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The Effect of Social Determinants of Health on End-Stage Kidney Disease Mortality Across Diverse Adult Populations: Systematic Review and Meta-Analysis

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THE EFFECT OF SOCIAL DETERMINANTS OF HEALTH ON END-STAGE KIDNEY DISEASE MORTALITY ACROSS DIVERSE ADULT POPULATIONS: SYSTEMATIC REVIEW AND META-ANALYSIS

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This thesis is approved as a creditable and independent investigation by a candidate for the master's degree and is acceptable for meeting the thesis requirements for this degree. Acceptance of this does not imply that the conclusions reached by the candidate are necessarily the conclusions of the major department.

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ABSTRACT

THE EFFECT OF SOCIAL DETERMINANTS OF HEALTH ON END-STAGE KIDNEY DISEASE MORTALITY ACROSS DIVERSE ADULT POPULATIONS: SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: This systematic review and meta-analysis aimed to examine the influence of social determinants of health (SDOH) on End-Stage Kidney Disease (ESKD) mortality among diverse racial populations. Given the high morbidity and mortality associated with ESKD, understanding the impact of various SDOH factors across different racial groups is crucial for improving patient outcomes.

Methods: A comprehensive literature search was conducted to identify studies reporting on the relationship between SDOH and ESKD mortality using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) format. Citations were collated in EndNote 21 and screened in Covidence by two independent reviewers, with inter-rater reliability assessed using Cohen's kappa. Eligible studies involved U.S. adults over 18, measuring at least one SDOH, diagnosed with ESKD, and initiating dialysis. Methodological quality was appraised using JBI instruments by two independent reviewers, with discrepancies resolved through discussion or a third reviewer. All studies were included for data extraction regardless of quality scores. Data, including author, publication year, sample sizes, effect sizes, confidence intervals, and outcomes, were extracted using Covidence. Discrepancies were resolved through discussion or with a third reviewer, and authors were contacted for missing data. The meta-analysis primarily included studies reporting hazard ratios, using a random effects model to calculate pooled estimates and confidence intervals to ac-

commodate between-study heterogeneity. For education, a fixed effects model was used due to significance in the results of the model.

Results: A total of 1,828 studies were initially identified, and after thorough screening and application of eligibility criteria, 85 studies were included in the systematic review. The findings indicate that White populations have a higher risk of dying from ESKD compared to racial minorities, even after accounting for various social determinants of health (SDOH). Specifically, the risk of ESKD mortality was 19% lower in Black populations (HR 0.81, 95% CI 0.77-0.85), 38% lower in Asian populations (HR 0.62, 95% CI 0.59-0.66), and 16% lower in Native American populations (HR 0.84, 95% CI 0.80-0.87) compared to White populations. Hispanic populations had a 26% lower risk compared to Non-Hispanic White populations (HR 0.74, 95% CI 0.53-1.03) and a 9% lower risk compared to Non-Hispanic populations (HR 0.91, 95% CI 0.78-1.10), though these findings were not statistically significant. Additionally, urban patients experience an 8% lower risk of ESKD mortality compared to rural patients (HR 0.92, 95% CI 0.88-0.96). Higher education levels were associated with a 10% lower risk of ESKD mortality (HR 0.90, 95% CI 0.83-0.97).

Conclusion: The study demonstrates that social factors like race, insurance, education, and location significantly impact ESKD mortality. White patients have higher mortality rates, while minorities experience severe complications despite receiving equal care. Uninsured rural patients also have higher mortality rates. Higher education and urban living lead to improved outcomes. Targeted policies and infrastructure improvements are vital to address these disparities.

1 INTRODUCTION

1.1 BACKGROUND

End-stage kidney disease (ESKD), also referred to as stage 5 chronic kidney disease (CKD) is a critical and irreversible decline in kidney function, reaching a point where life cannot be sustained without the assistance of renal replacement therapy (RRT), which includes methods like dialysis (Hemodialysis and Peritoneal) or transplantation [43]. Despite significant advancements in dialysis technology over the past two decades, the mortality rate remains considerably high among individuals with ESKD [47]. Recent studies have shown that there are significant racial disparities in the incidence and prevalence of ESKD, with African Americans and other minority groups being disproportionately affected [41]. In the study by McClellan et al., Blacks experience a disproportionate risk of ESKD compared with whites. [37].

Social Determinants of Health(SDOH), including socioeconomic status, race, and ethnicity, play a critical role in the incidence, progression, treatment outcomes, and mortality of ESKD. Studies have consistently demonstrated that individuals from lower socioeconomic backgrounds and those belonging to racial or ethnic minority groups have a higher likelihood of developing ESKD, the clinical endpoint of ESKD [65] [28]. Systematic reviews and meta-analyses reveal that these individuals face a 1.24 to 1.55 times greater risk of developing ESKD compared to those from higher socioeconomic backgrounds. The disparities extend beyond incidence rates, influencing disease progression, access to and quality of treatment, and ultimately, patient outcomes [59].

The intersection of racial or ethnic minority status is significantly linked to an increased risk of ESKD. The 2017 data from the United States Renal Data System (USRDS) highlight the pronounced disparities in the incidence rates of ESKD among minority populations. For instance, Native Hawaiians/Pacific Islanders experienced

rates nine times higher, Black Americans nearly three times higher, and American Indians/Alaska Natives 1.6 times higher than White Americans. Hispanic Americans faced a 30% higher incidence rate of ESKD compared to non-Hispanics. These discrepancies are largely due to a more rapid progression towards ESKD among Hispanic and Black Americans [54]. Moreover, an analysis based on the USRDS data linked to the US Census found that there is a significant difference in mortality rates between black and white individuals who are young dialysis patients (aged 18-30). This difference is even more pronounced in lower-income neighborhoods, showing that economic difficulties may worsen the racial disparities in survival rates for dialysis patients [30]
.

Findings from Ward et al. (2015) reveal that individuals from lower socioeconomic backgrounds not only face a higher risk of progression to dialysis but also have poorer survival outcomes once on dialysis [60]. Socioeconomic status also plays a crucial role in determining the choice of dialysis modality; Black and Hispanic patients are less likely to opt for peritoneal dialysis (PD) compared to White patients, a disparity that diminishes when adjusting for socioeconomic factors. This indicates that socioeconomic barriers are a significant hurdle in accessing and deciding upon treatment options. Additionally, A seven-year study involving 3,288 participants from the Chronic Renal Insufficiency Cohort (CRIC) shed light on how ethnicity and health conditions together influence the likelihood of needing dialysis. This study found that, upon starting dialysis, White patients typically had more severe health problems, such as heart failure and obesity, than Black patients, who were generally in better health [34]. This difference in health status at the start of dialysis gave Black patients an initial survival advantage [34]. However, when further analysis was conducted on a larger group of 6,677 dialysis patients, this advantage disappeared after considering factors like demographic, social, and clinical characteristics [42]. This indicates that these factors significantly affect the mortality rate differences observed between racial

groups.

Despite the growing body of literature available on the mortality of patients with ESKD, the effects of SDOH on mortality among these patients have yet to be systematically reviewed and meta-analyzed. This notable gap points out the need for a detailed systematic review and meta-analysis to integrate findings across studies. This provides a clearer understanding of how SDOH influences ESKD patient survival outcomes.

1.2 END-STAGE KIDNEY DISEASE

In the U.S., about 808,000 people are battling with ESKD, and forecast data suggests that, by 2030, the number of individuals diagnosed with this condition could surpass the 2 million mark, leading to an overwhelming annual treatment expenditure exceeding $30 billion [55] [49] [53]. This has put a significant burden on the healthcare system, with the USRDS reporting marked fluctuations in incidence and prevalence rates alongside notable racial disparities. From 2001 to 2021, the number of new ESKD cases increased significantly, though the adjusted incidence rate decreased by 8.9%, highlighting an improvement in early intervention strategies. However, the incidence rate among Black, Native American, and Hispanic populations remains high [56] . This surge in cases spans across all major diseases that lead to ESKD, but diabetes mellitus and hypertension have been the primary drivers. Particularly striking increases have been observed among African American and Native American populations, with diabetes being a common cause and hypertension emerging as the leading factor for ESKD among African Americans [1].

