Degree Project

UNIVERSITY OF SKÖVDE

Effect of cardiovascular diseases on the severity of patients with renal failure

Master Degree Project in Bioscience

Second Cycle 60 credits

Autumn term 2022

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Abstract

Chronic kidney disease greatly raises cardiovascular disease risk. Heart disease and death risk grow proportionately with renal disease progression. Investigate the link between cardiovascular disease prevalence and chronic renal disease severity and mortality using meta-analysis. In this study, 155 publications were found after searching several databases (including PubMed and Google Scholar). 48 studies that matched the inclusion criteria were included in the literature review, however, only 20 were included in the meta-analysis. 17101 people had CKD, while 8883 had CVD or non-CVD. Using the R programming language, a meta-analysis was performed to get a pooled impact of the influence of CVD on the severity of CKD (odds ratio OR), and a funnel plot was also generated to check for publication bias. The outcomes of the meta-analysis indicate that cardiovascular disease has a moderate impact on the severity of chronic kidney disease (OR=2.28, 95% CI, 1.90-2.73). All data will give essential insights into the epidemiology of the cardiovascular disease in chronic kidney disease (CKD), disclose the influence of individual risk variables on bad outcomes, and serve as the platform for future interventional research. Further investigation of the particular (non-traditional) risk factors associated with the renal illness that contribute to accelerated atherosclerosis in this population is necessary to improve the efficacy of cardiovascular treatments for patients with CKD. The purpose of this research is to determine whether and how these variables affect the development of CKD.

Keywords: Chronic Kidney Disease, Cardiovascular disease, Meta-analysis, Odds ratio.

Popular Scientific Summary

The risk of cardiovascular disease increases dramatically in the presence of chronic renal disease. It has been shown that the danger of cardiovascular disease and mortality rises proportionally with the degree to which renal disease has progressed. Therefore, chronic kidney disease (CKD) diagnosis and therapy should begin as soon as possible to improve outcomes in nephropathy and proteinuria. Anticipate that these interventions will lead to parallel decreases in the prevalence of cardiovascular disease (CVD), leading to fewer people developing end-stage kidney disease (ESKD). All patients with cardiovascular disease should be screened for chronic kidney disease by calculating their estimated glomerular filtration rate (eGFR) and checking for proteinuria with a morning (or resting) spot urine albumin: creatinine ratio. This high-risk group requires aggressive care of conventional cardiovascular risk factors, including strict hypertension control, management of hyperglycemia and hyperlipidemia, and smoking cessation. Randomized trials assessing the effectiveness of cardiovascular therapies in people with CKD are required, and more research is needed to identify the specific (non-traditional) risk factors associated with the renal disease that contribute to accelerated atherosclerosis in this group. This study's rationale is to examine how these factors are related to the progression of CKD.

All searched online databases including PubMed and Google Scholar for recently published, peer-reviewed, scientifically-referenced publications (future-looking research) on the topic, and those were the ones used. These concerns were addressed by using the Population, Intervention, and Comparison. Relevance to the research question and absence of duplication in published material were also taken into account. To be reviewed and included in this study, papers had to meet both eligibility and inclusion criteria. The impact of CVD prevalence on CKD severity was estimated by a meta-analysis (using secondary data). This was accomplished using the computer language R. With the use of the created forest plot, the odds ratio for CVD among CKD varied from 1.16 to 6.58 among the 20 studies included in this review. The calculated odds ratio was 2.28 (95% confidence interval: 1.90-2.73). A funnel plot analysis was also performed to check for publication bias in the individual studies, and it was shown to be present. CVD has been found as a prominent co-morbid from the results of the literature of individual studies. Estimated glomerular filtration rate (eGFR), uremia, anemia, inflammation, oxidative stress, and dialysis-related variables are all thought to contribute negatively to the disease severity seen in CVD patients. The severity of CKD is affected by a number of risk factors for cardiovascular disease, including age, lifestyle, and pharmaceutical medication.

Abbreviations

aOR	Adjusted Odds Ratio
CHF	Chronic heart failure
CI	Confidence interval
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
eGFR	Estimated glomerular filtration rate
ESKD	End-stage Kidney Disease
HF	Heart failure
HFDMP	HF disease management program
HFrEF	Heart failure with decreased ejection fraction
MDRD	Modification of Diet in Renal Disease
OR	Odds Ratio

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1.0. Introduction

Chronic kidney disease (CKD) is a global health issue that affects up to 15% of adult populations (Major et al., 2018; Yamada et al., 2021), and it is linked to an increased risk of cardiovascular disease (CVD), comparable to diabetes mellitus or coronary heart (Major et al., 2018; Shajahan et al., 2021). As CKD progresses, this risk rises, as demonstrated by decreasing excretory function, often seen as a lowering glomerular filtration rate and increased proteinuria (Go et al., 2005; Yamada et al., 2021). Extra myocardial infarctions and strokes due to CKD account for 13% of the total cost of care, which equals 1.3% of healthcare budgets (Kerr et al., 2012).

CKD is a serious health problem linked to a high risk of cardiovascular death. Historically, males have been reported to have a higher risk of cardiovascular death than women in the general population. However, current data suggest that this risk is equivalent or even higher in women with CKD than it is in males. Clinical practice now includes assessing cardiovascular risk in the general population using prognostic models, especially for primary prevention. These prognostic models incorporate data from frequently gathered risk variables and may be integrated into normal clinical care utilizing patient data (Major et al., 2018). Because of this, it is possible that CKD-specific cardiovascular prognostic models should include risk factors like calcium and phosphate, which are related to arteriosclerosis and reduced vascular compliance (Goff et al., 2014). Equally important, taking into account the risk factors associated with cardiomyopathies, such as echocardiographic evidence of left ventricular dysfunction or systemic inflammation, may also be a justifiable course of action (Piepoli et al., 2016). These prognostic models incorporate data from frequently gathered risk variables and may be integrated into normal clinical treatment utilizing electronic medical records. CVD prognostic models built exclusively for CKD contain substantial methodological flaws, such as minimal external validation and restricted evaluation of model parameters, and so may underestimate CKD risk. This leads to their clinical inapplicability (Hippisley-Cox et al., 2008). CVD prognostic models built especially for CKD contain substantial methodological flaws, such as minimal external validation and restricted evaluation of model parameters, and so may underestimate CKD risk (Rabar et al., 2014).

Half of all people who suffer from heart failure also have chronic kidney disease (49%), which increases their risk of death and hospitalization. Regardless of age, duration of heart failure (HF), or diabetes, a deterioration in renal function increases the risk of death from HF and other causes (Damman et el., 2014; Löfman et al., 2017). Fluid overload symptoms, such as dyspnea and peripheral edema, are shared by both heart failure and chronic kidney disease, making diagnosis difficult (Warrens et al., 2022).

