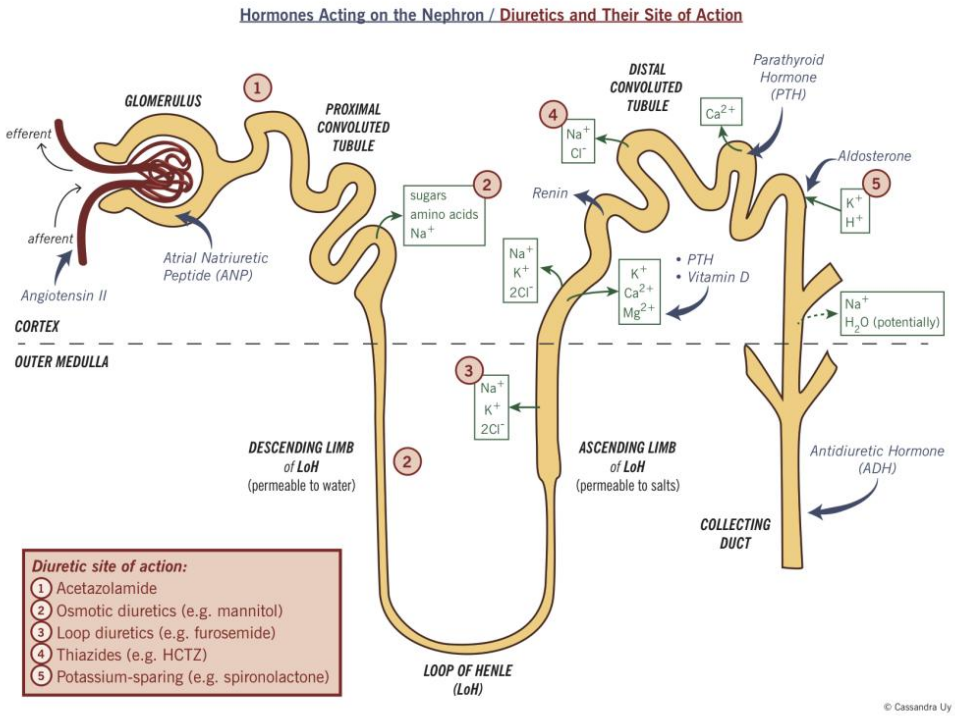

Figure 3. *Kidney nephron anatomy*

The direct impact of dietary intake on kidney function is important to consider. Protein intake is closely linked to kidney function, as higher protein consumption increases glomerular hyperfiltration, which, over time, may contribute to nephron injury and a decline in GFR.[52] Diets with a high dietary acid load, particularly those high in animal protein, increase tubulointerstitial injury.[53] CKD treatment through dietary modifications aims to reduce the glomerular filtration rate (GFR), control blood pressure, and slow the progression of kidney damage, thereby improving kidney function markers and reducing cardiovascular risk.[52] Although recommendations vary, they consistently emphasize moderation in protein and sodium intake and adherence to dietary patterns lower in animal protein and higher in fruits and vegetables.[54]

Metabolic Syndrome

Metabolic Syndrome (MetS) is classified by specific characteristics, including central obesity, insulin resistance, hypertension, and dyslipidemia, with diagnosis requiring three or more of these abnormalities. [55] Early identification and intervention strategies are crucial in MetS to prevent the development of cardiovascular disease and type II diabetes mellitus, which may eventually lead to CKM syndrome.[1] [55] The diagnostic criteria include the presence of three or more of the following five components: waist circumference (>40 inches in men and >35 inches in women), serum triglyceride concentration (≥150 mg/dL), reduced high-density lipoprotein cholesterol (HDL) (<40 mg/dL in men or <50 mg/dL in women), elevated fasting glucose (≥100 mg/dL), or elevated blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg).[56] [55] These abnormalities contribute to metabolic conditions that influence the development of CVD and CKD and, with cumulative progression, result in classification within the CKM framework. In a research paper by Gigante et al. (2025), one finding showed the highest prevalence of metabolic disease among patients with Stage 2 CKM.[57]

Diet and Metabolic Influences on CKM

Understanding the origin and progression of CKM is essential. Several early factors involved in the early stages of CKM progression, including chronic inflammation, influence CKM risk and contribute to worsening cardiometabolic and kidney outcomes. It is therefore necessary to examine how inflammatory dietary patterns influence CKM risk progression, particularly because a central component of this thesis intervention is behavioral weight loss through dietary modification and calorie deficit, along with increased light-to-moderate exercise. Studies have used the dietary inflammation index (DII) to assess the relationship between diet and systemic inflammation.[58] The objective is to clarify how diet may function as either a risk or a protective factor for CKM health. An NHANES analysis demonstrated a positive association between higher DII scores and progression to more severe stages of CKM. [59] This association was evaluated using measures of metabolic dysfunction, cardiometabolic risk, and likelihood

of kidney impairment. These findings suggest that diet plays an independent role in the progression of CKM.

Previous studies have shown that diets with higher DII scores are associated with increased risk of T2D, cardiovascular disease, and CKD. [59] An inflammatory diet involves high consumption of refined carbohydrates, saturated fats, and processed foods. This eating pattern induces systemic stress and elevates pro-inflammatory cytokines, including IL-6, TNF-α, and CRP. [60] These cytokines disrupt metabolic processes, impair insulin signaling, and promote insulin resistance. Insulin resistance serves as a mechanistic link between obesity, kidney hyperfiltration, and cardiovascular risk.

A comprehensive review by Vincent-Johnson et al. examined how dietary patterns influence kidney stress through metabolic acidosis. Diets high in animal protein, refined grains, and processed foods increase systemic acid load. In contrast, diets rich in fruits and vegetables exert a protective and alkalizing effect. The review reported that a greater dietary acid burden is associated with increased albuminuria and faster progression of kidney dysfunction, even before advanced CKD develops. These findings support the concept that diet-driven metabolic stress affects kidneys early in the disease trajectory, highlighting the importance of dietary quality in CKM progression and reinforcing the rationale for behavioral dietary interventions to improve early kidney health biomarkers. [53]

Genetic Factors

Current studies analyzing CKM prioritize the interconnected pathophysiology intertwining metabolic syndrome with chronic kidney disease and, subsequently, cardiovascular disease, following the established progression of CKM. It is also important to consider, alongside this discussion, the potential role of genetic factors in the progression of these conditions, as CKM is a relatively new framework with areas that remain incompletely understood. This raises the question of how genetic factors contribute to CKM progression beyond the effects of obesity or inflammation alone.

While the current CKM framework effectively describes the progression pathway through interconnected pathophysiological mechanisms, emerging evidence underscores the role of genetic factors in CKM. A recent article in BMC Medical Genomics considered candidate subtypes and genetic risk factors associated with CKM.[61] Identified genetic variants are associated with pathways involved in lipid metabolism, glucose regulation, renal function, and cardiovascular structure and signaling. These variants are expressed in the heart, kidney, liver, adipose tissue, and pancreas. These findings strengthen the understanding that CKM is a multi-organ syndrome.[61]

Acknowledging this evidence is crucial to advancing understanding of the influences and underlying causes of CKM, alongside SDOH and other health risk factors. However, this thesis focuses on modifiable, non-pharmacological interventions aimed at altering the disease trajectory regardless of its etiology.

NON-PHARMACOLOGICAL INTERVENTIONS TO PREVENT OR TREAT CKM

As of June 2025, no non-pharmacological intervention trials have been conducted specifically to prevent or treat CKM. The following sections review interventions targeting the individual conditions that compromise CKM syndrome.

Behavioral Weight Loss

Obesity is a significant risk factor for cardiovascular disease, chronic kidney disease, and metabolic syndrome. It contributes to an estimated 2.9 million deaths annually worldwide, many of which may be preventable with early detection and targeted interventions. Intentional and effective weight loss has been shown to improve risk factors for CVD, CKD, and metabolic syndrome. [62]

Behavioral weight-loss interventions and BMI reductions improve CVD risk factors by lowering blood pressure, improving lipid profiles, lowering blood glucose, and reducing insulin resistance and inflammation.[63] In lifestyle intervention trials for weight loss, the magnitude of benefit depends on the

percentage of weight lost.[64] Evidence suggests that clinically meaningful improvements begin at approximately 5% body weight loss, whereas reductions below this threshold are generally insufficient to produce significant metabolic changes. Achieving at least 5% weight loss is associated with improvements in HbA1c, lipid profiles, and blood pressure, thereby reducing the risk of hypertension and hyperglycemia. [64]

The Look AHEAD intervention trial compared intensive lifestyle intervention with diabetes support and education among adults with type II diabetes to assess effects on CVD events.[65] The initial results showed no significant reductions in the primary CVD outcome in the intensive lifestyle intervention group. A subsequent post hoc analysis by the Look AHEAD Research Group evaluated whether the magnitude of weight loss and changes in fitness during the first year were associated with CVD incidence. When stratified by percentage of weight loss achieved, participants who lost at least 10% of their body weight experienced a 20% reduction in risk of the primary composite outcome, defined as "death from cardiovascular causes, non-fatal acute myocardial infarction, non-fatal stroke, or admission to hospital for angina."[66]