The selection of vascular access for dialysis is critical for the effectiveness of the treatment and minimizing the patient's risk of complications. Unfortunately, recent trends have shown an alarming increase in the use of catheters from 2018 to 2021. Catheters are associated with higher infection and mortality rates. In 2021, White patients used

catheters the most (25.1%), followed by Black (23.2%) and Asian patients (17.5%). Furthermore, there were evident racial disparities in access preferences. Black patients more frequently used grafts (22.5%) compared to other racial groups ($\leq$ 15.6%) and were less likely to opt for fistulas, the preferred access type, with only 54.2% using them compared to more than 61.5% in other groups [56].

The journey of those battling End-Stage Kidney Disease (ESKD) has seen its share of ups and downs, especially when it comes to survival rates. For almost a decade, up until 2019, there was a glimmer of hope as we witnessed a meaningful drop in the number of lives lost to ESKD. Sadly, this promising trend took a heartbreaking turn in 2020, with an unexpected rise in mortality. The very next year, the situation only slightly worsened for patients receiving hemodialysis (HD), with a marginal increase [56].

1.3 SOCIAL DETERMINANTS OF HEALTH

The World Health Organization defines the SDOH (SDOH) as "The non-medical factors that influence health outcomes. They are the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life" [62]. The Healthy People 2023 and the World Health Organization (WHO) recognize five key domains of social determinants of health, which are critical to understanding and improving health outcomes across populations.

Figure 1: Illustration of the Social Determinants of Health as outlined in Healthy People 2030

[57]

Economic Stability: Economic stability reflects the direct impact of income, employment status, and financial security on access to healthcare services, nutritious food, and stable housing. Financial strain or poverty often leads to compromised health care, increased stress, and a higher risk of disease. In the U.S, a staggering 10% of the population struggles with poverty with little or no detectable change, facing significant barriers to accessing essentials such as nutritious food, medical care, and stable housing [45]. Financial strain or poverty often leads to compromised health care, increased stress, and a higher risk of disease. Policies that support job creation, provide adequate wages, and reduce household food insecurity and hunger can significantly enhance this domain's positive effects on health [57].

Education Access and Quality: Access to quality education plays a significant role in shaping an individual's health, influencing employment opportunities, income, and the development of healthy habits. Thus, ensuring access to quality education from early childhood to higher education is crucial for empowering individuals and promoting health equity. Children from low-income families, in particular, face significant hurdles, including a decreased likelihood of graduating from high school or pursuing a college education. Children living in areas with underperforming schools and those whose families cannot afford educational expenses potentially affect their brain development and academic success. Targeted interventions designed to support children and adolescents' academic performance and assist families with higher education costs are essential for fostering long-term health benefits [57].

Health Care Access and Quality: Access to comprehensive, quality healthcare services is essential for promoting and maintaining health and preventing and managing disease. In the U.S, approximately 10% of the population lack health insurance [2]. This lack of coverage means many do not have a primary care doctor and might struggle to pay for necessary health services and medications. Therefore, it's essen-

tial to implement strategies that boost insurance coverage to ensure broader access to crucial healthcare, including preventative measures and chronic disease management [57].

Neighborhood and Built Environment: The neighborhoods and environments in which people live play a crucial role in shaping their health and overall quality of life. [7] In the U.S., several neighborhoods face challenges, such as prevalent violence, compromised air and water quality, and various other risks to health and safety. Racial and ethnic minority groups, as well as individuals facing economic hardships, are often more susceptible to these hazards. Additionally, specific occupational environments expose workers to harmful conditions, including secondhand smoke and excessive noise. Taking steps through interventions and legislative reforms at various government levels can significantly mitigate these risks, providing a healthier, safer living environment [57].

Social and Community Context: The influence of society on individual health encompasses aspects like social support from friends and family, engagement with the community, and experiences of equity or discrimination. A sense of belonging and active participation in community life can shield against health risks, positively affecting mental and physical health. Conversely, facing violence, feeling excluded, or encountering discrimination can degrade health and restrict access to resources essential for well-being. Therefore, addressing these social determinants is critical for improving health equity and enhancing overall health. [57]

2 METHODOLOGY

The methodology used in this study involves systematic review and meta-analysis. Systematic review methods are employed to ensure a structured and comprehensive search, selection, and appraisal of relevant studies. This approach provides a robust

framework that enhances our ability to navigate the complexities of research synthesis. In the meta-analytic approach, we look at effect sizes and significant numerical indicators of the relationship between two variables. We use the fixed and random effects models to account for the variability within and between studies. We also evaluate the homogeneity of the included studies to measure the consistency of effect sizes. By combining systematic review and meta-analysis methodologies, we can offer a clearer and more insightful understanding of the synthesis of reported associations between SDOH factors and all-cause mortality.

2.1 SYSTEMATIC REVIEW

A systematic review is a comprehensive process that aims to collect and analyze all available evidence related to a specific question. The process involves identifying relevant studies, evaluating their quality, and synthesizing their findings [17]. Through systematic reviews, researchers can develop new insights and conclusions by combining data from various studies or investigating specific topics. To achieve this goal, the following steps are followed.

Search Strategy: Our search strategy is in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) format. We aimed to identify both published and unpublished studies relevant to the topic. Initially, we conducted a limited search in MEDLINE (PubMed), CINAHL (EBSCOhost), the Web of Science Core Collection, which includes the Science Citation Index Expanded, Social Sciences Citation Index, Arts and Humanities Citation Index, and the Cochrane Central Register of Controlled Trials (CENTRAL), to identify articles relevant to the study. We examined the text words in the titles and abstracts of relevant articles and the index terms used to describe these articles to develop a comprehen-

sive search strategy for MEDLINE (PubMed). Our search strategy encompassed all identified keywords and index terms tailored for each included information source. The search terms included subject headings, text words, and phrases related to end-stage kidney disease, social determinants of health, racial and ethnic disparities, and mortality.

Study Selection: Following the search, all identified citations were collated into EndNote 21 (Clarivate Analytics, PA, USA), facilitating the removal of duplicate entries. The refined citation list was then imported into Covidence for a rigorous title and abstract screening. A preliminary pilot test was conducted to refine the screening criteria, ensuring consistency in the subsequent review process. This stage involved two independent reviewers systematically evaluating titles and abstracts against the established inclusion criteria.

Inter-rater reliability for the title and abstract screening was assessed using Cohen's kappa [38]. Following this phase, citations that passed the initial screening were subjected to a thorough full-text review by the same reviewers to confirm eligibility based on the inclusion criteria. Inter-rater reliability for the full-text review phase was similarly quantified using Cohen's kappa. Discrepancies encountered at any stage of the selection process were amicably resolved through discussion or, when necessary, adjudication by a third reviewer. We presented the results of the search strategy, study selection, and inclusion process in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram [40].

To establish the eligibility of the study, we used the following inclusion criteria: (a) studies must include participants who are adults over the age of 18 years, residing in the United States; (b) studies must measure at least one SDOH; (c) participants must have a diagnosis of ESKD, equivalent to Chronic Kidney Disease (CKD) Stage 5; (d) participants must have initiated dialysis treatment.

Exclusions were meticulously documented, with reasons for each exclusion noted for transparency. Although race can be classified as an SDOH, we removed studies that focused only on race with no other social determinants of health.

Assessment of methodological quality: Eligible studies were critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from JBI for experimental, quasi-experimental, and observational studies [52]. Authors of papers were contacted to request missing or additional data for clarification, where required. Any disagreements that arose between the reviewers were resolved through discussion with the systematic review team when feasible or with a third reviewer. The results of the critical appraisal were reported in a table with an accompanying narrative. All studies, regardless of the results of their methodological quality, underwent data extraction and synthesis (where possible) to ensure a broad capture of SDOH across all domains and the impact on ESKD mortality. Results of the critical appraisal were reported in tabular format. Additionally, proper context was provided while reporting results for articles that had low appraisal scores.

Data Extraction: Two independent reviewers reviewed the studies and ensured they met our eligibility criteria. The data was extracted using the standardized Covidence data extraction tool. The data extracted included the following details: name of the first author, year of publication, sample sizes, effects sizes, confidence intervals, study population, study methods, the domain of SDOH explored, interventions, and outcomes of significance to the review question, such as differences in mortality among different races and the related SDOH. Any disagreements between the reviewers were resolved through discussion when feasible or with a third reviewer. If necessary, the systematic review team reached out to the authors of papers to request missing or additional data.