In stages 1–3 of chronic kidney disease (CKD), pharmacological therapy of heart failure with decreased ejection fraction (HFrEF) is effective. Evidence for its usage, however, is limited since patients in stages 4-5 of CKD are often not included in clinical studies. Drugs that block the renin-angiotensin-aldosterone pathway are recommended for CKD-HF but are neglected due to concerns about hyperkalemia (Murphy et al., 2021). Drug resistance and electrolyte disturbances are possible side effects of using diuretics and ß-blockers for alternative pharmacological treatment (Warrens et al., 2022). Moreover, improving CKD-related diseases might lessen the severity of HF. Treatment of iron deficient anemia in CKD-HF with intravenous iron is supported by robust evidence. Empagliflozin, in particular, has shown success in treating HFrEF and HF with maintained ejection fraction, conditions for which there were no prior therapies.

Type 2 diabetes is a major CKD cause and comorbidity, and empagliflozin, an inhibitor of sodium-glucose cotransporter 2, was first used to treat this condition (Packer et al., 2020). Renal function decrease may be slowed with this treatment, studies demonstrate, even in the most severe cases of chronic kidney disease (Zannad et al., 2021).

The risk of cardiovascular mortality is connected to biological sex, age, smoking, and obesity (Liabeuf et al., 2015). Males have traditionally been thought to have a higher life-long risk of cardiovascular mortality than females in the general population (Mikkola et al., 2013). However, few studies have looked at sex differences in cardiovascular outcomes in the CKD group. According to a meta-analysis of renal function and the link between sex and cardiovascular mortality (Nitsch et al., 2013), males had a higher mortality risk than women at all levels of renal function.

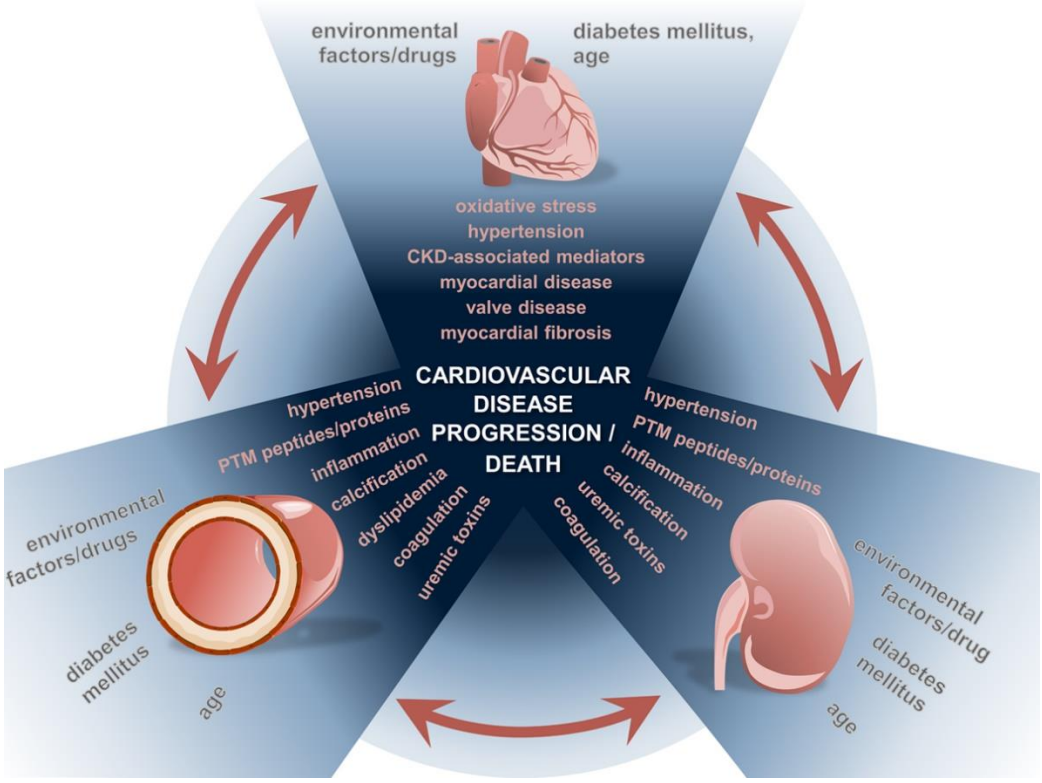

Figure 1: Relationship between CVD and CKD. Adapted from Jankowski et al., 2021. *Circulation*, *143*(11), 1157-1172.

In the figure 1, traditional risk factors for cardiovascular disease, such as high blood pressure and diabetes, are extremely prevalent in CKD. Additional risk factors for cardiovascular disease that are associated with CKD include uremia, anemia, inflammation, oxidative stress, and variables connected to dialysis. These variables connected to CKD contribute more to a decrease in the estimated glomerular filtration rate (eGFR) (Sarnak et al., 2019). This is mirrored in the pathophysiology of cardiovascular disease in individuals with CKD, as non-atherosclerotic cardiac events become increasingly prevalent as the progression of CKD continues (Wanner et al., 2016).

In patients with CKD, cardiovascular disease and associated events may manifest in unusual ways and with fewer symptoms. When compared with individuals who have retained renal function, only 44% of patients with late-stage CKD experience classical pain with acute myocardial infarction (AMI) (Sosnov et al., 2006). Patients with this condition typically appear with acute myocardial infarction rather than persistent angina (Go et al., 2011). They also manifest with non-ST segment elevation myocardial infarction more frequently than ST-elevation myocardial infarction (Shroff et al., 2017). As a result, a high level of clinical suspicion needs to be preserved.

According to the International Diabetes Federation, 351.7 million working-age individuals (20–64 years) had diabetes in 2019, with that figure anticipated to rise to 417.3 million by 2030 (Thomas et al., 2019). In the United States, type 2 diabetes is the major cause of chronic kidney disease (CKD), accounting for around 36% of adult CKD (Saran et al., 2019). CKD combined with diabetes mellitus (DM) can lead to end-stage renal disease (Jiang et al., 2019), which has a dismal prognosis. Furthermore, type 2 diabetes and chronic kidney disease increase the risk of cardiovascular disease (Yamada et al., 2021). As a result, the care of individuals with type 2 DM and CKD must include the prevention of CKD development and cardiovascular events.

There is a need for CKD-specific validation because, as CKD progresses, the relative importance of atherosclerosis in CVD outcomes decreases and is replaced by the confounding—'non-traditional' CVD risk factors. With the progression of CKD, these risk factors associated with uremia may play a larger role (Menon et al., 2005). This may justify including arteriosclerosis and impaired vascular compliance risk variables like calcium and phosphate (Covic et al., 2009) in CKD-specific CVD prognosis models. Similarly, taking into account risk factors associated with cardiomyopathies, such as echocardiographic evidence of left ventricular dysfunction or systemic inflammation, may be justified. As a result, additional innovative routinely collected risk variables must be included for the validation of CVD prognostic models in CKD (Menon et al., 2005).