This comparison is important because it does not negate the findings of the original Look AHEAD study, which found that assignment to a lifestyle intervention did not reduce overall CVD incidence, but rather clarifies that achieving substantial weight loss is associated with reduced CVD incidence.[66] A 5-10% weight loss significantly reduces fasting glucose, triglycerides, and cholesterol ($p < 0.001$). In contrast, weight loss >10% improves all risk factors except HDL cholesterol. These factors influence the risk of developing type II diabetes and cardiovascular disease. [67] These benefits reinforce the role of weight reduction as an effective preventive strategy against CKM progression. A 10-15% reduction in weight increases the likelihood of lowering major cardiovascular disease risk factors in individuals with diagnosed obesity or type II diabetes who are at higher cardiometabolic risk. [68]

Although evidence directly linking weight-loss interventions to a reduced incidence of CVD events, such as myocardial infarction (MI), stroke, or heart failure, remains limited, research suggests that sustained weight loss after the initial intervention can maintain reductions in cardiovascular risk factors for at least 5 years, even with partial weight regain.[69]

A systematic review and meta-analysis by Navaneethan et al. (2009) found that nonsurgical behavioral weight-loss interventions in patients with CKD reduced BMI, albuminuria, and systolic blood pressure while stabilizing GFR. Behavioral weight-loss strategies extend beyond weight loss; increased physical activity and broader lifestyle modifications are integral components of these interventions. Among individuals with obesity class 3 (BMI ≥ 40) and glomerular hyperfiltration, surgical weight-loss interventions may be urgently required. Postoperative outcomes have demonstrated reductions in albuminuria and blood pressure, along with increases in GFR. [70] These findings suggest that weight reduction can effectively mitigate key factors contributing to CKD progression. [70]

A recent review by Peterseim et al. (2024) examined the effects of behavioral, pharmacological, and surgical weight-loss interventions on metabolic syndrome.[71] Behavioral weight loss, including lifestyle modifications, was identified as an effective first-line treatment. $\geq 5\%$ weight loss was associated with improvements in metabolic syndrome risk factors, including elevated blood pressure, fasting glucose, triglycerides, and HDL cholesterol. These interventions improved insulin sensitivity and reduced central adiposity – core indicators of metabolic syndrome and early CKM stages (Stages 1 and 2). Obesity classes, such as class I (BMI 30–34.9), class II (BMI 35–39.9), and class III (BMI ≥ 40), refer to standardized BMI ranges used to categorize obesity severity. Behavioral weight loss may also reduce progression of type II diabetes and cardiovascular disease in at-risk individuals.[71]

Building on the benefits of weight loss, the review by Ma et al. reported that aging is associated with a reduction in functional nephron reserve and a decline in glomerular filtration, with the decline becoming more pronounced after age 40.[72] Renal inflammation and oxidative stress are further exacerbated by

age-related shifts in body composition, particularly sarcopenic obesity and redistribution of visceral fat. The review emphasizes the importance of weight loss in mitigating these effects by preserving lean mass and improving renal perfusion, and supports gradual, moderate weight reduction over rapid weight loss. Rapid weight loss substantially decreases lean mass, often with a proportionally smaller reduction in fat mass.[73] Short-term weight loss is typically defined as approximately 0.5-1.0 kg per week, whereas long-term weight loss is defined as a 5-10% reduction in total body weight over 3-6 months. [73] [74]

Water Intake and Hydration

A study by Wagner et al. (2022) examined how water intake influences the progression of chronic kidney disease. Adults with Stages 3-4 CKD were grouped by total daily water intake. Participants were divided into five groups: less than 0.5 L/day, 0.5-1.0 L/day, 1.0-1.5 L/day, 1.5-2.0 L/day, and more than 2.0 L/day, with the 1.0-1.5 L/day group serving as the reference category. The highest-intake group (>2.0 L/day) had a notably faster decline in eGFR than the lowest-intake group (<0.5 L/day), with declines of 2.48 mL/min/1.73 m2 and 1.43 mL/min/1.73 m2, respectively. These findings support a U-shaped relationship between water intake and kidney outcomes, indicating that both very low and very high water consumption may worsen CKD progression in patients with Stages 3 and 4. The proposed optimal water intake range was approximately 1-2 liters per day.[75]

In a cross-sectional study by Wang et al. (2021), participants at risk of CKD with eGFR ≥30 mL/min/1.73 m2 were categorized into three groups based on daily water intake: low (<500 mL/day), moderate (≥500-<1200 mL/day), and high (≥1200 mL/day). CKD prevalence was 10.7%, 8.2%, and 5.6% in the low-, moderate-, and high-intake groups, respectively. The high-intake group had the lowest prevalence of albuminuria at 9.5%. In comparison, the moderate- and low-intake groups showed higher rates: 12.8% and 14.1%, respectively. Multivariable logistic regression analysis showed that the low-intake group had 35% higher odds of CKD and 42% higher odds of albuminuria than the high-intake group. Water intake

was positively correlated with eGFR. It was negatively correlated with the urinary albumin-to-creatinine ratio, plasma osmolality, and urine osmolality.[76]

Hydration significantly influences biomarkers related to CKM syndrome and kidney function. Increased water intake, typically defined as more than 1.5-2.0 liters per day or producing at least 2.0-2.5 liters of urine in 24 hours, has been shown to suppress vasopressin (AVP) secretion. This hormone regulates water balance, and its suppression reduces copeptin levels. Copeptin, a stable surrogate marker for AVP, is linked to a higher risk of CKD progression and metabolic disorders. Individuals with higher 24-hour urine volume exhibit lower plasma copeptin levels and experience a slower yearly decline in eGFR, thereby helping preserve kidney function.[77]

A French epidemiological study, Data from an Epidemiological Study on the Insulin Resistance Syndrome (D.E.S.I.R.), examined the effect of daily water intake on the incidence of hyperglycemia in 3,615 middle-aged adults with normal baseline fasting glucose over a 9-year follow-up. Participants were divided into three water intake groups: <0.5 L/day, 0.5–1.0 L/day, and >1.0 L/day. Compared with the lowest intake group (<0.5 L/day), the 0.5–1.0 L/day group had a 32% lower risk of developing hyperglycemia, and the >1.0 L/day group had a 21% lower risk. However, the latter did not reach statistical significance. These findings indicate an association between low water intake and an increased risk of hyperglycemia. Increasing water intake may help maintain glucose regulation and delay the onset of metabolic dysfunction.[78]

These findings collectively suggest that hydration influences kidney and metabolic outcomes in a dose-dependent manner. Insufficient intake increases the risk of disease progression, whereas excessive intake may be detrimental in individuals with advanced CKD. This underscores the need for evidence-based hydration guidance that keeps intake within the research-supported optimal range of 1-2 L/day.

GAPS IN RESEARCH

Because CKM syndrome is a relatively new construct, the American Heart Association did not formally highlight it until October 2023, leaving research limited. Most available evidence is derived from observational studies. To date, no intervention trials have been published specifically targeting improvements in CKM-related renal and cardiometabolic indicators. Furthermore, sex-specific differences in CKM progression and the potential contribution of genetic factors remain understudied. The mechanisms linking CKM risk factors to CVD and CKD through vascular, myocardial, and renal dysfunction are not yet fully elucidated.[2] General clinical guidelines for screening, prevention, and management of CKM have not yet been standardized or widely adopted in clinical practice. The heterogeneity of CKM risk factors and their relative contributions to disease progression require further investigation. The bidirectional relationship between cardiovascular and kidney dysfunction, and the underlying pathways driving CVD development within CKM, represent key research gaps.[1] This thesis seeks to address several of these gaps.

Chapter 3: Manuscript

Examining the Impact of Behavioral Weight Loss and Increased Water Intake on Kidney Health in Adults Aged 50+ with Stage 1 or 2 Cardiovascular Kidney Metabolic (CKM) Syndrome: A Randomized Controlled Trial

ABSTRACT

Recent advances in understanding the pathophysiological integration among the cardiovascular, renal, and metabolic systems have led to the identification of Cardiovascular-Kidney-Metabolic (CKM) syndrome. CKM describes the interconnected progression of these systems, beginning with metabolic syndrome (MetS). MetS contributes to the development of chronic kidney disease and ultimately increases the risk of cardiovascular disease, creating a progressive cycle of multiorgan dysfunction. By focusing on the early stages of the syndrome, individuals have an opportunity to engage in treatment strategies aimed at slowing further progression across the CKM spectrum. The objective of this analysis was to assess the influence of behavioral lifestyle changes on biomarkers associated with CKM progression. This randomized controlled trial evaluated a targeted lifestyle intervention in middle-aged and older adults (≥ 50 years) with Stage 1 or Stage 2 cardiovascular-kidney-metabolic (CKM) syndrome and a low baseline habitual water intake (<1500 mL/day). The intervention combined prescribed water intake with behavioral weight loss and was grounded in established evidence linking metabolic dysfunction, kidney impairment, and cardiovascular risk through modifiable behavioral pathways. Participants (mean age = 61 ± 7 years, mean BMI = 33.6 ± 5.7 kg/m^2, 74.4% female) were randomized to either a water intervention group, which was prescribed increased water intake (1500 mL/day), a tailored hypocaloric diet, and increased physical activity, or a control group that received the diet and physical activity interventions alone for 12 weeks. The final analysis included 125 completers (water group, n = 87; control group, n = 38). The primary outcome, urinary albumin-to-creatinine ratio (uACR), did not differ significantly between groups after 12 weeks (water vs. control: +5.1 ± 34.7 vs. +1.8 ± 24.2; p = 0.53). Secondary renal and exploratory cardiometabolic outcomes were similarly unchanged between groups, except for hydration-related measures, such as urine osmolality (p = 0.02), specific gravity (p = 0.01), and 24-hour urine volume (p = 0.01). Measures of adherence to prescribed interventions for water intake, physical activity, and dietary intake showed no meaningful differences between groups after the intervention. These findings indicate that the water prescription did not improve the targeted kidney-related outcomes within the study timeframe. However, future research is needed to evaluate this possibility with larger sample sizes and longer study durations.