2.2 META-ANALYSIS

Glass was one of the early pioneers in defining meta-analysis. He described it as "the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings" [16]. In a meta-analysis, the computation of effect size is the backbone of the study as it determines the findings across studies [4]. In quantitative research, particularly in clinical, epidemiological, and public health studies, assessing and interpreting effect sizes are paramount. Effect sizes provide a robust measure of the magnitude of relationships or differences observed in research [9]. Among the various effect size metrics, Risk Ratios (RR), Odds Ratios (OR), and Hazard Ratios (HR) are especially critical in understanding outcomes in this study. The Risk Ratio (RR), also known as the relative risk, is a measure used to determine the relative likelihood of an event occurring in a treatment group compared to a control group. It is defined as the ratio of the probability of the event occurring in the exposed or treatment group to the probability in the control or unexposed group. Consider the table:

Table 1: 2x2 Contingency Table

	Exposed	Unexposed
Group 1	a	b
Group 2	c	d

The basic calculation of RR for each study is performed using the formula :

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} \tag{2.1}$$

This represents the ratio of the probability of an event occurring in the treatment group to the probability in the control group. If the Risk Ratio (RR) is 1 or close to 1, it indicates there is no or minimal difference in risk between the two groups, implying that the incidence of the outcome is the same for both; an RR greater than

1 indicates an increased risk of the outcome in Group 1, suggesting that exposure may be associated with a higher likelihood of the event; conversely, an RR less than 1 signifies a reduced risk in the Group 1, implying that the exposure might be protective against the occurrence of the outcome.

The RR is often log-transformed to stabilize variances and normalize distributions [5]. The log transformation of RR is calculated as $\log(RR) = \ln\left(\frac{a}{a+b}\right) - \ln\left(\frac{c}{c+d}\right)$ Furthermore, the variance of the log-transformed RR is a crucial component in the meta-analysis and is computed using the formula $\text{Var}[\log(RR)] = \frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}$ This variance is used for weighting studies in the meta-analysis.

When analyzing case-control studies where the proportion of cases in the entire population-at-risk is unknown, one cannot measure the incidence of the health outcome or disease, making the odds ratio a useful tool. The Odds Ratio (OR) is a statistical measure used to compare the odds of an event occurring in a cases group to the odds in a control group.

Consider the 2x2 contingency table in Table 1. The OR is calculated using the formula:

$$OR = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{a \times d}{b \times c}$$

This formula represents the ratio of the odds of an event occurring in the cases group to that in the control group. The interpretation of OR is pivotal for understanding the association between exposure and event outcomes in epidemiological studies. Specifically, an OR equal to 1 implies that the odds of the event are the same for both the exposed and unexposed groups, indicating no association between the exposure and the outcome. Conversely, an OR greater than 1 suggests that the exposure is associated with an increase in the odds of the event, pointing towards a potential risk factor. Lastly, an OR less than one indicates that the exposure may reduce the odds

of the event, suggesting a protective effect against the outcome.

Similar to RR, the OR is often log-transformed in meta-analyses to stabilize variances and normalize distributions [5]. The log transformation of the OR is calculated as $\log(OR) = \ln\left(\frac{a}{b}\right) - \ln\left(\frac{c}{d}\right)$. The variance of the log-transformed OR is a critical component in the meta-analysis and is computed using the formula $\text{Var}[\log(OR)] = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$.

In studies where the timing of events is crucial, the Hazard Ratio (HR) offers insight into the risk of event occurrence over time between two groups. HR is a measure used in survival analysis to compare the risk of an event occurring at any given time in two different groups. It's a relative measure of effect, giving us an idea of how much the hazard (risk of the event occurring) in one group is higher or lower than in the other [13].

The hazard function in the Cox model is given by:

$$h(t|X) = h_0(t)\exp(\beta' X).$$

Here, $h(t|X)$ represents the hazard function at time t for an individual characterized by covariate values X, $h_0(t)$ denotes the baseline hazard function that reflects the hazard when all covariate values are set to zero, and $\exp(\beta' X)$ is the exponential function of the linear predictor, itself a linear composition of the covariates X and their respective coefficients β [10].

Let's consider two groups with covariate vectors X_1 and X_2. Their hazard functions are $h_1(t) = h_0(t)\exp(\beta' X_1)$ $h_2(t) = h_0(t)\exp(\beta' X_2)$ respectively. The hazard ratio (HR) of group 1 to group 2 is defined as $HR = \frac{h_1(t)}{h_2(t)}$. Substituting in the hazard functions, we get $HR = \frac{h_0(t)\exp(\beta' X_1)}{h_0(t)\exp(\beta' X_2)}$, which simplifies to:

$$HR = \exp(\beta'(X_1 - X_2)). \tag{2.2}$$

When comparing two groups, an HR greater than 1 indicates that Group 1 has a higher hazard rate, implying an increased risk of the event occurring, compared to Group 2; an HR equal to 1 signifies no difference in hazard rates between the two groups, suggesting that the risk of the event is the same for both. An HR less than 1 indicates that Group 1 has a lower hazard rate, indicating a reduced risk of the event occurring compared to Group 2.

2.2.1 Fixed and Random Effects Models

The fixed-effect model operates under the assumption that all studies in a meta-analysis estimate the same underlying effect size. Observed variations across study results are attributable solely to random error within studies rather than true heterogeneity in effect sizes. Consequently, the fixed-effect model is most appropriately applied in scenarios where the included studies are methodologically homogeneous, implying they are similar in design, population, interventions, and outcomes. The model is given by:

$$y_i = \theta + \epsilon_i, \tag{2.3}$$

where y_i is the effect estimates and ϵ_i are the errors which are normally and independently distributed with mean zero and variance σ_i^2, thus $\epsilon_i \sim \mathcal{N}(0, \sigma_i^2)$. In the absence of variability between studies, the effect estimates are influenced solely by sampling error, represented by σ_i^2. Consequently, these estimates follow a normal distribution, with a mean equal to θ and a variance of σ_i^2—notated as $y_i \sim \mathcal{N}(\theta, \sigma_i^2)$, particularly when considering large sample sizes [5].

Summary Effect Size Under FEM[1]

Let y_i represent the observed effect size in study i, k represent the number of studies, and w_i represent the weight assigned to study i. It is important to note that $i = 1, 2, \ldots, k$. The summary effect size $\hat{\theta}$ in a fixed-effects model (FEM) is calculated

using the formula:

$$\hat{\theta} = \frac{\sum_{i=1}^{k} w_i y_i}{\sum_{i=1}^{k} w_i}. \tag{2.4}$$

The weights in a FEM are based on the precision of each study, calculated as:

$$w_i = \frac{1}{\text{Var}(y_i)}, \tag{2.5}$$

where $\text{Var}(y_i)$ is the variance of the effect size in study i. The variance of the summary effect is estimated as the reciprocal of the sum of the weights, that is:

$$\text{Var}(\hat{\theta}) = \frac{1}{\sum_{i=1}^{k} w_i}. \tag{2.6}$$

Then, 95% lower and upper limits for the summary effect are estimated as $L_{\hat{\theta}} = \hat{\theta} - 1.96 \times SE(\hat{\theta})$ and $U_{\hat{\theta}} = \hat{\theta} + 1.96 \times SE(\hat{\theta})$ respectively. The standard error of $\hat{\theta}$, denoted as $SE(\hat{\theta})$, is calculated as $SE(\hat{\theta}) = \sqrt{\text{Var}(\hat{\theta})}$. [5]

The assumption of the fixed-effect model is often invalid due to differences in the settings and populations of the studies [14]. The idea behind combining studies in a meta-analysis is that they are similar enough to be synthesized. However, expecting them to be identical is unrealistic. For example, when investigating the impact of air pollution on asthma exacerbation rates in different urban environments, we expect the effect of air pollution to be consistent but vary across different cities or regions. Urban infrastructure, population characteristics, or specific pollutants measured can account for the differences in effect size. This heterogeneity among the studies suggests the presence of varying underlying effect sizes.