In both patients with CKD and those with CVD, these conditions are highly prevalent. Each condition increases the risk of and accelerates the development of the other when present. There are considerable gaps in our understanding of how to best care for this at-risk population, even though these co-occurring illnesses are quite common and can lead to serious or even fatal outcomes. Patients with CKD are severely underrepresented in CVD studies, reducing the generalizability of findings. The risk of CKD is likely underestimated by the standardized risk scores that are often used to guide investigations and therapy in CVD. The sensitivity and specificity of these studies are also lower, and they may cause undesirable side effects.

The ability of CVD risk prediction systems to stratify, investigate, and manage patients with CKD is severely constrained by the fact that CKD and related factors such as eGFR and albuminuria are rarely included. As an added downside, these methods are thought to overestimate the risk of CVD in CKD. More recent data-driven evidence has improved effectiveness in CKD's early stages, but its applicability to ESKD remains low (Anker et al., 2016).

Insufficient data, dosage modifications owing to renal function, and side effects all add up to make drug management difficult. This means that the recommended care for these individuals is less likely to be provided. There is substantial evidence to support the use of interventions in stages 1-3 of CKD, however, this evidence is lacking for the later stages of the illness. However, the risks of these problems and side effects increase with the later use of treatments in stages 4 and 5 of CKD.

A meta-analysis is a type of statistical study in which the findings of many scientific investigations are combined (Glass, 1976). Meta-analyses can be conducted when numerous scientific studies address the same subject and each study reports measurements that are expected to have some degree of inaccuracy. Meta-analysis yields a more exact treatment impact estimate. The most appropriate form of impact size is determined by the review team depending on the type of outcomes and treatments under consideration. Therefore, it is assumed in random-effects models that the true effects being estimated in each trial are independent and skewed around some central value. Within-study and between-study variance contributions are accounted for in the 95% CIs around the mean (Barili et al., 2018). The odds ratio (OR) was used as effect size and a funnel plot will be performed for evaluating to influence of publication bias.

2.0. Aim & Objectives

The purpose of this study is to establish if cardiovascular diseases have a significant impact on the severity of the renal failure. Meta-analysis will be applied to evaluate the impact of cardiovascular disease prevalence on the severity of renal failure patients. The following objectives will help us get closer to our aim:

• Utilizing meta-analysis, investigate the relationship between the observed prevalence of cardiovascular diseases and the severity and mortality of chronic kidney diseases.

• Combine and analyze (using meta-analysis) the data obtained from various prospective studies that have investigated cardiovascular diseases to be a factor in the severity of renal dysfunction.

• Formulate a conclusion that lends credence to the medical findings that link the severity of renal failure and mortality rates to cardiovascular diseases.

3.0. Methods

This research used the meta-analysis method. The purpose of a meta-analysis is to pool the findings of many related investigations. To rephrase, meta-analysis is the process of comparing and contrasting the findings of several research using comparable methods and designs. It allows for pooled analysis that is sensitive to differences across studies (Haidich, 2010).

3.1. Literature Reviewed

Inquiries were made between February and March of 2022 in the databases of Pub Med, Google Scholar, and the Cochrane Library (due to their worldwide recognition for containing thousands of reviewed scientific articles, medical research studies, and clinical trials). Renal diseases, "Cardiovascular Disease and severe chronic kidney disease (CKD)," and " Cardiovascular Disease and Chronic kidney disease (CKD)" were among the terms used in the search. Using the "advanced search form," was able to locate more recent and relevant articles and data on CVD and CKD that were published between January 2000 and January 1, 2022. For the Pubmed MeSH Term search, use the following terms: (cardiovascular diseases AND chronic kidney disease AND odds ratio NOT hazard ratio) AND (cardiovascular disease and severe chronic kidney disease [MeSH Terms]). At this point in the research, the Patient/Population/Problem, Intervention, Comparison, and Observation (PICO) structure was also adopted to aid in the production of more pertinent papers. Patients (P) are those with cardiovascular disease who participated in each trial. All patients were receiving similar medical care in the form of hospitalization, medication, and/or therapy, which we'll refer to as "the Intervention" (I). In-hospital CVD patients with known pre-existing CKD cases constituted the Comparative (C). Pooled effect assessment of the intervention was denoted by Outcome (O). Both articles discovered by an electronic database search and those retrieved by hand while perusing the reference list were used in this study (Horsley et al., 2011). Because it influences computation and helps define the purpose of the research when interpreting the outcome, the choice of effect model for a meta-analysis was crucial. Meta-analysis often employs one of two effect models: the fixed effect model or the random effect model (Borenstein et al., 2010). In contrast to the random effect model, which considers that effect sizes across included studies would vary from study to research, the fixed effect model implies that all included studies will have the same effect size; hence, any reported discrepancies in effects are due to sampling error (Borenstein et al., 2010). A random effect model was employed for the analysis in this research. More papers that were relevant to this investigation were found by manually combing the reference list.

3.2. Criteria for inclusion

This study will only include cited works published in English that address the association or link between cardiovascular disease and severity in chronic kidney diseases, and statistical information on the prevalence of CVD as a co-morbidity to CKD severity with the odds ratio as effect size and also review articles under "Potential mechanisms" that address the treatment of CKD in patients with CVD. In this preliminary phase, published meta-analysis served as a resource for locating relevant publications but did not form the basis for the conclusions drawn from this investigation. It served as a rule of thumb for identifying and eliminating duplicate research that utilized the same statistical method. Twenty distinct studies were considered for meta-analysis, all of which examined the impact of the aforementioned co-morbidities on the severity of CKD. All of the authors had previously conducted their own clinical trials, and all of the trials had employed primary data gathered from hospitalized patients.

3.3. Criteria for exclusion

Studies that do not directly address the research questions posed in the title or abstract will not be considered for review or inclusion (the association between CVD and severe CKD). Similarly, articles with incongruent methodology and results will not be reviewed, nor will those that do not address the prevalence of CVD as a co-morbidity to the severity of CKD. Information from newspapers, letters, or hospital websites will not be used either because there have been insufficient clinical trials, ethical approval, or evidence-based research conducted.

3.4. Data collections

This was the initial stage in the statistical analysis. The authors' names, the year of publication, of the individual studies used for the meta-analysis, the sample size (or total number) of CVD patients in each study (in table1), the number of CVD patients with pre-existing cases of either CKD (in table1), the pooled Odd ration (OR) from the individual studies, and the upper and lower bounds (CI) of the OR from these studies were all manually entered into an Excel file. For the sake of compatibility with the R program, the Excel file was converted to a "CSV" format.