INTRODUCTION

Cardiovascular-Kidney-Metabolic Syndrome is defined as the synonymous occurrence of cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic syndrome (MetS). The CKM framework unifies these three conditions and necessitates the recognition of their interdependent, multisystem progression.[79] Shared underlying pathophysiological mechanisms, including systemic inflammation, hypertension, and insulin resistance, influence CKM.[2] The CKM staging criteria categorize patients into four stages: Stage 1 for overweight or obesity, Stage 2 for metabolic syndrome and early kidney damage, Stage 3 for subclinical cardiovascular disease, and Stage 4 for clinical cardiovascular disease, which is further divided into 4a without kidney failure and 4b with kidney failure.[2] The significance of this classification lies in its ability to identify early, modifiable risk factors (e.g., excess adiposity) that may predict progression toward more severe and often irreversible outcomes: cardiovascular disease and chronic kidney disease.[80]

The rising prevalence of CKM, particularly among adults who meet criteria for overweight or obesity, highlights the need for integrative, cost-effective, and accessible lifestyle interventions that can mitigate the syndrome at its earliest stages and reduce reliance on long-term, costly, and potentially avoidable pharmacologic treatment.[8][19][69] The CKM framework aims to improve clinical care for patients with the syndrome by enabling guidelines that help healthcare providers deliver more effective treatment through early identification, prevention, and integrated management of these interrelated conditions. There is a necessity to increase public awareness of the interconnectedness of these three conditions by integrating this syndrome across the translational science spectrum.[23]

The American Heart Association (AHA) presidential advisory and the accompanying synopsis of research were among the first to formally introduce the syndrome, establishing staging, treatment, and prevention strategies for affected individuals.[1 2] More recently, an implementation guide has been released to support the clinical application of CKM by staging and managing patient care through algorithm-based

flowcharts.[81] CKM syndrome provides a pathophysiological framework linking cardiovascular disease to chronic kidney disease, and it is explained by mechanisms including volume overload, vascular calcification, inflammation, and neurohormonal activation.[79] Within the CKM framework, chronic kidney disease is a progressive decline in kidney function, assessed by a reduced glomerular filtration rate and/or markers of kidney damage, including albuminuria, which is commonly quantified by the urine albumin-to-creatinine ratio.[28] Metabolic syndrome further contributes to CKD progression through a cluster of interrelated metabolic abnormalities that accelerate renal and cardiovascular dysfunction.

In research, as emphasized in nutritional and exercise education, the concepts of "*food is medicine"* and "*exercise is medicine"* encourage the premise that healthcare treatments should prescribe nutrition and physical activity as therapeutic interventions for chronic disease.[82] Behavioral modifications have consistently demonstrated significant benefits across cardiovascular, metabolic, and renal outcomes.[11]. Focusing on early-stage CKM (the "reversible" phases), hydration emerges as an additional modifiable factor: adequate fluid intake is associated with improved renal hemodynamics and reduced physiological stress on the kidneys, as shown in prior CKD research, prompting its prescription in this study of CKM.[75] As supported by existing research, adequate fluid intake is defined as an optimal range of approximately 1-2 L/day to maintain hydration and avoid both underhydration and overhydration.[75]

Despite growing recognition of CKM as a unified syndrome, there is a lack of research intervention trials specifically designed to treat or address this condition. This investigation aims to evaluate the effects of a behavioral weight-loss intervention combined with prescribed water intake on biomarkers of kidney health in adults aged 50 years and older with Stage 1 or Stage 2 CKM syndrome and low habitual water intake (<1500 ml/d). If effective, this intervention could be used to delay or prevent progression of CKM syndrome in an aging population.

AIMS AND HYPOTHESIS

This research aimed to contribute novel evidence on the nonpharmacological treatment of CKM syndrome by evaluating a behavioral intervention that integrates increased water intake with a structured weight-loss program. The study investigated whether a prescribed daily water intake, in combination with an energy-restricted diet and increased physical activity, improved early indicators of CKM-related renal dysfunction, hydration status, and cardiometabolic outcomes.

The primary aim was to examine the effects of a 12-week intervention in adults aged ≥50 years with Stage 1 or Stage 2 CKM syndrome, who were adhering to a hypocaloric diet with prescribed water intake (1500 mL/d), on kidney health, as measured by the primary outcome, uACR. The primary hypothesis was that participants prescribed increased water intake, combined with behavioral weight loss, would improve kidney function, as reflected by reductions in the urinary albumin-to-creatinine ratio, compared with those following a hypocaloric diet without a prescribed water intake regimen.

The second aim was to evaluate changes in hydration and cardiometabolic indicators after the intervention. Secondary outcome assessments evaluated changes in hydration biomarkers and cardiometabolic/cardiovascular-anthropometric indicators. The secondary hypothesis was that the prescribed combined intervention would improve hydration markers and cardiometabolic outcomes relative to the control group. Exploratory analyses evaluated associations between cardiometabolic factors and renal function.

STUDY DESIGN AND METHODS

Data Source and Study Setting

This thesis derived data from an ongoing randomized controlled trial (RCT) approved by the Virginia Tech Institutional Review Board (#22-624) and registered at ClinicalTrials.gov (NCT05843318). While the parent study investigated the relationship between water intake and weight control in adults aged 50+, this thesis conducted a secondary analysis of renal biomarkers and cardiometabolic indicators among

study participants classified as having Stage 1 or Stage 2 Cardiovascular-Kidney-Metabolic (CKM) syndrome.

Standard diagnostic criteria were used to classify participants into CKM stages in accordance with the AHA guidelines.[2] The research team collected all relevant measures—including blood biomarkers, urine samples, and anthropometric data—in accordance with the study protocol. A de-identified dataset, including trial data collected at baseline and at week 12 (i.e., the weight-loss phase), was used to evaluate the primary and secondary kidney and cardiometabolic health outcomes. This thesis research activity was approved by the Virginia Tech Institutional Review Board (IRB) (#25-968).

Overview

This investigation used data from a 12-week randomized controlled trial to assess whether prescribed water intake, combined with a hypocaloric diet and physical activity recommendations, improved renal and cardiometabolic outcomes in adults aged 50 years or older with Stage 1 or Stage 2 CKM syndrome.

Data collection included body weight, waist circumference, blood samples, and urine biomarkers, all assessed at baseline and at week 12. Blood measures included a complete metabolic panel and a lipid profile. Urine measurements were obtained from 24-hour urine samples and included urinary albumin, creatinine, osmolality, specific gravity, and total volume.

The study's primary outcome was the change in the urinary albumin-to-creatinine ratio (uACR), measured at baseline and at week 12. uACR was selected as the primary renal outcome because it is a sensitive biomarker of kidney injury and is strongly associated with cardiometabolic risk, often preceding declines in eGFR.[83 84] uACR has been shown to respond to short-term behavioral changes (over 8-12 weeks), including weight loss and exercise, and to reflect hemodynamic alterations influenced by hydration status, making it a mechanistically relevant outcome for evaluating the effects of increased fluid intake.

Secondary renal outcomes included eGFR, urinary creatinine, albuminuria, urine osmolality, urine specific gravity, and 24-hour urine volume. Exploratory outcomes included cardiometabolic markers (fasting blood glucose, triglycerides, total cholesterol, LDL-C, HDL-C, and VLDL-C) and cardiovascular-anthropometric indicators (BMI, body weight, waist circumference, and blood pressure).

Participants and Randomization

Participant eligibility was determined by age (≥50 years), BMI (≥25 kg/m2), body weight (<400 lbs. due to equipment limitations), weight stability (±2 kg over the past 6 months), and willingness to provide informed consent and to comply with study protocols.

Exclusion criteria included current water intake (>1500 mL/d), uncontrolled hypertension (>159/99 mmHg), uncontrolled diabetes (HbA1c ≥ 8.0), medical conditions requiring specialized dietary prescriptions (e.g., Type 1 diabetes, insulin-treated Type 2 diabetes, or congestive heart failure with fluid restrictions), conditions that precluded participation in an exercise program, or current treatment for obesity (including anti-obesity medications).