In contrast, the random-effects model is used to address this complexity when there are inherent differences among the studies, indicating that the effect size varies across studies. This model is instrumental even without significant heterogeneity test re-

[1] FEM stands for the Fixed Effects Model.

sults, as it considers both within-study variability and between-study differences. The model under the random effects is given by:

$$y_i = \mu + u_i + \epsilon_i, \tag{2.7}$$

where u_i and ϵ_i are sources of variability impacting y_i. These are quantified by between-studies variance, denoted τ^2, and within-study variance, σ_i^2. The distribution of y_i is normally and independently distributed with mean θ and a combined variance of $\tau^2 + \sigma_i^2$ – denoted by $y_i \sim \mathcal{N}\left(\mu, \tau^2 + \sigma_i^2\right)$ [24].

Estimating tau-squared $\hat{\tau}^2$

The parameter $\hat{\tau}^2$, serves as the estimated variance between studies in the context of random effects models. It quantifies the heterogeneity or variability in effect sizes across a collection of studies, highlighting the differences in true effect sizes among them. The estimation of $\hat{\tau}^2$ is pivotal for adjusting the weights of individual studies to account for both within-study accuracy and between-study variability properly. An approach for estimating $\hat{\tau}^2$ is through the DerSimonian and Laird estimator, a method of moments estimator [11]. This technique calculates $\hat{\tau}^2$ as:

$$\hat{\tau}^2 = \begin{cases} \frac{Q-(k-1)}{\sum_{i=1}^{k} w_i - \frac{\sum_{i=1}^{k} w_i^2}{\sum_{i=1}^{k} w_i}} & \text{for } Q > (k-1) \\ 0 & \text{for } Q \leq (k-1), \end{cases} \tag{2.8}$$

where Q is Cochran's heterogeneity statistic defined in Equation 2.12, k is the number of studies, and w_i are the initial weights of the studies before adjusting for between-study heterogeneity. To prevent the occurrence of negative values for $\hat{\tau}^2$ when Q is less than $(k-1)$, we set $\hat{\tau}^2$ to 0. As a result, for any collection of studies, the precision of a summary estimate from a random effects model will not surpass that of a summary estimate from a fixed effects model [29].

The detection of a non-zero $\hat{\tau}^2$ value indicates heterogeneity among the studies' effect sizes, suggesting that the true effect sizes vary across studies more than what would be anticipated by sampling error alone. This variability is a critical aspect in the adoption of random effects models, as it incorporates the differences in study outcomes into the evidence synthesis. By accurately estimating $\hat{\tau}^2$, we can more effectively combine results from various studies, acknowledging the diverse study characteristics and contexts that may influence the observed effects. Among the techniques for weighted estimation in random-effects models, the DerSimonian and Laird method is commonly utilized due to its simplicity. Furthermore, for meta-analyses including fewer than ten studies, the Hartung-Knapp-Sidik-Jonkman method is recommended to lower the risk of committing a type I error, offering an advantage over the DerSimonian and Laird method in such scenarios [15, 20–23, 35, 46].

Summary Effect Size Under REM[2]

Let y_i represent the observed effect size in study i, k represent the number of studies, and w_i^* represent the weight assigned to each study. The summary effect size, denoted as $\hat{\mu}$, in a REM is calculated using the formula:

$$\hat{\mu} = \frac{\sum_{i=1}^{k} w_i^* y_i}{\sum_{i=1}^{k} w_i^*}. \tag{2.9}$$

The weights in the REM take into account both the within-study variance σ_i^2 and an estimate of the between-study variance ($\hat{\tau}^2$), calculated as:

$$w_i^* = \frac{1}{\sigma_i^2 + \hat{\tau}^2}. \tag{2.10}$$

The variance of the summary effect is estimated as the reciprocal of the sum of the weights, that is:

$$\mathrm{Var}(\hat{\mu}) = \frac{1}{\sum_{i=1}^{k} w_i^*}. \tag{2.11}$$

[2]REM stands for the Random Effects Model.

Then, 95% lower and upper limits for the summary effect are estimated as $L_{\hat{\mu}} = \hat{\mu} - 1.96 \times SE(\hat{\mu})$ and $U_{\hat{\mu}} = \hat{\mu} + 1.96 \times SE(\hat{\mu})$ respectively. The standard error of $\hat{\mu}$, denoted as $SE(\hat{\mu})$, is calculated as $SE(\hat{\mu}) = \sqrt{\text{Var}(\hat{\mu})}$. [5]

2.2.2 Evaluating Study Homogeneity

Combining studies in a systematic review and meta-analysis often reveals differences in design, methodology, participants, and outcomes. This variation, known as methodological or clinical heterogeneity, may explain differences in study results. Statistical heterogeneity, indicating actual differences in study effects, poses a challenge for meta-analysis. Assessing this variability is crucial for choosing a suitable statistical model, whether fixed or random effects.

In meta-analysis, Cochran's Q statistic serves as a fundamental tool for assessing the presence of heterogeneity across study results. Introduced by Cochran in 1954 and further elaborated by Hedges and Olkin [25, p. 123][8], this statistic calculates the weighted sum of squared differences between each study's effect size and the overall effect size. Specifically, it is given by:

$$Q = \sum_{i=1}^{k} w_i (y_i - \hat{\theta})^2 \sim \chi^2_{k-1}. \tag{2.12}$$

Here, y_i represents the effect size derived from the i^{th} study, while $\hat{\theta}$ denotes the summary effect size estimated under the assumption of a fixed effects model. The term k stands for the total number of studies included, and w_i refers to the initial weights assigned to the studies prior to any adjustments for observed heterogeneity.

A significant challenge with the Q statistic in meta-analysis is that its statistical power is contingent on the number of studies included. This results in low power for analyses comprising a small number of studies and a high power for those with a large number [19]. To address the limitations associated with the Q statistic, such as its varying power and the difficulty in comparing the between-study variance τ^2 across different

meta-analyses with various effect-size metrics, Higgins and Thompson proposed the I^2 statistic [27]. This statistic assesses heterogeneity by comparing the observed Q statistic to its expected value under the assumption of homogeneity, essentially using the degrees of freedom ($df = k - 1$) as a basis for this comparison. The I^2 statistics is defined as:

$$I^2 = \begin{cases} 100\% \times \left(\frac{Q-(k-1)}{Q}\right) & Q > (k-1) \\ 0 & Q \leq (k-1). \end{cases} \tag{2.13}$$

The I^2 statistic is essential for assessing the proportion of total variance in meta-analysis outcomes that arises from genuine heterogeneity versus random chance. A critical first step in analyzing study variability involves evaluating the I^2 value. A low I^2 suggests that the variations observed among study results are primarily due to chance, indicating little to no true heterogeneity. This scenario often negates the need for further investigation. On the other hand, a high I^2 signifies that a substantial part of the observed variance is real, reflecting actual differences across studies. Such a finding warrants a deeper investigation into potential sources of heterogeneity, possibly employing techniques like subgroup analysis or meta-regression to shed light on the factors contributing to the variance in study outcomes. The I^2 statistic, therefore, guides the analytical strategy in a meta-analysis, facilitating a more informed interpretation of the data. Higgins et al. (2003) offer provisional guidelines for interpreting the I^2 statistic, proposing that values approximately around 25%, 50%, and 75% could be indicative of low, moderate, and high levels of heterogeneity, respectively [26].

3 RESULTS

A total of 1,828 studies (Figure 2) were identified through various databases, including MEDLINE, CINAHL, Web of Science, and CENTRAL, with a few unspecified

sources. After the removal of 19 duplicates, 1,809 studies were screened. Of these, 1,494 studies were excluded based on predefined criteria. The remaining 315 studies were assessed for eligibility, with another 230 studies excluded for reasons such as not being US-based, being abstracts only, having the wrong study design, or focusing on race without including social determinants of health (SDOH).