3.5. Statistical Analysis

To get an objective evaluation of all obtained evidence, a meta-analysis of the common impact of CVD on the severity of CKD will be conducted. Type II errors can be avoided if there are at least 30 people in an experiment. To perform a meta-analysis, this study will make use of the freely available statistical software R and the commercial software "Stata" (R Core Team & StataCorp, 2019). A random effect model will use odds ratio (OR) as effect size and a funnel plot and forest plot will be produced to evaluate publication bias using the R package Meta.

In meta-analyses, the data was shown as a forest plot. A forest plot was created to display the effect estimates and confidence intervals from each research. Forest plots showed not just the confidence interval but also the influence of the meta-analysis. A forest plot is a statistical tool for visually gauging levels of variation (Anzures-Cabrera & Higgins, 2010).

Cochran's Q test was used to check for heterogeneity (figure 5). Given the limited power of the test, it is widely acknowledged that a significance threshold of 0.10 is appropriate for Cochran's Q test (Deeks et al., 2022). The I2 statistic was used to quantify the level of heterogeneity found by testing for it. It is the proportion of total variance attributable to the heterogeneity that is reported by the I2 statistic (Higgins, 2003). A conventional x2 test and the I2 statistic for heterogeneity were used to investigate the existence of variation in risk estimates across studies. Inter-study variability is measured by a statistic called I2. Random effects meta-

regression analysis was used to investigate the factors that contribute to the observed variation in study outcomes. In the second phase of the statistical analysis, a forest plot was created to display the aggregated studies' pooled effects estimate (OR) (figure 3). After getting R up and running, downloaded two libraries: Meta and metaphor. The forest plot was generated using imputed R programs as follows, which were then carefully edited in the R editor.

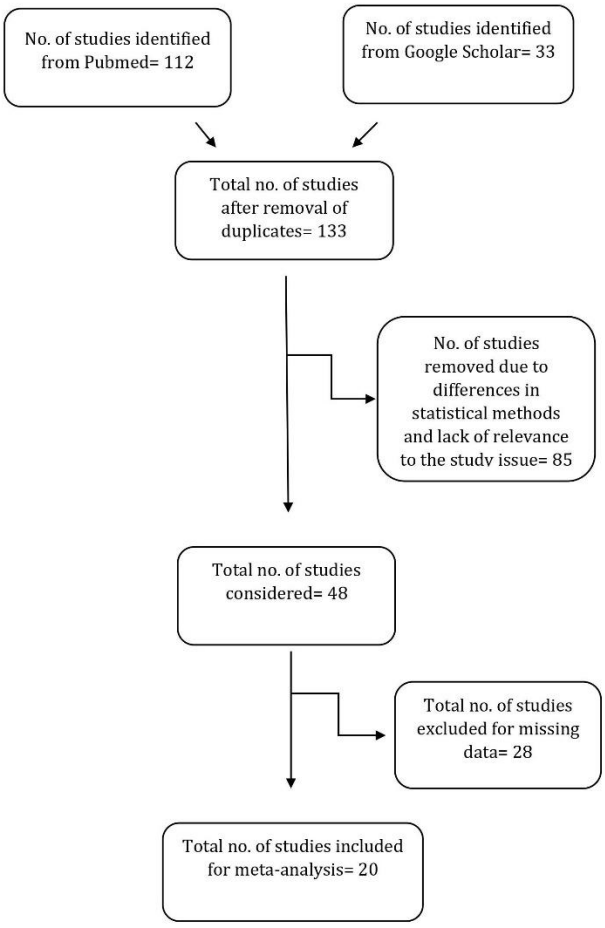

Figure 2: Conversational flowchart of studies being included in a literature review and meta-analysis.

4.0. Results

Articles were collected, reviewed, and included in this research in a methodical manner, as shown in the chart in Figure 2. In all, 155 publications were found after searching several databases (including PubMed and Google Scholar). The number of articles was reduced by 22 (duplication). There were 133 publications initially checked for eligibility, however, 85 were thrown out due to differences in statistical methods and lack of relevance to the study issue. The remaining 48 publications that satisfied the inclusion criteria were included in the literature review, whereas data from just 20 of these 48 studies were included in the meta-analysis portion of this research and 28 articles were excluded for missing data. In the table 1, 17101 individuals were diagnosed with CKD throughout these 20 investigations, and 8883 had either CVD or non-CVD. The average age of study participants was 65.5±5. For this meta-analysis, all 20 studies were kept because they matched the following criteria: they utilized primary data, reported using a consistent treatment technique (all participants were hospitalized), used OR as the effect size, and showed CVD to be a significant factor in the severity of CKD.

The pooled odds ratio OR from this study was 2.28 (95% CI, 1.90-2.73), as shown in figure 3. The lowest odds ratio and confidence intervals were found in the studies conducted by (Petretta et al., 2007; Alehagen et al., 2009; Hebert et al., 2010) (OR=1.16 CI: 0.55-2.44; OR=1.29 CI: 0.86-1.92; OR=1.38 CI: 0.90-2.12). Bruch et al., (2007) and Carrasco et et., (2011) found the greatest pooled odds ratio (OR=6.58 CI: 3.58-12.12 and OR=5.56 CI:2.89-10.70), which is an intriguing result from this research. Petretta et al., (2007) and Alehagen et al., (2009) had the smallest low limits on their confidence intervals (0.55-2.44 and 0.86-1.92), indicating a potentially different conclusion from others. Figure 4 is a funnel plot created to examine potential publication bias.

Table 1: A spreadsheet with all the data from the studies that made up the meta-analysis. The total case is a representation of all patients with CKD across all studies. Patients with CKD from both CVD and non-CVD causes are included. Upper level-Lower level reflects the upper and lower limit of the 95% Confidence interval l(CI) from each research, whereas OR is the pooled odds ratio from all the studies.