The CKM Implementation Guide, released by the AHA, was used to stratify participants based on available study variables.[2 81] Stage 1 was defined by the presence of excess or abdominal adiposity, categorized as BMI ≥ 25 kg/m^2 or waist circumference ≥ 102 cm in men and ≥ 88 cm in women. Stage 2 was classified as Stage 1 adiposity combined with at least one metabolic or renal risk factor: hypertriglyceridemia (triglycerides ≥ 150 mg/dL), hypertension (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg), hyperglycemia (fasting glucose ≥ 126 mg/dL), or reduced kidney function (eGFR < 60 mL/min/1.73 m^2). Initial staging reflected a modified application of the CKM framework, as classification did not include HDL cholesterol, HbA1c levels, albuminuria, or medication use due to data availability.

Participants were assigned to groups using block randomization, stratified by age (50–64 years vs. ≥65 years), BMI category (25–29.9 kg/m^2 vs. ≥30 kg/m^2), and sex, to ensure balanced allocation.

Experimental Design

This study utilized a 12-week randomized controlled trial with a three-group parallel design. Participants were randomized into one of three intervention groups, all following a uniform hypocaloric diet aligned with the Dietary Guidelines for Americans 2020-2025[85]:

1. 500 mL of pre-meal water three times per day (30 minutes before a meal)
2. 1500 mL total daily water intake (throughout the day)
3. No water intake prescription

For analysis, the two hydration groups were first evaluated for differences in pre-to-post changes (Δ) in primary and key secondary outcomes. If no significant differences were observed between the two groups (all $p > 0.05$), they were combined into a single "water" group and compared with the control group to assess the effect of increased water intake on kidney biomarkers.

Combined Behavioral Weight Loss and Hydration Intervention

Participants were assigned to a hypocaloric diet based on estimated initial energy needs, with reductions intended to promote modest weight loss while maintaining nutritional adequacy. Hypocaloric meal plan options included vegetarian, Mediterranean, and typical U.S. dietary patterns to enhance feasibility, adherence, and generalizability. The hypocaloric diet provided 1200, 1500, or 2000 kcal/day, depending on estimated individual energy requirements (kcal) based on body weight. Macronutrient composition aligned with obesity treatment guidelines (15–25% protein, 20–40% fat, and 45–65% carbohydrates) and emphasized fruits, vegetables, lean proteins, and whole grains.

After the initial dietary instruction, participants met weekly with a dietary counselor (an MS RDN or an MS student in dietetics) during the 12-week weight-loss phase to review dietary patterns, adjust energy needs, and reinforce adherence. Counseling was grounded in Social Cognitive Theory, emphasizing

behavioral self-regulation and sustainable dietary change. To assess adherence to the dietary intervention, dietary intake was measured at baseline and at week 12 using the Nutrition Data System for Research (NDSR) via three 24-hour dietary recalls at each time point, which were averaged to determine baseline and week 12 dietary intake.

Participants self-reported and logged daily water intake (water groups) or fruit and vegetable intake (control group), along with pedometer step counts, to reinforce adherence to the intervention protocols.

Testing Procedures

At the screening visit, eligibility was confirmed using anthropometric, clinical, and behavioral measures. Once deemed eligible, participants were enrolled and completed study procedures as outlined in Table 5. Assessments were conducted at baseline and at week 12, and all testing visits were performed in a fasted state (≥8 hours overnight).

Table 5. *Protocol summary: participant testing, biological measurements, and assessments across the 12-week intervention testing period*

Visit No.	Participant Testing	Measurements/Assessments
Screening	· Consent form signed · Health history questionnaire · BEV-Q questionnaire · 24-hour dietary recall · Provided ActiGraph and 24-hour urine collection instructions and materials	· Blood pressure · Body weight · BMI · Waist circumference
Baseline: Visit I	· ActiGraph and 24-hour urine collection returned · 24-hour dietary recall · Randomization	· 24-hour urine osmolality, specific gravity, and volume · Blood pressure · Body weight
Baseline: Visit II	· 24-hour dietary recall	· Blood pressure · Body weight · Complete metabolic panel, serum osmolality, sodium, and eGFR
Week 12: Visit I	· Provided ActiGraph and 24-hour urine collection instructions and materials · Health history questionnaire · 24-hour dietary recall	· Blood pressure · Body weight · BMI · Waist circumference
Week 12: Visit II	· ActiGraph and 24-hour urine collection returned · 24-hour dietary recall	· Blood pressure · Body weight · Complete metabolic panel, serum osmolality, sodium, and eGFR

BEV-Q = Beverage Questionnaire; DXA = dual-energy x-ray absorptiometry; BMI = body mass index. Activities and measures correspond to baseline and 12-week testing visits in the randomized controlled trial protocol.

Procedure: Kidney Health Biomarkers

Details on study methods, including manufacturer information for equipment and devices and laboratory assessment methods (e.g., assay kits), are provided in Table 6. A 24-hour urine collection was used to assess renal function because it accounts for diurnal variation in creatinine and solute excretion.[86] Participants collected urine in a urine container, discarding the first void to establish the collection start time and avoid contamination.[87] All subsequent voids were collected over the next 24 hours, culminating in the final void, which documented the end time.

Upon returning to the lab, total urine volume was measured with graduated cylinders. If the volume exceeded a single cylinder's capacity, the sample was split among multiple cylinders, and the total volume was calculated by summing the measured values. Urine osmolality and specific gravity were used as markers of hydration status. Urine osmolality was measured by freezing-point depression osmometry, with quality control performed using standardized reference solutions.[88 89] [90] [91] [92] Samples were analyzed in duplicate, and mean values were recorded when replicate measurements were within acceptable variance limits.

Urine specific gravity was measured with a handheld clinical refractometer. Measurements were obtained from aliquots brought to room temperature, and values were recorded directly from the refractometer scale.

Urine samples were analyzed for albumin and creatinine at the HNFE Metabolic Phenotyping Core Laboratory, and aliquots were stored at −80 °F. Urinary albumin was measured by enzyme-linked immunosorbent assay (ELISA), and urinary creatinine was quantified using an enzymatic method standardized to isotope-dilution mass spectrometry.[93] [94] [95] [96] [97] The albumin-to-creatinine ratio (uACR) was calculated and reported in mg/g.[98]

Renal biomarkers were interpreted using established clinical thresholds for uACR and eGFR to evaluate kidney function and disease progression.[83 99]

Urine completeness was evaluated using collection duration (20-28 hours), reported missed voids (<2), and total urine volume (>500 mL).[100] Samples inconsistent with complete 24-hour urine collections were excluded from urine-based analyses, and the corresponding urine biomarkers for that time point were treated as missing. A total of 7 urine samples were excluded due to incomplete 24-hour urine collections (5 at baseline and 2 at week 12), as assessed by collection duration and total urine volume. Creatinine-based completeness criteria (>0.1 mmol/kg/d) were not applied because of variability in age, sex, and lean body mass among middle-aged and older adults.[101] [102]

Procedure: Cardiometabolic Biomarkers

Blood samples were collected via venipuncture by a phlebotomy-certified research assistant during the second testing visits at baseline and at week 12. Physical activity was assessed using one week of ActiGraph accelerometer wear time, from which moderate-to-vigorous physical activity (MVPA) and daily step counts were derived. [103]

Fasting blood samples were analyzed by a local CLIA-certified clinical laboratory (LabCorp) using a complete metabolic panel (CMP) that included glucose, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), BUN-to-creatinine ratio, sodium, potassium, chloride, carbon dioxide, calcium, protein, albumin, globulin, A/G ratio, bilirubin, and alkaline phosphatase.[104] eGFR was calculated from serum creatinine using the CKD-EPI 2021 equation.[84]

The HNFE Metabolic Phenotyping Core Laboratory analyzed a fasting lipid panel measuring total cholesterol, triglycerides, HDL-C, LDL-C, and VLDL-C. Serum osmolality was measured by freezing-point depression osmometry.

Cardiometabolic outcomes included fasting glucose (from CMP), lipid parameters (total cholesterol, triglycerides, HDL, and LDL-VLDL), blood pressure, body weight, BMI, and waist circumference.

Blood pressure was measured after 10 minutes of seated rest in a quiet environment, with three readings obtained at 3-minute intervals and averaged using an automated monitor. [105 106] Body weight was measured using a calibrated digital scale, with participants wearing light clothing and no shoes.[107] BMI and waist circumference were assessed at baseline and at week 12. Waist circumference was measured twice at the umbilicus using a tape measure, and the two measurements were averaged.