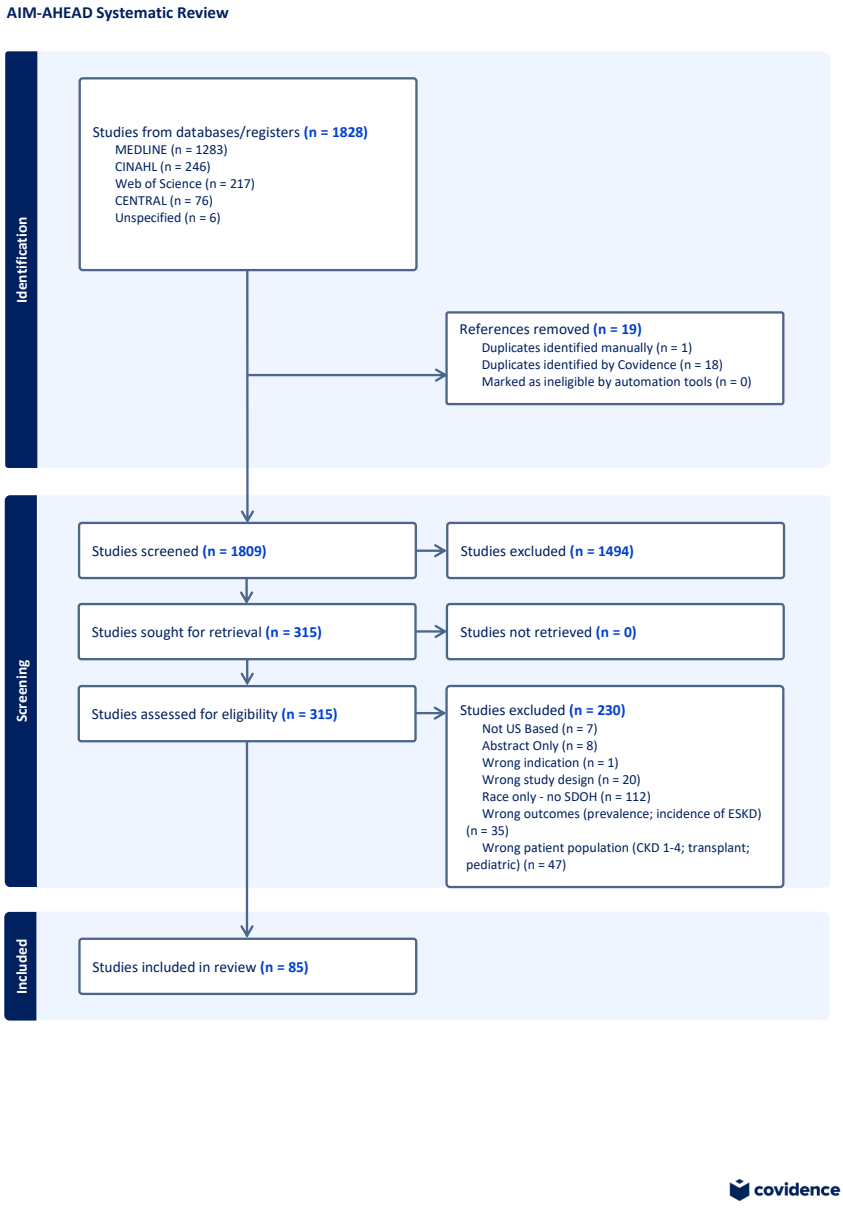

Figure 2: Prisma flow diagram showing the workflow of

The systematic review analyzed the distribution of studies across various SDOH domains. Among the articles extracted, some of the diseases found in ESKD patients include Type I diabetes, HIV-associated nephropathy (HIVAN), hepatitis C virus (HCV) infection, lupus nephritis, cardiovascular disease, chronic kidney disease, hypertension, glomerulonephritis, septicemia, heparin-induced thrombocytopenia, and stroke. Additionally, the review includes studies on the impacts of COVID-19, malnutrition, nephrology access time, and the effects of natural disasters on ESKD patients. The articles frequently discussed hemodialysis and peritoneal dialysis as common treatment modalities for patients with ESKD. Hemodialysis was particularly prevalent in the studies, highlighting its widespread use and importance in managing patients with ESKD. The sample sizes in these studies ranged from 84 to 384,276, reflecting the variability in study scope and design.

The studies often reported on multiple SDOH domains. Specifically, in Table 2, 13 instances were recorded under Economic Stability, eight under Education Access and Quality, 21 under Healthcare Context, 18 under Neighborhood and Built Environment, and 53 under Social and Community Context. It's important to note that the total number of studies included in the review was 85, with many studies addressing more than one SDOH domain.

Table 2: Distribution of SDOH

SDOH Domain	**SDOH Variables**	**# Studies**
Economic Stability	Income, Employment	13
Education Access and Quality	Literacy, Level of Education	8
Healthcare Context	Health Insurance	21
Neighborhood and Built Environment	Distance to Healthcare facilities	18
Social and Community Context	Race, Ethnicity	53

The study incorporated data from multiple studies, with effect sizes represented as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). The random effects model was employed to calculate pooled estimates to accommodate the

between-study heterogeneity. The figures below present the pooled hazard ratios and 95% confidence intervals (CIs) for ESKD mortality among different demographic groups and SDOH factors. In one instance, the fixed effects model was used.

In figure 3, Erickson's 2019 study reveals that patients who start dialysis without insurance have a 30% lower risk of mortality from end-stage kidney disease (ESKD) compared to those who are insured. Jurkovitz's 2013 research presents contrasting findings: individuals without insurance face a 46% higher risk of mortality compared to those with private insurance, and those with public insurance experience a 91% higher risk relative to those with private insurance. Kucirka's 2011 studies further elaborate on these disparities, showing that individuals with Medicaid or no insurance have a 38% higher risk of mortality compared to those with private insurance, while Medicare recipients face a 35% higher risk. Interestingly, Kucirka also notes that those with private insurance have a 47% higher risk compared to Medicare recipients. Additionally, Nee's 2019 study highlights that individuals with dual eligibility for Medicare and Medicaid have a 20% lower risk of mortality compared to those with Medicare alone, those with employer group health insurance have a 13% lower risk compared to Medicare recipients, and those on Medicaid have a 4% higher risk compared to Medicare recipients. Salerno's 2021 study adds another layer to these findings, showing that Medicare patients have a 30% higher risk of mortality compared to those with Medicare Fee-For-Service coverage

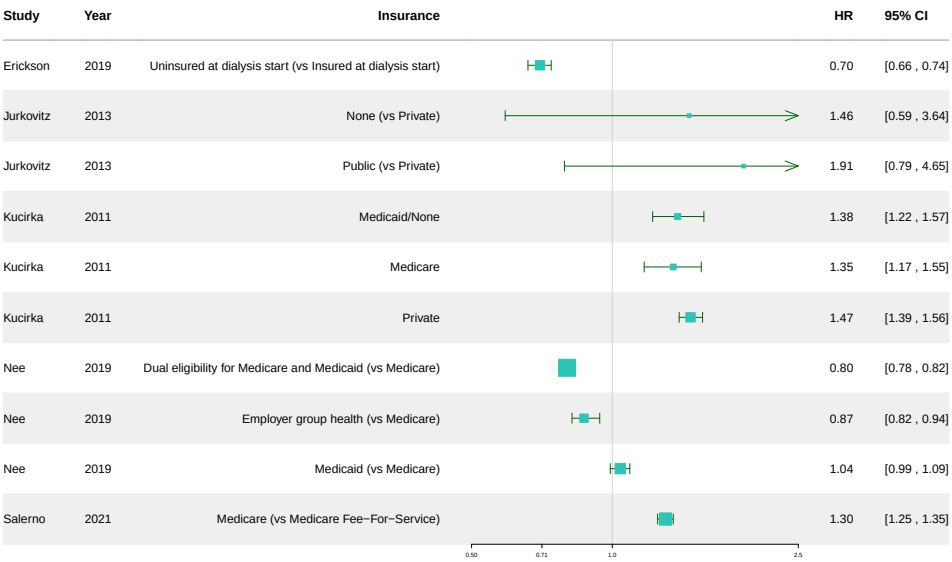

Figure 3: SDOH - Insurance Status; SDOH Domain - Healthcare Context.