Authors	**Year**	**Total Case**	**CVD with CKD**	**Non-CVD with CKD**	**CVD with Non-CKD**	**NonCVD with Non-CKD**	**OR**	**95% CI**
Madsen et al.	1994	190	22	22	38	108	2.84	1.42, 5.71
Aronson et al.	2004	541	112	172	65	192	1.92	1.33, 2.78
Petretta et al.	2007	153	15	36	27	75	1.16	0.55, 2.44
Takagi et al.	2009	194	14	61	8	111	3.18	1.27, 8.02
Manzano et al.	2011	138	17	49	10	62	2.15	0.90, 5.12
Carrasco et al.	2011	198	53	46	17	82	5.56	2.89, 10.70
Campbell et al.	2009	240	32	87	21	100	1.75	0.94, 3.26
Roik et al.	2006	498	67	81	70	280	3.31	2.18, 5.02
Scrutinio et al.	2009	266	48	90	20	108	2.88	1.59, 5.21
Alehagen et al.	2009	464	76	159	62	167	1.29	0.86, 1.92
Hebert et al.	2010	1,301	34	304	72	891	1.38	0.90, 2.12
Anand et al.	2009	5,010	703	2,213	273	1,821	2.12	1.82, 2.47
Vaz perez et al.	2010	128	28	26	22	52	2.55	1.23, 5.28
Pimenta et al.	2007	283	13	31	35	204	2.44	1.17, 5.12
Shalaby et al.	2008	330	49	160	17	104	1.87	1.02, 3.43
Bruch et al.	2007	269	66	69	17	117	6.58	3.58, 12.12
Martin et al.	2009	104	28	13	34	29	1.84	0.81, 4.19
Kimura et al.	2009	711	61	327	20	303	2.83	1.67, 4.79
Hillege et al.	2000	1,866	288	645	146	787	2.41	1.92, 3.01
Wali et al.	2010	4,217	414	2,152	166	1,485	1.72	1.42, 2.08
Total		**17,101**					**2.28**	**1.90, 2.73**

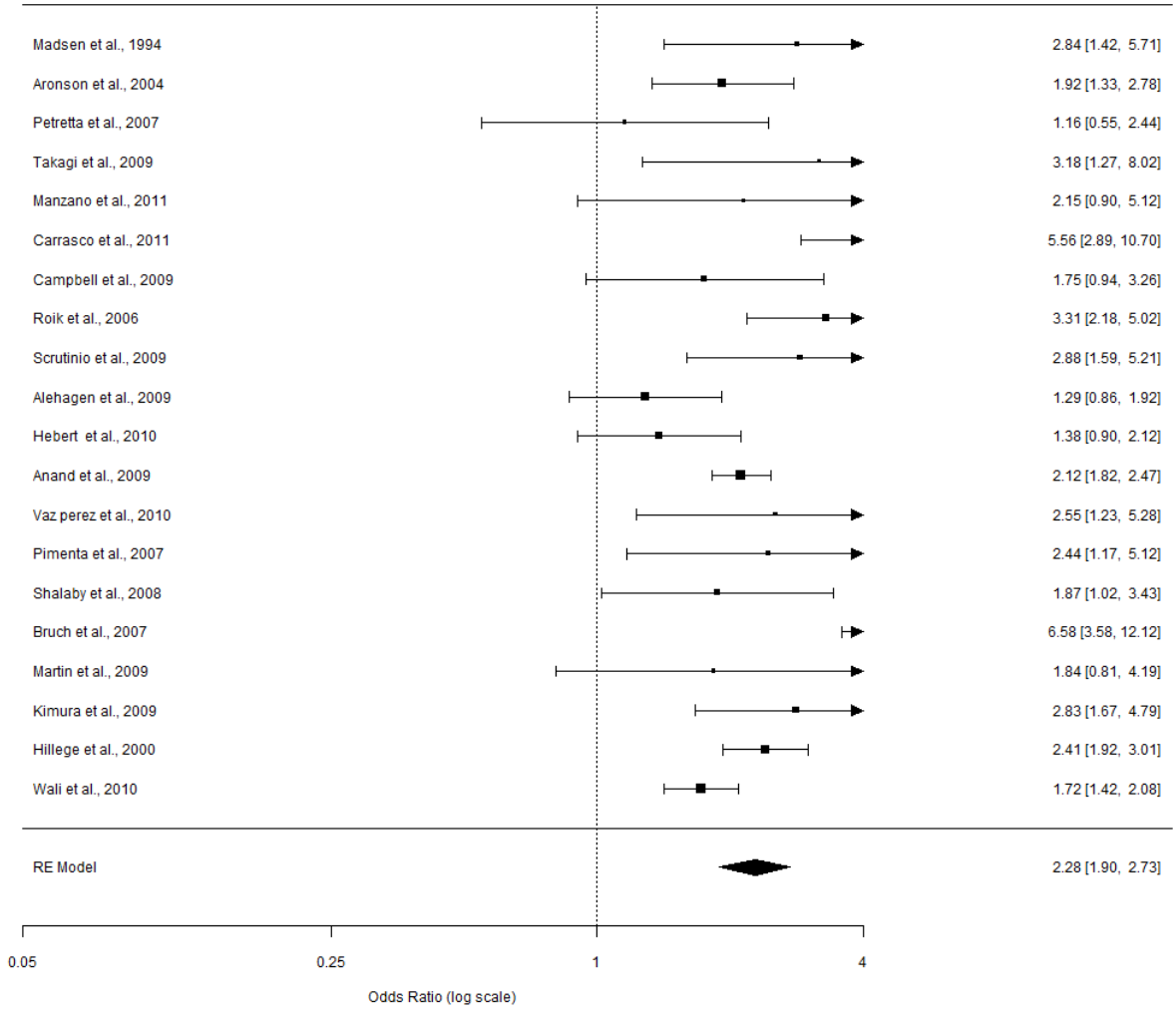

Figure 3: The pooled odds ratio for CVD's impact on CKD was 2.28, which was derived using a forest plot. A 95% confidence interval is used to express this certainty. The confidence interval has lower and upper bounds of 1.90 and 2.73 respectively.

Forest plots of pooled effect estimates demonstrate that all included studies (represented by shaded squares with a thin arrow) clustered towards the edge of the plot (on the influence of CVD on CKD patients). Indicative of a congruence in the overall conclusions drawn from the many studies. However, the odds ratio and 95% CI in the two trials (Bruch et al., 2007; Carrasco et al., 2011) are much larger than in the other investigations. Two extremely long arrows on the plus side of the figure represent the benefits of these large odds ratios. Within-study characteristics, such as variations in sample size, odds ratio, or confidence interval, are expected to be the primary causes of this variation, according to the random effect model. Figure 4 displays the outcome of a funnel plot generated to test for this and any possible publication bias. Fifteen of the twenty studies clustered within the funnel, while the other five were spread out around the funnel and represented by the black dots. Most of the individual results have adopted the shape of an inverted funnel and are clustered inside the funnel's inner rim. Cochran's Q test was used to check for heterogeneity (figure 5). The tau^2 (estimated amount of total heterogeneity) was 0.0985 (Standard Error = 0.0543), tau (square root of estimated tau^2 value) was 0.3139, I^2 (total heterogeneity/ total variability) was 70.62% and H^2 (total variability / sampling variability) was 3.40, as in shown figure 5.