Table 6. *Outcome variables, clinical thresholds, and measurement methods of the examined biomarkers*

Outcome	Clinical Thresholds	Measurement Method
uACR mg/g	<30 = normal 30–300 = moderately ↑ >300 = severely ↑	= albumin/creatinine
eGFR mL/min/1.73 m^2	≥90 = normal 60–89 = mildly ↓ 30–59 = moderately ↓ 15–29 = severely ↓ <15 = failure	Serum creatinine (CKD-EPI 2021 equation), LabCorp
Urinary creatinine g/day	0.8–2.0 = normal	Colorimetric assay (ALPCO, Cat. No. 74-CRNHU-E02)
Albumin mg/day	<30 = normal 30–300 = moderately ↑ >300 = severely ↑	ELISA (Albumin ELISA; Cat. No. 30-KR6330)
Serum osmolality mOsm/kg	275-295 = normal	Freezing-point depression osmometry (Osmo1; Advanced Instruments).[88]
Urine osmolality mOsm/kg	300-900 = normal	Freezing-point depression osmometry (Osmo1; Advanced Instruments), Osmolality quality assurance control (Control Renol™ Urine Osmolality; Advanced Instruments)
Specific gravity	1.005-1.030 = normal ≥ 1.020 = dehydration	Handheld refractometer (Fisherbrand™ Handheld Analog Clinical Refractometer).[83]
24-h urine volume mL	800-2000 = normal <500 = oliguria >3000 = polyuria	Urine collection container (Samco™ SW-3000; Thermo Scientific™), graduated cylinders (Nalgene™; Thermo Scientific™ Nalgene™) [77] [78]
Blood pressure mmHg	<120/80 = normal 120–129/<80 = elevated ≥130/80 = hypertension	Automated monitor (Professional Intellisense® HEM-907XL; Omron).
Heart rate beats/min	60–100 = normal	Automated monitor (Professional Intellisense® HEM-907XL; Omron).
Waist circumference cm	>102 (men) = ↑ risk >88 (women) = ↑ risk	Standard measuring tape (Gulick II Measuring Tapes; Country Technology, Inc.) [108]
Weight kg	N/A	Digital scale (SCALE-TRONIX; Welch Allyn)
BMI kg/m2	<25 = normal 25–29.9 = overweight ≥30 = obese	= weight (kg)/height^2 (m^2)
Glucose mg/dL	70–99 = normal 100–125 = impaired ≥126 = diabetes	Complete metabolic panel (LabCorp)
Triglycerides mg/dL	<150 = normal 150–199 = borderline ↑ 200–499 = ↑ ≥500 = very ↑	Enzymatic assay (LabAssay (TM) Triglyceride; FUJIFILM), [92]
Total cholesterol mg/dL	<200 = normal 200–239 = borderline ↑ ≥240 = ↑	Enzymatic assay (LabAssay (TM) Cholesterol, FUJIFILM)
LDL/VLDL mg/dL	<100 = normal 130–159 = borderline ↑ ≥160 = ↑	Enzymatic assay (EnzyChrom™ HDL and LDL/VLDL Assay Kit, Cat. No: EHDL-100)
HDL mg/dL	60-80 = normal <40 (men) = ↓ <50 (women) = ↓	Enzymatic assay (EnzyChrom™ HDL and LDL/VLDL Assay Kit, Cat. No: EHDL-100)

eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; AHA = American Heart Association; BMI = body mass index; CMP = complete metabolic panel. Thresholds and measurement methods per sources[107 109-111] [91 106 109 112].

Statistical Analysis

Only participants with complete baseline and week 12 outcome data were included in the analysis due to the laboratory resources and expenses required for sample analysis. Groups 1 and 2 were combined into the Water Group after evaluating pre-to-post changes in study outcomes. Independent samples t-tests comparing Groups 1 and 2 showed no significant differences in changes in uACR, BMI, eGFR, or hydration-related variables (all $p > 0.05$), supporting their combination into a single "water" intervention group (Table 7).

Table 7. *Variable analysis for combining the two water intervention groups 1 and 2*

Variable	Group 1 Δ (Mean ± SD)	Group 2 Δ (Mean ± SD)	p-value
uACR mg/g	+9.3 ± 5.4	+1.0 ± 5.4	0.28
BMI kg/m2	-1.6 ± 1.3	-1.7 ± 1.2	0.67
eGFR mL/min/1.73 m^2	+0.3 ± 10.5	+1.2 ± 9.3	0.66
Urine osmolality mOsm/kg	-124.4 ± 172.1	-107.6 ± 147.5	0.63
24-h urine volume mL	+393.6 ± 939.1	+438.6 ± 741.9	0.81

Values are presented as mean change (Δ = Week 12 – Baseline) ± standard deviation (SD). P-values reflect between-group differences in changes between Group 1 and Group 2, as determined by independent-samples t-tests. Abbreviations: uACR = urinary albumin-to-creatinine ratio; BMI = body mass index; eGFR = estimated glomerular filtration rate.

Descriptive statistics summarize baseline characteristics. Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as counts and percentages. Baseline differences were evaluated using independent-samples t-tests for continuous variables and chi-square ($\chi 2$) tests for categorical variables.

Between-group differences at week 12 were evaluated using analysis of covariance (ANCOVA), adjusting for baseline values and CKM stage. Adjusted least squares means (LSMeans) ± standard error (SE) were reported.

Missing data were minimal (<5%) across outcomes; therefore, a complete-case analysis was performed. Participants were included in the analysis only if they had the required baseline and week 12 data. Change

scores (Δ = week 12 – baseline) were calculated and presented descriptively. Dietary intake data were available for a subset of participants and are presented descriptively.

Statistical significance was set at $p < 0.05$. Analyses were conducted in JMP Student Edition (version 19.1.0; JMP Statistical Discovery LLC, Cary, NC).

RESULTS

Participant Flow

The flow of participants through the study is shown in the CONSORT diagram (Figure 4). A total of 158 participants were enrolled in the study. Of these, 125 completed the 12-week intervention, had complete outcome data, and were included in the completers-only analysis: Water (n=87) and Control (n=38). Participants were excluded for incomplete or missing baseline or week 12 outcome data, as shown in Figure 4.

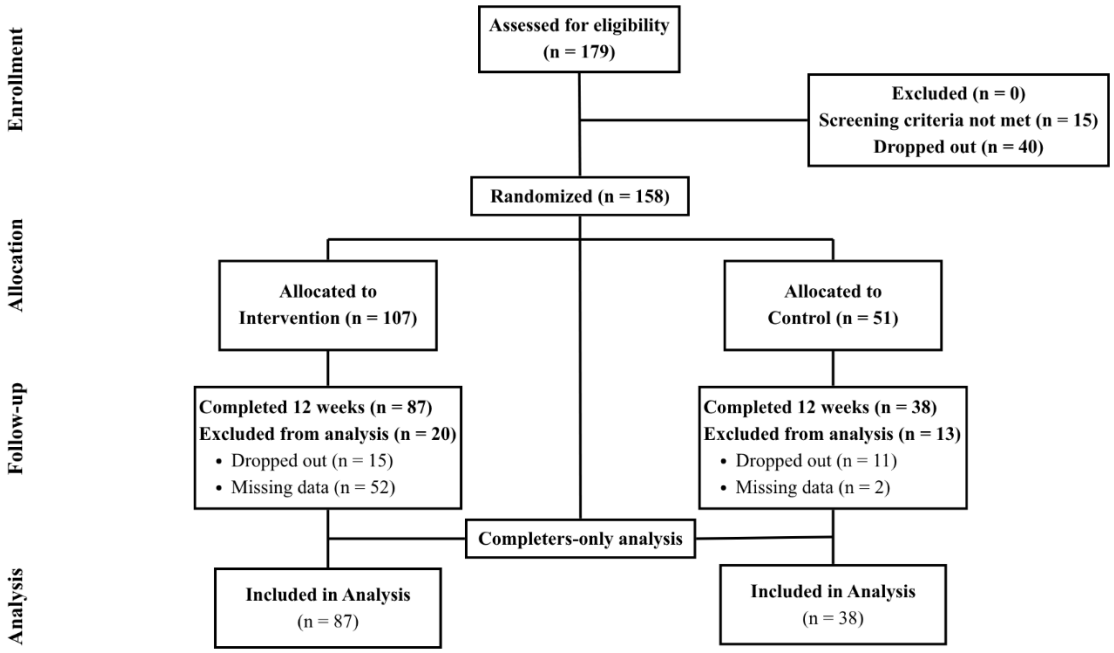

Figure 4. *CONSORT flow diagram of participant enrollment, allocation, follow-up, and inclusion in the completers-only analysis*

Baseline Participant Characteristics

Baseline participant characteristics are summarized for the full sample and by group in Table 8. Participants ranged in age from 50 to 80 years, with a mean of 61 ± 7 years. The sample was predominantly female (74.4%) and White (96%). Mean baseline BMI was classified as "obesity." Most participants were classified as CKM Stage 2 (77.6%), and the remainder were in Stage 1 (22.4%). The median baseline uACR was 7.4 mg/g, which falls within the normal range. Other baseline kidney function biomarkers and hydration indicators (eGFR, urinary creatinine, urine osmolality, and 24-h urine volume) were within normal ranges. There were no significant baseline group differences in demographic, anthropometric, kidney function, hydration, or behavioral variables ($p > 0.05$).