Maripuri's 2012 studies indicate that patients living more than 50 miles away from a healthcare facility have a 7% higher risk of ESKD mortality compared to those living closer, with a hazard ratio (HR) of 1.07, increasing to 30% in another cohort (HR 1.30). For those living 11-20 miles away, the risk is 5% higher in one study and 11% higher in another. Similarly, patients living 21-50 miles away face an 8% higher risk and 14% higher risk in the different cohorts. Additionally, those living 5-10 miles away have a risk increase of 3% and 4% across different cohorts. Thompson's 2012 study highlights that individuals living more than 100 miles away face a 21% higher risk of ESKD mortality. However, the risk decreases for those living between 11-25 miles (HR 1.01), 26-45 miles (HR 0.99), and 46-100 miles. These studies collectively suggest that greater distances to healthcare facilities are associated with increased ESKD mortality risks.

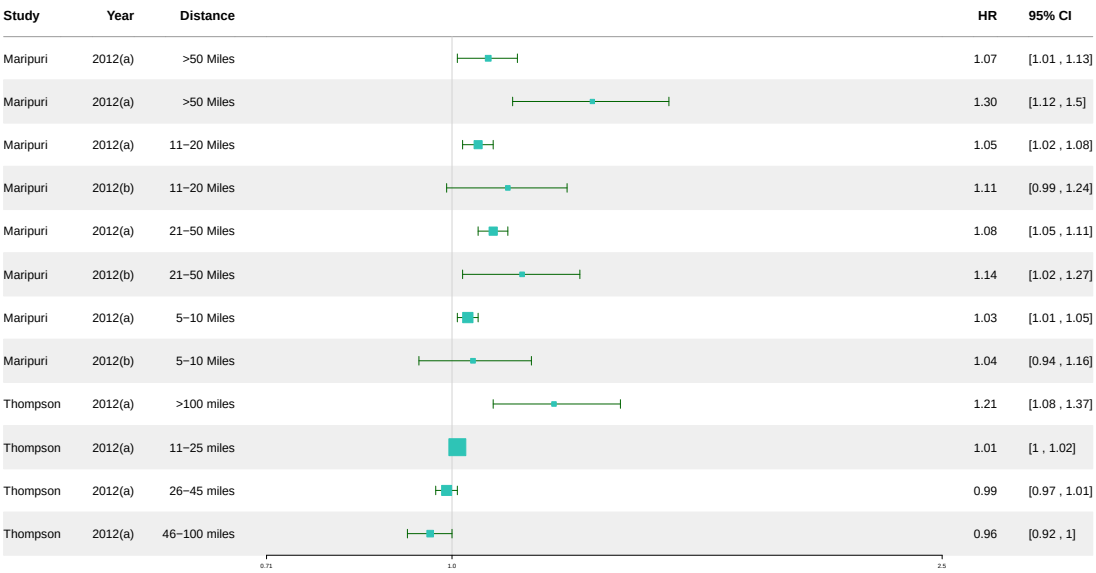

Figure 4: SDOH - Distance to Healthcare Facility; SDOH Domain - Neighborhood and Built Environment.

Kosnik's 2019 studies show that patients living in the most urban areas have a 12% and 8% lower risk of ESKD mortality compared to those in rural areas. Maripuri's 2012 studies provide mixed results, with one cohort showing no significant difference in risk (HR 1.00) and another indicating an 11% lower risk for urban dwellers compared to rural ones. Salerno's 2021 study also indicates a 10% lower risk for urban patients compared to their rural counterparts. Overall, figure 5 of the meta-analysis reveals a summary effect where urban patients generally experience an 8% lower risk of ESKD mortality compared to rural patients. These results highlight the importance of improving healthcare access and resources in rural areas to mitigate these disparities.

Figure 5: SDOH - Rurality; SDOH Domain - Neighborhood and Built Environment; Levels - Urban vs Rural (reference group).

In figure 6, Khattak's 2012 studies demonstrate that higher levels of education are associated with reduced risks of ESKD mortality. Specifically, college graduates have a 19% lower risk compared to those with less than 12 years of education, while individuals with some college education have a 10% lower risk , and those with a high school diploma show no significant difference (HR 0.99). Cavanaugh's 2010 study indicates that patients with adequate health literacy face a 34% lower risk of mortality compared to those with limited health literacy. Lockridge's 2011 study reveals a striking 85% lower risk for high school graduates or higher compared to those with less education. Overall, the meta-analysis summary effect indicates that higher education levels generally correspond to a 10% lower risk of ESKD mortality.

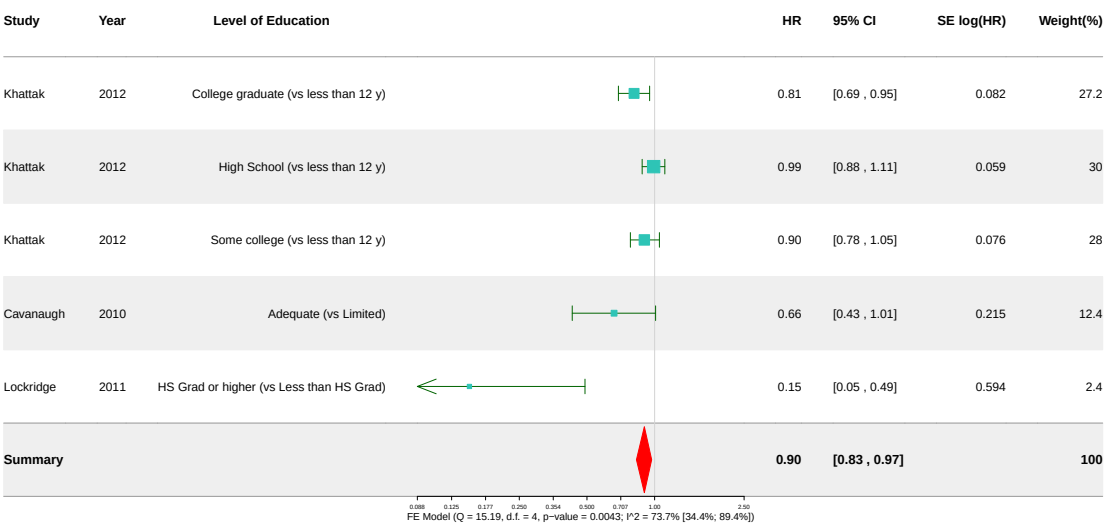

Figure 6: SDOH - Education; SDOH Domain - Education Access and Quality; Levels - High Levels vs Low Levels (reference group).

In the Figures 7-11, the comparisons show the risk of ESKD all-cause mortality for various race and ethnicity groups. It is shown that 19% lower risk of all-cause mortality in Black populations compared to White populations (HR 0.81, 95% CI 0.77-0.85), and 38% lower in Asian populations compared to White populations (HR 0.62, 95% CI 0.59-0.66). The risk is 16% lower in Native American populations compared to White populations (HR 0.84, 95% CI 0.80-0.87). For Hispanic populations, the risk is 26% lower compared to Non-Hispanic White populations (HR 0.74, 95% CI 0.53-1.03), but this is not statistically significant. The risk is 9% lower in Hispanic populations compared to non-Hispanic populations (HR 0.91, 95% CI 0.78-1.10), which is also not statistically significant.

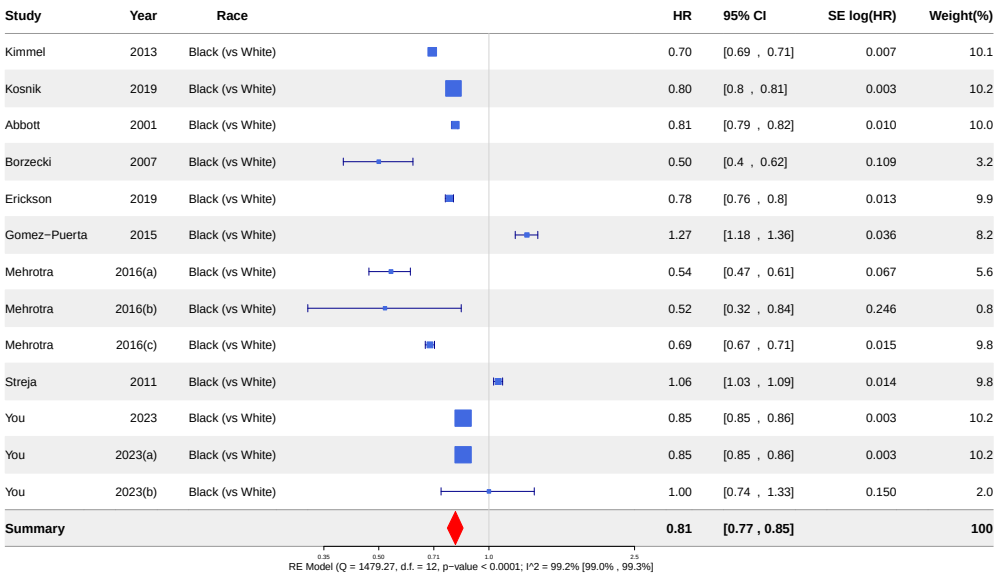

Figure 7: SDOH - Race; SDOH Domain - Social and Community Context; Levels - Black vs White (reference group).