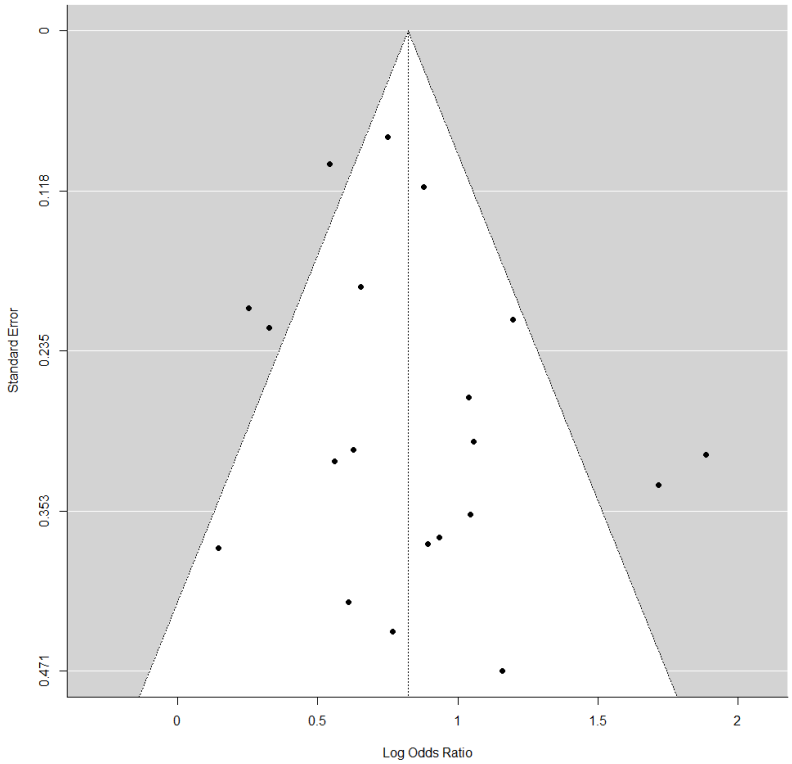

Figure 4: A visual representation of the heterogeneity of the various studies included in a meta-analysis, shown as a funnel plot. The numbers for the observed result were represented on the Y-axis, while the standard error figures were put on the X-axis. Each research is represented by a shaded dot.

```
       estimate   ci.lb   ci.ub
tau^2    0.0985  0.0275  0.3141
tau      0.3139  0.1658  0.5605
I^2(%)  70.6189 40.1453 88.4559
H^2      3.4035  1.6707  8.6624



Random-Effects Model (k = 20; tau^2 estimator: REML)

  logLik  deviance       AIC       BIC      AICc
-11.1100   22.2199   26.2199   28.1088   26.9699

tau^2 (estimated amount of total heterogeneity): 0.0985 (SE = 0.0543)
tau (square root of estimated tau^2 value):      0.3139
I^2 (total heterogeneity / total variability):   70.62%
H^2 (total variability / sampling variability):  3.40

Test for Heterogeneity:
Q(df = 19) = 48.9179, p-val = 0.0002

Model Results:

estimate      se    zval    pval   ci.lb   ci.ub
  0.8226  0.0935  8.7992  <.0001  0.6394  1.0059  ***

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Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
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Figure 5: A Cochran's Q test for heterogeneity result from meta-analysis.

5.0. Discussion

The random effects model was used for the analyses in this study. Given that the impact size does not seem to be consistent across the included trials, a random effects model is appropriate for the meta-analyses. It is likely that the impact magnitude would vary depending on variables including how the research was conducted. Random effects meta-analysis was used because of the substantial variation across the studies (Borenstein et al., 2010). Due to the use of a random effects model, it is clear that the weights given to particular studies do not reflect their actual sample sizes. Both the fixed effects model and random effects model meta-analysis use the inverse of the variance as the weight. However, the variation in the random effects model meta-analysis incorporates the between-study variance in addition to the within-study variance. However, in the fixed effects model meta-analysis, all studies are assumed to have the same genuine effect size, thus only within-study variation is taken into account. In other words, the goal of a random effects model meta-analysis is to calculate an average for the range of observed effect sizes. The random effects model meta-analysis compensates for the underrepresentation of a population by giving greater weight to studies with lower sample sizes. The data from just 20 of these 48 studies were included in the meta-analysis portion of this research and 28 articles were excluded for missing data. 17101 individuals were diagnosed with CKD throughout these 20 investigations, and 8883 had either CVD or Non-CVD. Based on the meta-analysis results, it can be shown in Figure 3 that CVD has a beneficial impact on the severity of CKD (OR=2.28, 95% CI, 1.90-2.73).

190 consecutive patients with clinically stable ischemic heart disease were included in the study. There were 136 males and 54 women in the patient population, and the median age was 66 years. A multivariate analysis was conducted among the different subgroups (OR=2.84, 95% CI: 1.42-571) and it was found that CKD patients in the severe group were people who received treatment in a community setting as opposed to the case-control group, which consisted of people who received treatments in a contained facility (Madsen et al., 1994). This finding was based on the fact that the effect of CVD was examined alongside many other diseases.

The risk of death from any cause was seen to rise with each quartile of CKD in multivariable Cox regression models, with an adjusted odds ratio of 1.92 in patients in the higher quartiles compared with the lower quartiles (95% confidence interval [CI]: 1.33 to 2.78). A substantial risk of death occurs after release from the hospital for patients who have been hospitalized for decompensated heart failure (Aronson et al., 2004). When someone has heart failure, their renal function is linked to both their cardiovascular and their hemodynamic states. Researchers investigated whether renal impairment was associated with a higher risk of death in individuals who were hospitalized with decompensated heart failure.

Evaluated the data from a prospective cohort consisting of 153 patients with CVD who were sent to our medical center. The patients' mean age was 64 years. All patients had clinical, echocardiographic, and laboratory data collected on them while they were recovering in the hospital (Petretta et al., 2007). Anemia was defined as having a hematocrit of less than 35%, and kidney dysfunction was defined as having a glomerular filtration rate (GFR) of less than 60 ml/min. According to the findings of multivariate analysis, CKD patients who also had CVD had an adjusted odds ratio (aOR) as high as 1.16 (95% confidence interval [CI], 0.55-2.44) for a worsening of their condition while they were CKD patients. In individuals diagnosed with cardiovascular disease, independent risk factors for death include impaired renal function but not anemia.

The research has a significant impact on our outcome (Petretta et al., 2007; Alehagen et al., 2009) (OR=1.16 CI: 0.55-2.44 and OR= 1.29 CI: 0.86-1.92 respectively) stand out as noteworthy research

in this meta-analysis. Although both studies utilized sizable samples for their separate analyses, the meta-analysis provided a lower limit on the confidence interval for just one of them (0.55 vs. 0.86), which is why the margin is skewed to the negative side. Researchers discovered that age and sex were significant predictors of CKD severity in those with CVD. Investigated 194 individuals treated with sudden cardiac failure between January 2002 and February 2005. High eGFR patients (eGFR 60 ml/min, n = 75) and low eGFR patients (eGFR 60 ml/min, n = 119) were separated for analysis (Takagi et al., 2010). The eGFR value was derived using the MDRD (modification of diet in renal disease) research equation. An independent predictor of long-term mortality from heart failure may be an eGFR that is lower upon admission. Standardized use of estimated glomerular filtration rate (eGFR) and monitoring of renal function seems to be an essential and practical approach to the treatment of heart failure patients since heart failure is one of the most frequent illnesses in coronary care units in Japan. Patients hospitalized due to CKD were shown to have a higher likelihood of having a history of CVD (OR= 3.18 CI: 1.27-8.02). Patients with CKD and cardiovascular disease had a lower eGFR upon admission than those without CKD, according to their research. They also found that individuals with CKD and CVD were more likely to have acute respiratory distress syndrome (Manzano et al., 2011). Cystatin C was associated with an increased incidence of severe renal disease in their research (OR=2.15 CI: 0.90-5.12). Using the Modification of Diet in Renal Disease Shortcut Formula. Out of a total of 4217 participants, 2566 (60.8%) had CKD and 50.4% were given carvedilol. Carvedilol reduced all-cause and cardiovascular mortality within the CKD group (OR, 1.72; 95% CI, 1.42 to 2.08) (Wali et al., 2011).