Table 8. *Baseline participant characteristics*

Variable	Total (n = 125)	Water Group (n = 87)	Control Group (n = 38)	p-value
DEMOGRAPHICS				
Age, years	61 ± 7	61 ± 7	61 ± 7	0.85
Sex, n (%)	…	…	…	$\chi2 = 0.61$
Male	32 (25.6%)	24 (27.6%)	8 (21.1%)	…
Female	93 (74.4%)	63 (72.4%)	30 (78.9%)	…
Race/Ethnicity, n (%)	…	…	…	$\chi2 = 2.35$
Asian	4 (3.2%)	3 (3.4%)	1 (2.6%)	…
White	120 (96.0%)	84 (96.6%)	36 (94.7%)	…
Black	1 (0.8%)	0 (0.0%)	1 (2.6%)	…
ANTHOPOMETRICS				
Height, cm	166.2 ± 9.0	167.1 ± 8.8	164.1 ± 9.3	0.10
Weight, kg	93.1 ± 19.3	94.1 ± 19.1	90.8 ± 19.8	0.40
BMI, kg/m^2	33.6 ± 5.7	33.6 ± 5.6	33.6 ± 5.9	1.00
BMI category	…	…	…	$\chi2 = 0.10$
Overweight	37 (29.6%)	25 (28.7%)	12 (31.6%)	…
Obesity	88 (70.4%)	62 (71.3%)	26 (68.4%)	…
KIDNEY FUNCTION				
CKM Stage	…	…	…	$\chi2 = 1.35$
Stage 1	28 (22.4%)	17 (19.5%)	11 (28.9%)	…
Stage 2	97 (77.6%)	70 (80.5%)	27 (71.1%)	…
uACR, mg/g	11.6 ± 14.4	11.4 ± 13.7	12.1 ± 15.8	0.81
eGFR, mL/min/1.73 m^2	81.1 ± 13.6	80.4 ± 13.7	82.9 ± 13.2	0.34
Creatinine, mg/dL	0.88 ± 0.15	0.89 ± 0.15	0.86 ± 0.16	0.26
Urine osmolality	457 ± 189	475 ± 196	415 ± 167	0.08
24h urine volume, mL	2074 ± 813	2040 ± 839	2153 ± 754	0.50
HYDRATION AND BEHAVIORAL				
Water intake, mL/d	794 ± 412	791 ± 426	798 ± 385	0.84
Steps/Day	9460 ± 2515	9321 ± 2442	9776 ± 2683	0.37
MVPA, min/week	1054 ± 382	1029 ± 370	1110 ± 408	0.30
Wear time, days	6.8 ± 0.5	6.9 ± 0.4	6.8 ± 0.5	0.30

Values are presented as mean ± standard deviation (SD) for continuous variables and as frequency (n) and percentage (%) for categorical variables. P-values reflect between-group differences between the water intervention group and the control group. Comparisons were conducted using independent-samples t-tests for continuous variables and chi-square tests for categorical variables. Abbreviations: CKM = cardiovascular-kidney-metabolic; BMI = body mass index; uACR = urinary albumin-to-creatinine ratio; eGFR = estimated glomerular filtration rate; MVPA = moderate-to-vigorous physical activity.

Primary and Secondary Outcomes

Between-group differences in kidney and cardiometabolic outcomes at baseline and at week 12 are presented in Table 9. After adjusting for baseline values and CKM stage, there was no statistically significant difference in the primary outcome, uACR, between the intervention and control groups at week 12 ($p = 0.53$).

Secondary renal outcomes, including eGFR, urinary creatinine, and albumin, did not differ significantly between groups after adjustment (all $p > 0.05$).

Hydration-related outcomes showed significant between-group differences: urine osmolality ($p = 0.02$), urine specific gravity ($p = 0.01$), and 24-hour urine volume ($p = 0.01$). Urine osmolality decreased substantially in the intervention group ($\Delta = -116 \pm 160$ mOsm/kg H2O) compared with the control group ($\Delta = -30 \pm 139$ mOsm/kg H2O). Urine specific gravity decreased in the intervention group and differed significantly between groups. 24-hour urine volume increased in the intervention group ($\Delta = +416 \pm 836$ mL), whereas the control group showed minimal change.

Cardiometabolic outcomes, including blood pressure, body weight, BMI, fasting glucose, or lipid parameters, showed no significant between-group differences after adjustment (all $p > 0.05$). Body weight and BMI decreased in both groups, corresponding to approximately 4.7% and 5.1% reductions in body weight in the water and control groups, respectively. Fasting glucose and lipid parameters (triglycerides and total cholesterol) showed modest changes over the intervention period but did not differ significantly between groups (all $p > 0.05$).

Table 9. *Kidney and cardiometabolic health variables at baseline and 12 weeks of intervention in water vs. control groups*

Variable	Water Baseline (Mean ± SD)	Water Week 12 (LSMean ± SE)	Water Δ (Mean ± SD)	Control Baseline (Mean ± SD)	Control Week 12 (LSMean ± SE)	Control Δ (Mean ± SD)	p-value
uACR mg/g	11.4 ± 13.7	20.6 ± 3.9	5.1 ± 34.7	12.1 ± 15.8	16.8 ± 5.3	1.8 ± 24.2	0.53
eGFR mL/min/1.73m2	80.4 ± 13.7	81.3 ± 1.1	0.7 ± 9.8	82.9 ± 13.2	80.0 ± 1.5	-1.4 ± 9.1	0.46
Urinary creatinine g/day	1.02 ± 0.5	1.0 ± 0.04	-0.02 ± 0.5	1.04 ± 0.4	1.1 ± 0.06	0.08 ± 0.4	0.08
Serum creatinine mg/dL	0.89 ± 0.1	0.88 ± 0.01	0.00 ± 0.1	0.86 ± 0.2	0.88 ± 0.02	0.01 ± 0.08	0.90
Albumin mg/day	10.6 ± 12.2	16.5 ± 2.8	3.9 ± 24.9	10.4 ± 9.9	14.4 ± 3.8	2.3 ± 16.3	0.63
Serum osmolality mOsm/kg	293 ± 12	292 ± 1	-1 ± 12	291 ± 4	290 ± 1	-1 ± 7	0.16
Urine osmolality mOsm/kg	472 ± 192	349 ± 17	-116 ± 160	414 ± 169	410 ± 23	-30 ± 139	0.02*
Urine specific gravity	1.01 ± 0.01	1.01 ± 0.00	0.01 ± 0.1	1.01 ± 0.01	1.01 ± 0.00	0.00 ± 0.00	0.01*
24-hour urine volume mL	2078 ± 826	2540 ± 89	416 ± 836	2159 ± 764	2189 ± 120	30 ± 652	0.01*
Systolic bp mmHg	126 ± 15	120 ± 1	-6 ± 10	125 ± 13	119 ± 2	-6 ± 8	0.92
Diastolic bp mmHg	89 ± 9	73 ± 1	-16 ± 7	89 ± 9	72 ± 1	-17 ± 6	0.64
Heart rate beats/min	66 ± 9	63 ± 1	-3 ± 5	66 ± 8	62 ± 1	-4 ± 4	0.52
Waist circumference cm	110.4 ± 13.0	107.0 ± 1.4	-3.1 ± 9.8	110.1 ± 18.5	103.8 ± 1.8	-9.6 ± 26.4	0.13
Body weight kg	94.1 ± 19.1	88.6 ± 0.4	-4.5 ± 3.5	90.8 ± 19.8	88.2 ± 0.6	-4.8 ± 3.0	0.55
BMI kg/m2	33.6 ± 5.6	31.9 ± 0.2	-1.6 ± 1.2	33.6 ± 5.9	31.7 ± 0.2	-1.8 ± 1.2	0.39
Fasting glucose mg/dL	101 ± 15	98 ± 1	-3 ± 10	98 ± 12	98 ± 1	-1 ± 9	0.72
Triglycerides	108 ± 59	98 ± 6	-8 ± 56	116 ± 62	101 ± 8	-10 ± 58	0.77

Variable	Water Baseline (Mean ± SD)	Water Week 12 (LSMean ± SE)	Water Δ (Mean ± SD)	Control Baseline (Mean ± SD)	Control Week 12 (LSMean ± SE)	Control Δ (Mean ± SD)	p-value
mg/dL							
Total cholesterol mg/dL	207 ± 47	203 ± 6	-5 ± 52	209 ± 47	212 ± 8	3 ± 56	0.39
LDL/VLDL mg/dL	122 ± 45	128 ± 6	3 ± 53	124 ± 44	139 ± 8	14 ± 62	0.23
HDL mg/dL	63 ± 23	57 ± 2	-7 ± 18	62 ± 27	54 ± 2	-9 ± 19	0.15

*p<0.05. Baseline values are presented as mean ± standard deviation (SD). Week 12 values are presented as adjusted least squares means (LSMeans) ± standard error (SE) from ANCOVA models that adjust for baseline values of the respective outcome, CKM stage, and group. P-values reflect between-group differences at week 12. Physical activity and water intake variables were available for all participants, whereas dietary intake variables were available for a subset of participants (n = 113) and are presented descriptively. Abbreviations: MVPA = moderate-to-vigorous physical activity; HEI = Healthy Eating Index.

Adherence to Intervention

Adherence-related variables are shown in Table 10. At Week 12, there were no differences between the intervention and control groups in self-reported water intake, physical activity (steps/day and MVPA), or wear time (all $p > 0.05$).

Changes in steps per day did not differ between groups ($p = 0.34$). MVPA levels remained stable, with no significant differences ($p = 0.71$).

Dietary intake variables, available for a subset of participants ($n = 113$) at the time of this analysis, are presented descriptively and show no meaningful group differences. The reductions in total energy intake in both groups are consistent with the hypocaloric intervention. Macronutrient intake did not differ between groups.