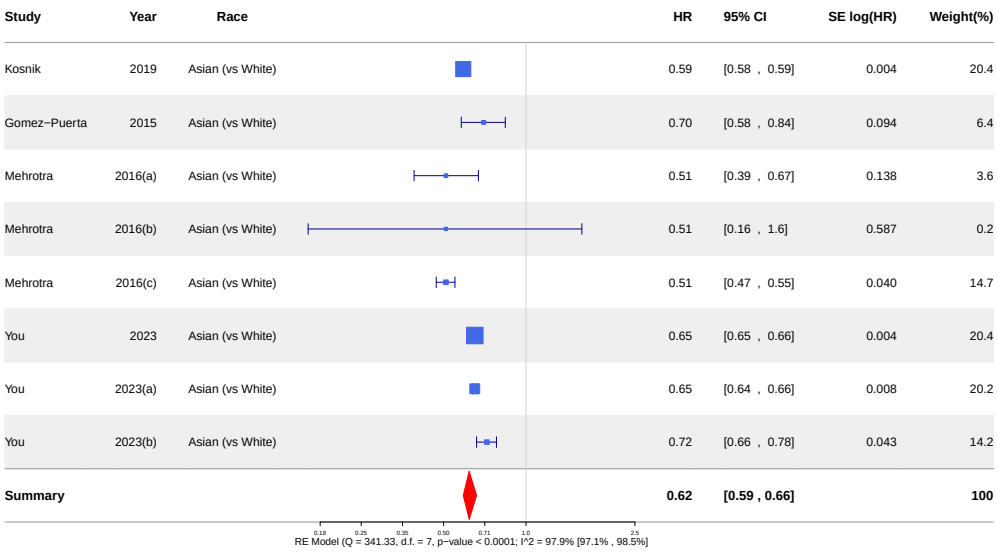

Figure 8: SDOH - Race; SDOH Domain - Social and Community Context; Levels - Asian vs White (reference group).

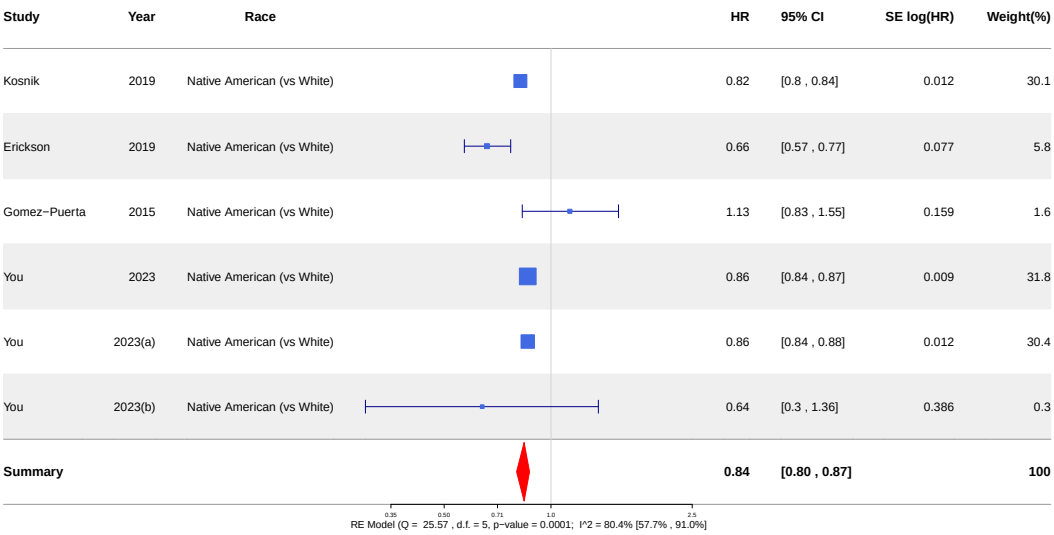

Figure 9: SDOH - Race; SDOH Domain - Social and Community Context; Levels - Native American vs White (reference group).

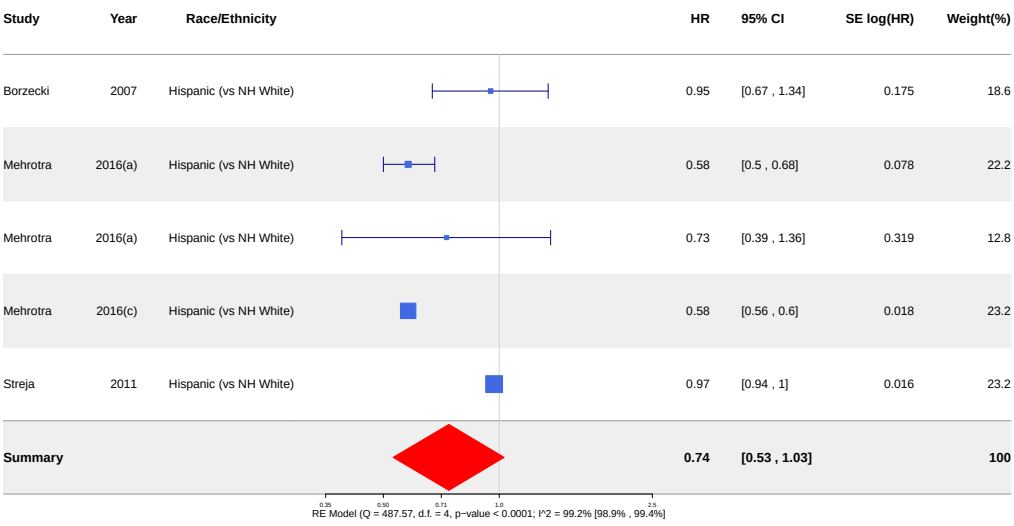

Figure 10: SDOH - Race; SDOH Domain - Social and Community Context; Levels - Hispanic vs Non-Hispanic White (reference group).

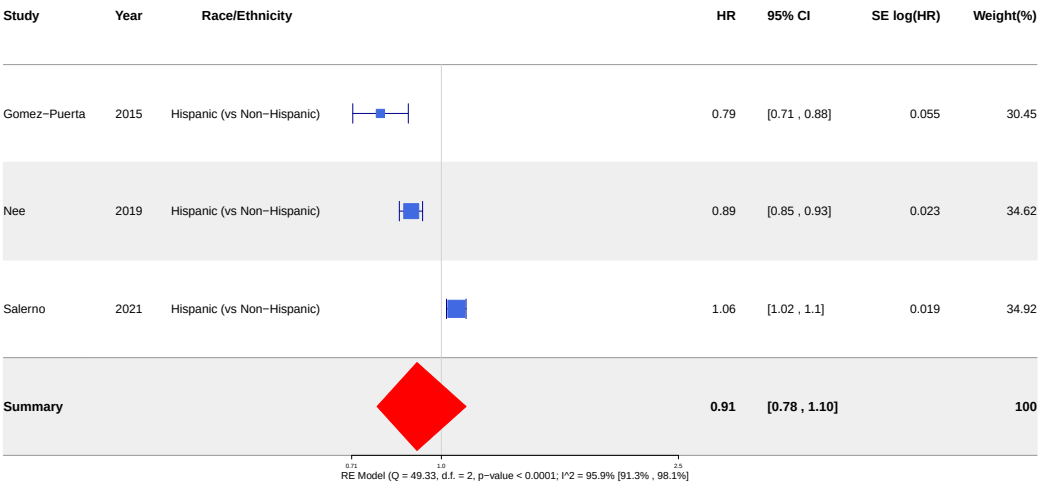

Figure 11: SDOH - Race; SDOH Domain - Social and Community Context; Levels - Hispanic vs Non-Hispanic (reference group).