The research by (Carrasco et al., 2011) had a substantial impact on our outcome despite using a lower sample size due to its strong pooled effect (OR=5.56 CI: 2.89-10.70). Researchers found that age was the single most important predictor in determining CKD severity among those with CVD. It results imply that cystatin C is an independent and powerful predictor of death and/or readmission in individuals with acute heart failure with normal or modestly impaired systolic LV function. As a bonus, cystatin C may predict poor outcomes even in the absence of severe renal impairment (stages 1 and 2 CKD). Serum cystatin C measurement has the potential to significantly enhance the early evaluation of renal-independent heart failure with intact or modestly diminished ejection fraction (Campbell et al., 2009).

Renal dysfunction was shown to be a significant and independent risk factor for death among CVD patients in a multivariate study (OR=3.31, 95% CI=2.18-5.02). Patients with Chronic heart failure who have renal dysfunction may be stratified into a high-risk category and provided with appropriate treatment, both of which have been shown to reduce mortality (Roik et al., 2006). In chronic heart failure, a decline in renal excretory function is recognized as a major prognostic marker (Scrutinio et al., 2009). Patients having an echocardiographically determined ejection fraction of 40% or less were eligible for enrollment in a systolic HF disease management program (HFDMP). The Modification of Diet in Renal Disease Study equation was shortened for use in estimating the glomerular filtration rate. The National Kidney Foundation's categorization method was used to place patients into one of five CKD stages (Hebert et al., 2010). The prevalence of CKD was determined to be 26% or 338 individuals. Chronic kidney disease patients tended to be older, Hispanic, low-income, had high systolic blood pressure, and have diabetes. Prevalence did not vary significantly between the sexes. Patients with CKD had a worse chance of survival. Hyperuricemia increased the risk of cardiovascular disease (Anand et al., 2009), and this risk multiplied the CKD risk negatively. In groups with a low risk of cardiovascular disease, the aOR was 5.51 (95% CI 4.03-7.52), whereas, in those with a medium to high risk, the aOR was 2.12 (95% CI 1.82-2.47).

Independently of one another, researchers observed that the entry creatinine level, diuretics, and digoxin were the strongest predictors of long-term death in these individuals (Vaz perez et al., 2010). These findings emphasize the significance of renal impairment during a cardiovascular disease episode even years after the initial event. These findings may bolster existing concerns regarding the potential for adverse consequences from diuretic and digoxin maintenance medication in individuals with cardiovascular disease. Low-to-moderate CKD (eGFR, 30-59) was associated with little or a small increase in risk for both outcomes among CVD patients, in comparison to those with eGFR,60-89. Severe CKD (eGFR, 15-29) was the only subgroup for whom the odds of hospitalization were adjusted upwards: OR 2.44 (95% CI 1.17-5.12). When comparing the risk of CVD for patients with CKD in the community and the context of acute HF, there are important distinctions. Patients with mild CKD are at no increased risk of hospitalization or mortality in the community, but those with severe CKD, or CKD in addition to other comorbidities are at high risk (Pimenta et al., 2007).

Edema decreased cutaneous blood flow, and discomfort is all symptoms of chronic renal insufficiency, as are a history of cognitive pathology and long-term therapy with nitrates. The capacity to sit upright in a chair was the only statistically significant predictor of a favorable outcome (Martin et al., 2009). Renal function, which is impacted by chronic heart failure (CHF), should have added prognostic significance because of its relationship to cardiovascular and hemodynamic features. To determine whether or not renal function is a predictor of mortality in advanced CHF and to evaluate the relative contribution of renal function compared to other recognized risk variables, researchers conducted this study. It also, looked at how the neurohormonal activity relates to renal function (Hillege et al., 2000).

The purpose of this study was to learn how renal function and anemia influence the development and progression of chronic heart failure (CHF). In this study's aimed to follow 711 patients who were hospitalized in the Cardiology Unit at Fujita Health University Hospital over 5 years. According to their Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rates (eGFR), the individuals were split into four groups. Both renal function and anemia were shown to have substantial effects on CVD outcomes (Kimura et al., 2010).

135 individuals with CKD (estimated glomerular filtration rate (eGFR) 60 ml/min/1.73 m2) were included out of a total of 269 patients with stable CHF. Left ventricular volumes and dimensions, ejection fraction, mitral E/A-ratio, deceleration time, and tissue Doppler mitral annular velocities (S′, E′, A′) were all measured by echocardiography. Conduction disturbances within the heart and worsening diastolic function are both symptoms of chronic kidney disease in individuals with congestive heart failure. Both processes may have a role in the higher morbidity and death seen in these individuals (Bruch et al., 2007). Sixty-six patients, or 20.0%, out of the 330 investigated died over a mean follow-up period of 19.7 9.0 months (range 1–44). Creatinine tertiles of 0.6-1.0, 1.1-1.3, and 1.4-3.0 mg/dL were used to analyze the cohort. The death occurred more often (28.7% vs 14.0%, P = 0.008 for death) and the composite endpoint occurred more frequently (41.6% vs 21.5%, P = 0.001) among patients in the highest creatinine tertile than in those in the other tertiles. Maintaining its role as an independent predictor of death, high creatinine levels (odds ratio [OR] 1.87, 95% CI [1.02-3.43]) remained a concern (Shalaby et al., 2008).

This meta-analysis looked at individuals with CVD and showed that renal impairment, even mild impairment, was linked to a 56% increase in relative mortality risk. The results of our latest meta-analysis expand this finding even further.

A surprisingly comparable connection was discovered between any degree/moderate CKD and the outcome of our research, which included nearly 10 times the number of patients with CVD. However, there are a few key distinctions to be made. Patients with CVD and HF who still had a

functional ejection fraction were included in our current research. Among the studies analyzed, a subset revealed that CKD was dependent on CVD for increased mortality risk, indicating that CKD may be an even stronger predictor of outcome in patients with CVD.

As can be seen in figure 4, a funnel analysis was also done in this study to test for publication bias. In the figure 5, the Cochran's Q test was done to check for heterogeneity. The majority of the studies with a small standard error value (shown by the shaded dots) fell within the funnel, suggesting that the results of the individual studies whose clinical data were analyzed were consistent. It was possible to make out a few dots on the outside of the funnel and a more uniform distribution of dots on the interior. This meta-analysis may have been limited in scope since there were so few individual studies included. One may argue that this research suffers from publication bias since the few outlier studies are scattered among the more reliable ones. Because of the possibility of publication bias, this study's funnel plot analysis incorporates this limitation into its interpretation.

6.0. Conclusion