Overall, adherence measures indicate both groups engaged with the behavioral intervention components with similar patterns observed across water intake, physical activity, and dietary intake.

Table 10. *Self-reported adherence to intervention diet and PA outcomes at baseline and week 12*

Variable	Water Baseline	Water Week 12	Water Δ	Control Baseline	Control Week 12	Control Δ	p-value
Water intake mL/d	792 ± 426	1329 ± 79	551 ± 666	798 ± 385	1160 ± 106	372 ± 707	0.17
Steps/Day	9321 ± 2442	10360 ± 207	733 ± 1786	9776 ± 2683	10055 ± 276	409 ± 3181	0.34
MVPA min/week	1029 ± 370	1145 ± 29	66 ± 241	1110 ± 408	1128 ± 39	42 ± 240	0.71
Wear time days	6.9 ± 0.4	6.9 ± 0.06	6.9 ± 0.04	6.8 ± 0.5	6.9 ± 0.09	6.8 ± 0.5	0.65
Energy total kcal	1813 ± 59	1577 ± 67	-215 ± 546	1896 ± 85	1618 ± 92	-218 ± 372	0.70
% Carbohydrates	43.0 ± 0.9	41.4 ± 1.1	-2.0 ± 9.9	43.3 ± 1.3	42.8 ± 1.5	-0.9 ± 5.2	0.44
% Fat	37.4 ± 6.5	36.9 ± 0.9	-0.3 ± 8.5	38.3 ± 4.1	37.9 ± 1.3	-0.06 ± 5.6	0.52
% Protein	16.7 ± 4.3	19.4 ± 0.6	2.4 ± 5.0	16.4 ± 3.4	18.2 ± 0.8	1.4 ± 4.5	0.23
Added sugars g	40.3 ± 29. 5	25.1 ± 2.3	-15.1 ± 25.7	45.8 ± 22.9	26.7 ± 3.2	-17.1 ± 19.8	0.66
Dietary fiber g	21.3 ± 7.2	22.0 ± 1.1	0.4 ± 8.9	20.0 ± 6.4	22.8 ± 1.4	2.1 ± 7.2	0.62
Sodium mg	3129 ± 1019	2731 ± 139	-406 ± 1308	3047 ±1115	2797 ± 191	-276 ± 963	0.76
Potassium mg	2470 ± 642	2523 ± 101	6 ± 765	2521 ± 632	2439 ± 138	-106 ± 688	0.60
HEI-2015 score	55 ± 12	63 ± 2	7 ± 14	56 ± 12	65 ± 2	8 ± 12	0.54

Values are presented as mean ± standard deviation for baseline and change (delta), and as least squares means (LSMeans) ± standard error for Week 12. P-values reflect between-group differences from baseline to 12 weeks and are derived from analysis of covariance (ANCOVA) with adjustments for baseline values, CKM stage, and group. Physical activity and water intake variables were available for all participants, whereas dietary intake variables were available for a subset of participants (n=113) and are presented descriptively. MVPA = moderate-to-vigorous physical activity; HEI = Healthy Eating Index.

CKM Stage Classification

Changes in CKM stage classification indicated that a subset of participants transitioned to a lower CKM stage (42.53% in the water group and 42.11% in the control group); however, there were no significant between-group differences in stage transitions ($p = 0.85$).

Table 11. *Changes in CKM Stage Classification over 12 Weeks*

CKM Stage	Water Group (n =)	Control Group (n =)	p-value
CKM Stage Change	…	…	0.85
Improved CKM stage	37 (42.53%)	16 (42.11%)	…
No change in CKM stage	49 (56.32%)	21 (55.26%)	…
Worsened CKM stage	1 (1.15%)	1 (2.63%)	…

Values are presented as n (%). CKM stage change was categorized as improved (Stage 2 → Stage 1), worsened (Stage 1 → Stage 2), or no change in stage. Percentages were calculated within each group. The p-value reflects the between-group differences in CKM stage change classification over time and was assessed using Fisher's exact test.

DISCUSSION

Main Findings

The present study evaluated the effects of a prescribed water-intake intervention, combined with a hypocaloric diet and a physical activity program, on renal and cardiometabolic outcomes in adults with early-stage CKM syndrome. Contrary to our initial hypothesis, no significant differences were observed between the intervention and control groups for the primary outcome, uACR, after 12 weeks. These findings suggest that adding prescribed water intake did not confer measurable improvements in kidney-related outcomes within the timeframe of this study. Although hydration-related biomarkers, including urine osmolality, specific gravity, and 24-hour urine volume, showed significant changes consistent with increased fluid intake, these physiological changes did not translate into improvements in renal biomarkers. Secondary and cardiometabolic outcomes also showed no significant between-group differences.

Combined Intervention Adherence

Hydration was conceptualized in this study as an active behavioral component of the weight-loss intervention. The underlying hypothesis was that increased water intake may confer additional renal benefits beyond caloric restriction alone through proposed mechanisms, including hemodynamic modulation and potential suppression of vasopressin-mediated renal stress.

Assessing participants' adherence to the prescribed behavioral components is a necessary step in evaluating the intervention's validity relative to the observed outcomes. Adherence indicators showed expected and beneficial changes across intervention targets, including increases in reported water intake, significant changes in hydration biomarkers, and meaningful reductions in body weight over the 12 weeks. These results demonstrate that participants successfully engaged with the prescribed intervention.

Adherence to the physical activity intervention was also analyzed. Both groups demonstrated increases in daily step counts and moderate-to-vigorous physical activity (MVPA); these changes were modest and did not differ significantly between groups ($p > 0.05$). For the nutritional counseling interventions, participants adhered to the dietary prescription. Observed reductions in total energy intake and modest shifts in macronutrient composition reflect this adherence. Protein intake increased slightly, while added sugar intake decreased.

Primary Outcome

It is warranted to carefully interpret the lack of improvement in uACR among the participants. uACR is a sensitive marker of early renal dysfunction. Research shows it is responsive to hemodynamic changes and variations in hydration status, even in intervention trials with similar timelines. It is important to note that participants began the study with mostly normal uACR values (<30 mg/g). This may have limited the potential for measurable improvement due to a floor effect. The overall magnitude of change in hydration may not have been sufficient to meaningfully influence renal hemodynamics or filtration processes over 12 weeks, given the combined nature of the lifestyle behavior changes accompanying the water intake intervention.

Secondary Outcomes

Secondary renal outcomes (eGFR, urinary creatinine, and albumin) remained stable, with no significant between-group differences. The existing literature indicates that eGFR is insensitive to short-term interventions, especially in populations without advanced CKD. These findings are consistent with the

literature. Mean participants had mildly decreased eGFR values at baseline, while urinary creatinine and albumin values were within normal ranges.

Cardiometabolic outcomes also did not differ significantly between groups. Fasting glucose at baseline was within the normal or borderline impaired range (~100 mg/dL). Both groups showed small reductions over the intervention period and remained within clinically accepted ranges. Triglyceride levels were within normal ranges at baseline and demonstrated modest decreases in both groups. LDL/VLDL and HDL levels were within acceptable ranges at baseline but showed slight increases in LDL/VLDL in both groups and decreases in HDL over the intervention period.

Both groups experienced meaningful weight loss and reductions in BMI and waist circumference over the intervention period. Participants remained in the overweight or obese categories, but continued adherence to the intervention may yield further improvements in cardiometabolic risk profiles over time. Participants' blood pressure also improved in both systolic and diastolic measures, which is relevant for participants with early-stage CKM. These reductions are clinically important and can reverse the progression of CKM to higher stages, where CVD is prominent. A subset of participants transitioned to a lower CKM stage following the 12-week intervention, which could further support potential improvements in overall cardiometabolic health. Improvement in CKM stage classification is a clinically meaningful goal in the management of early-stage CKM.

These findings, although not statistically significant, reflect early signs and effects of hypocaloric diet and physical activity interventions, as evidenced by small shifts in cardiometabolic risk markers. This suggests that to detect meaningful differences, the intervention trial may require a longer duration or a more intensive regimen.

Previous research

Previous research has demonstrated significant reductions in uACR over 12 weeks following behavioral weight-loss interventions that included lifestyle modification.[113] It is crucial to highlight that few

studies have evaluated the combined effects of behavioral weight loss and increased water intake. The motivation for integrating both interventions is grounded in evidence supporting each strategy independently. This study represents an effort to examine the potential additive or synergistic effects of a combined lifestyle. This integrative model was designed to target multiple interrelated mechanisms underlying CKM progression, thereby promoting coordinated improvements across the renal, metabolic, and cardiovascular systems.

The findings of this study do not align with prior research reporting significant reductions in uACR with the prescribed intervention. The intervention was successfully implemented among participants, yet uACR did not improve significantly. Differences in intervention design, participant characteristics, or baseline renal status may explain this discrepancy.