Findings from this research have significant implications for CVD specialists caring for patients with chronic kidney disease. While cardiovascular disease (CVD) may not be directly linked to high mortality, it does have a very significant association with the severity of chronic kidney disease (CKD), as demonstrated in most publications included in this investigation and corroborated by the pooled odds ratio of the impact. When assessing a patient with CVD for CKD, age and diabetes medication regimen are two significant criteria to consider. Over half of the individuals who died in the papers were over the age of 65, highlighting the fact that both innate and adaptive immunity decline with age. Age-related declines in eGFR make it harder to manage cardiovascular disease, which in turn increases the risk of CVD complications. Cardiovascular disease (CVD) medications might worsen CKD symptoms, thus doctors treating CVD patients should be aware of this fact. Since people with CVD (particularly the elderly) are more susceptible to infection than those without CVD, they need to exercise additional care in their daily lives when health control authorities relax restrictions on social distances and outdoor activities. In addition to decreasing CVD treatment pills and working on better lifestyle factors like frequent exercise and dietary monitoring, doctors should educate their patients about the severity of CKD and its relationship to the medications they are on. The findings of this study lend credence to pharmacists' pleas for additional investigation into the role of medication in the treatment of cardiovascular disease. This meta-analysis has limitations because the individuals whose medical records were utilized to create the database were located in a wide variety of countries, some of which may have stricter guidelines on medical data collection and sharing than others. This suggests that the results of this research may be affected by the fact that not all hospital admissions in that study were due to severe CKD. A possible confounding factor for this study's findings is the publication bias shown by the funnel plot analysis. Thus, it may be concluded that the severity of sickness in CKD patients who also have CVD is highly connected to CVD.

7.0. Future Perspectives

This study must have involved hospital or medical treatment and adequate follow-up, as well as the participation of all participants in giving their informed consent. In addition, the articles must have been written in such a way that they have not misled any of the participants. This research, which attempts to establish a definite relationship between cardiovascular disorders and the degree of renal failure, will assist medical professionals in better managing patients who have been diagnosed with cardiovascular conditions and renal dysfunction. For the general public to comprehend the relevance of maintaining a balanced diet in the prevention and management of

cardiovascular disease, further information about the relationship that exists between cardiovascular illnesses and kidney infections is required. Patients who have the cardiovascular disease have a higher risk of developing severe symptoms from renal failure; thus, these patients must have a solid understanding of why it is so important for them to adhere to the recommendations. Most importantly, pharmacists will be able to utilize this knowledge to develop medicines for CVD that are less dangerous and have a less negative influence on the severity of CKD. The participants will give essential insights into the epidemiology of the cardiovascular disease in chronic kidney disease (CKD), disclose the influence of individual risk variables on bad outcomes, and serve as the platform for future interventional research.

8.0. Ethical considerations and study impact on the society

When working with human samples or information, it is extremely important to adhere to a set of criteria known as "ethical considerations" before beginning any kind of biological investigation. However, in the past, clinical research involving human and animal samples/data was undertaken and published without mentioning whether or not informed consents were obtained (Weingarten et al., 2004). Several ethics committees have been established since the Helsinki declaration in 1964 to examine ethical concerns in clinical research. A literature review will always include a different kind of ethical evaluation than would be required for a new clinical study. Literature reviews that take ethical concerns into account are crucial because they raise awareness (in the scientific community) of the need of maintaining rigorous standards and thorough oversight for any research involving human subjects. Following these guidelines, our literature review examined the ethical implications of each article used in this research. In this meta-analysis, ethics focused mostly on ensuring a transparent research process. Important methodological issues include the use of acceptable data-gathering methods, the disclosure of any potential publishing bias, and the use of clear and objective inclusion and exclusion criteria (Brown & Hedges, 2009). Some of the ethical challenges faced by "insider researchers," such as the power imbalance and continuous interactions with participants, are highlighted by (Fleming, 2018) in this Special Issue. But it's crucial to think more deeply about the basics of doing human subjects research responsibly. All of the articles that will be considered for inclusion in this study will be thoroughly checked for appropriate ethical clearances. Twenty (20) research articles are currently being reviewed. When conducting this review, only articles with sample sizes greater than 30 patients (to ensure sufficient statistical power) will be included. To be considered for inclusion in this review, articles must have relied exclusively on data collected from randomized, controlled human clinical trials, which must have involved hospital or medical treatment and adequate follow-up, as well as the participation of all participants giving their informed consent. This study, which aims to establish a definitive link between cardiovascular diseases and the severity of renal failure, will help doctors better manage cardiovascular patients who have been diagnosed with renal dysfunction. The public needs to know more about the connection between cardiovascular diseases and renal infection to understand the significance of a healthy diet in preventing and managing cardiovascular disease. Since patients with cardiovascular illness are more likely to develop severe symptoms from renal failure, it is crucial that they understand why it is so vital for them to follow the guidelines. Most significantly, pharmacists will be able to use this information to create CVD treatments that are safer and have a smaller detrimental impact on CKD severity.

9.0. Acknowledgement

For their unwavering encouragement and help all throughout my study, I am grateful to my supervisor, Niclas Norrström. I always looked forward to our meetings and sessions. There were other occasions when their words of support got me through a period of emotional instability. The sum of their insight and encouragement has been a source of great encouragement throughout this venture.
To my wonderful family, I give all my love and thanks. The completion of this research would not have been possible without the persistent prodding of my wife, Nazifa Hasan.

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