In a Japanese intervention trial, a 12-week lifestyle modification trial was conducted that incorporated dietary changes and combined aerobic/resistance exercise.[114] The results demonstrated reductions in uACR while maintaining eGFR. The study reported that reductions in uACR are associated with improvements in fasting glucose and systolic blood pressure, further reinforcing the relevance of uACR to the cardiometabolic framework of CKM.[114] In the present study, participants also showed improvements in certain cardiometabolic outcomes, including fasting glucose and systolic blood pressure. However, these changes did not translate into significant improvements in uACR. These findings suggest that cardiometabolic adaptations may begin within 12 weeks. Still, detectable changes in renal biomarkers may require a longer duration or a greater magnitude of physiological change to be measurable.[114]

The study by Straznicky et al. demonstrated reductions in albuminuria and improvements in eGFR following a 12-week weight-loss intervention among individuals with obesity and metabolic syndrome.[115] These findings support the premise that meaningful improvements in kidney health biomarkers can be achieved through a hypocaloric diet combined with aerobic exercise. Because the participants began the research trial with uACR values within the normal range, detectable improvement

may have been limited.[115] Research also shows that reductions in albumin were correlated with improvements in lipid concentrations, highlighting a potential interaction between renal and lipid metabolism.[114 115] This relationship supports the inclusion of lipid parameters as cardiometabolic outcomes in the present analysis.

Strengths and Limitations

The main strength of this study is that it is among the first to undertake an intervention trial among adults within the CKM framework. The intervention itself further strengthens the study, combining prescribed water intake with behavioral weight loss to evaluate renal and cardiometabolic outcomes. Including assessments of both outcome variables demonstrates an understanding of the integrative syndrome and provides a multidimensional evaluation of intervention effectiveness. This study is unique in its intention to address CKM risk factors through a holistic behavioral modification intervention in the early stages to prevent disease progression, prior to pharmacological intervention in the treatment of established pathology.

The short intervention duration (12 weeks) may have limited this study's ability to detect meaningful changes in renal outcomes, such as uACR and eGFR, as well as other cardiometabolic outcomes. A limitation to note is that dietary intake data are available only for a subset of participants, which limits the ability to fully evaluate participants' nutritional adherence. Other limitations, such as measurement error in self-reported behaviors or variability in individual responses to lifestyle interventions, may have influenced the observed results.

Conclusion

In conclusion, adding a prescribed water-intake intervention to a hypocaloric diet and physical activity program did not yield significant improvements in uACR or other renal and cardiometabolic outcomes compared with the control group over 12 weeks in adults with early-stage CKM syndrome. These findings reveal the complexity of CKM management and highlight the need for longer-duration studies.

To better understand the role of hydration in kidney health and its effects on CKM biomarkers, there is a demand for more targeted, tailored interventions.

Chapter 4: Conclusion and Future Directions

This thesis evaluated the effects of a hypocaloric diet and increased water intake on renal and cardiometabolic outcomes among adults with Stage 1 or 2 CKM syndrome. Despite the null findings, participants' adherence to these behavioral changes provides encouraging evidence that individuals can prioritize and engage with an accessible intervention that offers behavioral strategies for disease prevention and early CKM management.

While implementing lifestyle modifications, including increased water intake, modest weight loss, and increased physical activity, is expected to improve renal and cardiometabolic outcomes, the findings of this study suggest that these benefits may require a longer intervention duration or a population with greater baseline kidney dysfunction to produce measurable improvements in renal outcomes. This intervention aligns with established treatment recommendations for CKM stages as outlined by the AHA. Continued adherence may yield more substantial improvements over time.

Future research should investigate the effects of longer-duration interventions to determine whether extended exposure to combined dietary, physical activity, and hydration strategies yields measurable improvements in renal and cardiometabolic outcomes. Future intervention designs should assign the combined intervention to one group and compare it with a control group receiving no lifestyle intervention. This will help clarify the specific role of the combined intervention by avoiding the confounding effects of shared treatment. Studies with larger, more diverse populations are needed to improve generalizability and to better understand individual variability in response to lifestyle interventions.

Future work may also benefit from more precise measurement of hydration status. This includes biomarkers of vasopressin activity to further elucidate the mechanistic role of water intake in kidney function. Interventions that directly target adherence to prescribed water intake or tailor hydration

recommendations to individual physiological characteristics may provide greater insight into the clinical utility of hydration as a modifiable factor in CKM management.

The lack of significant changes in renal biomarkers may reflect participants' relatively normal baseline kidney function. In this population, the potential for measurable improvement over the 12-week intervention period may be limited. Future research should consider screening participants for evidence of early kidney dysfunction before enrollment, using elevated uACR or reduced eGFR, to ensure that participants have measurable renal risk at baseline. This would allow future studies to more effectively examine the combined intervention's influence on kidney health and its effects on CKM-related renal and cardiometabolic indicators, in line with this study's aim.

Future research based on this study's primary analysis should include subgroup analyses to assess the benefits of combined behavioral interventions for populations with greater clinical needs. This is crucial for clarifying the effectiveness of this intervention in individuals at higher risk of CKM progression.

The research presented in this thesis is intended to serve as a foundation for future investigations, providing guidance for building upon this intervention trial, refining its approach, and contributing to the expanding body of knowledge surrounding the intricate web of cardiovascular-kidney-metabolic syndrome.

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Appendices

Appendix A. Additional tables

Table A1. *Supplemental baseline participant characteristics presented separately for all three randomized groups in the trial.*

Variable	Total (n=)	Group 1 (n=)	Group 2 (n=)	Group 3 (n=)	p-value
DEMOGRAPHICS					
Age, years	61.3 ± 7.4	61.0 ± 7.0	61.5 ± 7.6	61.5 ± 7.6	0.95
Sex, n (%)	…	…	…	…	0.74
Male	32 (25.6%)	12 (9.6%)	12 (9.6%)	8 (6.4%)	…
Female	93 (74.4%)	32 (25.6%)	31 (24.8%)	30 (24.0%)	…
Race/Ethnicity, n (%)	…	…	…	…	0.61
Asian	4 (3.2%)	2 (1.6%)	1 (0.8%)	1 (0.8%)	…
White	120 (96%)	42 (33.6%)	42 (33.6%)	36 (28.8%)	…
Black	1 (0.8%)	0 (0%)	0 (0%)	1 (0.8%)	…
ANTHOPOMETRICS					
Height, cm	166.2 ± 9.0	167.2 ± 9.3	167.1 ± 8.4	164.1 ± 9.3	0.23
Weight, kg	93.1 ± 19.3	92.3 ± 18.2	95.9 ± 20.0	90.8 ± 19.8	0.47
BMI, kg/m^2	33.6 ± 5.7	32.9 ± 4.9	34.3 ± 6.3	33.6 ± 5.9	0.51
BMI category	…	…	…	…	0.91
Overweight	37 (29.6%)	12 (9.6%)	13 (10.4%)	12 (9.6%)	…
Obesity	88 (70.4%)	32 (25.6%)	30 (24.0%)	26 (20.8%)	…
KIDNEY FUNCTION					
uACR, mg/g	11.6 ± 14.4	11.5 ± 15.3	11.2 ± 12.2	12.1 ± 15.8	0.96
eGFR, mL/min/1.73 m^2	81.1 ± 13.6	80.9 ± 13.6	79.9 ± 14.0	82.9 ± 13.2	0.61
Creatinine, mg/dL	0.88 ± 0.15	0.88 ± 0.13	0.90 ± 0.17	0.86 ± 0.16	0.39
Urine osmolality	457.1 ± 189.0	470.2 ± 203.0	480.6 ± 191.0	415.4 ± 166.8	0.26
24h urine volume, mL	2074.4 ± 812.6	1967.2 ± 864.5	2114.5 ± 814.9	2153.3 ± 754.1	0.54
HYDRATION AND LIFESTYLE					
Water intake, mL/d	793.8 ± 412.2	724.7 ± 415.7	860.4 ± 429.9	798.4 ± 384.5	0.31
Steps/Day	9459.9 ± 2515.2	9382.4 ± 2202.9	9259.7 ± 2689.4	9776.3 ± 2683.4	0.63
MVPA, min/week	1053.8 ± 382.4	1061.4 ± 352.3	996.1 ± 389.6	1110.2 ± 407.6	0.41
Wear time, days	6.8 ± 0.5	6.9 ± 0.3	6.8 ± 0.6	6.8 ± 0.5	0.19

Table A2. *Baseline Participant Characteristics of Dietary Intake*

Variable	Total	Water Group	Control Group	p-value
DIETARY INTAKE				
Energy total, kcal	1840 ± 432	1813 ± 59	1896 ± 85	0.42
% Carbohydrates	43.1 ± 6.6	43.0 ± 0.9	43.3 ± 1.3	0.87
% Fat	37.7 ± 5.8	37.4 ± 6.5	38.3 ± 4.1	0.46
% Protein	16.6 ± 4.0	16.7 ± 4.3	16.4 ± 3.4	0.78
Added sugars, g	42.1 ± 27.5	40.3 ± 29. 5	45.8 ± 22.9	0.37
Dietary fiber, g	20.9 ± 6.9	21.3 ± 7.2	20.0 ± 6.4	0.41
Sodium, mg	3102.4 ± 1044.6	3129.1 ± 1018.8	3046.8 ±1114.9	0.75
Potassium, mg	2486.9 ± 634.8	2470.4 ± 641.6	2521.1 ± 631.8	0.73
HEI-2015 score	55.4 ± 11.8	55.0 ± 11.8	56.2 ± 12.0	0.64