Publication bias was assessed to determine its impact on the meta-analyses. Publication bias refers to the tendency for studies with significant results to be published more frequently than those with non-significant results, leading to selective publication. This bias can affect meta-analyses by overestimating true effect sizes if they predominantly include studies with significant findings. A small p-value (typically < 0.05) suggests evidence of publication bias. The following table presents p-values for Egger's and Begg's tests across different meta-analyses, indicating the potential presence or absence of publication bias:

The results indicate that there is no significant evidence of publication bias in most comparisons, as evidenced by the p-values for Egger's and Begg's tests being well above 0.05 for most groups. The exception is the Education meta-analysis, where Egger's test yielded a p-value of 0.0227, suggesting potential publication bias in studies examining the impact of education on ESKD mortality.

Table 3: Publication Bias

Meta-Analysis	**P-Value**	
	Egger's Test	**Begg's Test**
Black vs White	0.6231	0.9512
Native American vs White	0.5679	0.3476
Asian vs White	0.9412	0.4579
Hispanic vs Non-Hispanic White	0.8657	1.0000
Rurality	0.8848	1.0000
Education	0.0227	0.0500

4 DISCUSSION AND CONCLUSION

This study explored the impact of social determinants of health (SDOH) on end-stage kidney disease (ESKD) mortality in diverse groups by analyzing various research findings, systematic reviews, and meta-analyses. The results provided strong evidence of a complex relationship between race and ESKD mortality in the presence of SDOH factors. The meta-analysis revealed that White populations faced a higher risk of ESKD mortality compared to racial minorities. Young (2003) reported that among diabetic individuals receiving treatment in a national healthcare system, racial minorities had higher odds of diabetic nephropathy and ESKD, but a lower risk of cardiovascular disease (CVD) and mortality compared to Whites [64]. This suggests that when access to care is similar for ESKD patients, racial minority groups are more likely to experience microvascular complications, while Whites are more susceptible to macrovascular disease and mortality.

Access to healthcare services in the United States is severely limited for uninsured adults, who often receive inadequate care and suffer worse health outcomes compared to their insured counterparts [18, 39]. This gap is especially pronounced among patients with ESKD, where insurance status plays a crucial role in determining survival rates. Jurkovitz et al. (2013) found that uninsured participants in the Kidney Early Evaluation Program (KEEP) were 82% more likely to die than those with private

insurance, highlighting the significant barriers they face in obtaining timely and effective treatment [32].

Furthermore, Medicare coverage for most dialysis patients typically begins only in the fourth month of treatment. Before the Medicaid expansion, up to 20% of non-elderly patients initiated dialysis without any insurance [48]. This lack of coverage often leads to inadequate access to essential predialysis care, resulting in the underdiagnosis of diabetes and hypertension, the two primary causes of ESKD [61] [58]. However, patients in states that expanded Medicaid under the Affordable Care Act (ACA) experienced lower 1-year mortality rates when initiating dialysis [48].

Higher levels of education significantly enhance health literacy, enabling individuals to better comprehend health information and navigate complex healthcare systems. Educated patients are more likely to engage in effective self-management practices and adhere to prescribed treatment regimens, thereby improving their overall health outcomes [12]. Additionally, education often correlates with higher socioeconomic status (SES), which further influences health through improved income, stable employment, and better living conditions [50]. Consistent with findings from other studies, Cavanaugh et.al (2010) observed that patients who are male, have fewer years of education, and are of Non-white race are more likely to possess lower health literacy skills [6]. The study by Cavanaugh et.al is notable as it is the first to investigate the impact of health literacy on mortality risk within a cohort of patients recently started on hemodialysis. The findings indicate that lower health literacy is moderately associated with a higher risk of mortality, suggesting it may be a significant factor contributing to mortality in this high-risk patient population [6].

In the meta-analysis, a similar trend was observed, where higher educational attainment was associated with better survival rates among ESKD patients. This is aligns with the hypothesis proposed by Khattak et al. (2012), who found that ESKD patients with a college education had higher survival rates compared to those who did

not finish high school, highlighting the critical role of education in improving outcomes for individuals undergoing dialysis [33].

The study revealed that people in urban areas are less likely to die from end-stage kidney disease (ESKD). This finding aligns with several studies that highlight the challenges faced by patients in micropolitan and rural areas. Maripuri et al. (2010) found that peritoneal dialysis (PD) patients in these regions often live farther from their dialysis centers, resulting in a higher risk of mortality [36]. The increased distance can lead to gaps in PD training, dietary education, and timely response to complications. Providing home visits and reinforcing PD training, which has been shown to reduce peritonitis episodes in several observational studies, is more challenging for patients living far away [3].

Additionally, local healthcare factors significantly impact PD patients in these areas. Rural hospitals often lack the necessary resources to manage acute cardiovascular events or sepsis effectively, leading to higher 30-day mortality rates compared to urban hospitals [31]. Access to medical specialists is also limited in rural areas, with providers mostly concentrated in urban centers [36].

Both PD and hemodialysis (HD) patients face a higher risk of mortality the farther they live from their dialysis unit, with PD patients living more than 50 miles away experiencing worse outcomes. Interestingly, patients in micropolitan and rural areas are as likely or even more likely to receive a kidney transplant compared to urban patients, regardless of the type of dialysis they are receiving [36]. This unexpected trend might be explained by the generally better health status of transplant-eligible patients in rural areas. Furthermore, the impact of racial segregation in urban settings, which is linked to lower kidney transplant rates, might skew the comparison, making it seem like rural patients are more likely to receive transplants [44] [36].

Addressing the disparities in healthcare access, particularly in rural areas, is essential for reducing mortality rates and enhancing the quality of life for individuals with

ESKD. This may involve strategic investments in healthcare infrastructure, the establishment of more dialysis centers in underserved regions, and policies aimed at reducing the financial burdens of travel and treatment for rural patients.

Despite the challenges, the overall results indicate that it is crucial to address adverse social determinants in order to improve outcomes for ESKD patients. While most interventions focus on medical treatments and patient education, it is essential to also consider the broader social context in which patients live. To effectively reduce ESKD mortality, interventions and policies should be designed to address adverse social determinants. According to Thompson (2012), comprehensive strategies that include social support and community resources are necessary to improve health outcomes in ESKD patients [51]. Also, Rodriguez et al. (2007) highlight how urban residential segregation, a significant social determinant, impacts dialysis facilities and patient outcomes. Their study suggests that improving access to healthcare and addressing social disparities can lead to better health outcomes for ESKD patients [44]

The study had some limitations that need to be addressed. It mainly focused on articles related to SDOH factors, but there was insufficient data in some domains. Also, the categorization of racial groups posed significant challenges as these categories are often overly broad, potentially hiding disparities within smaller subgroups that are grouped into broader classifications.

Moreover, the study only looked at articles focusing on adult populations and individuals currently on dialysis, so the findings may not be applicable to other groups, such as pediatric patients. Additionally, due to variations in group comparisons, it was not possible to perform a meta-analysis for certain factors, such as insurance and distance.

Furthermore, the studies included in the systematic review and meta-analysis had several methodological limitations. Many studies had small sample sizes and lacked variation in SDOH factors, which could have influenced the reliability of the results.

Yan (2013) pointed out that studies with small sample sizes and insufficient power to detect significant differences have inherent limitations that can affect the reliability of the findings [63]. Additionally, some studies reported risk ratios and odds ratios instead of hazard ratios, which were not suitable for the meta-analysis as most studies reported hazard ratios. This inconsistency in the reported metrics complicates the aggregation and comparison of data across studies.

In conclusion, this study emphasized the significant impact of SDOH on mortality among ESKD patients. These factors include race, insurance status, education, and geographical location. The study findings reveal that although White populations face higher ESKD mortality risks, racial minorities are more likely to experience severe microvascular complications when they have equal access to care. Uninsured patients, especially those in rural areas, encounter significant barriers to receiving timely and effective treatment, leading to higher mortality rates. Conversely, higher education levels and living in urban areas are linked to better outcomes. It is crucial to address these disparities through targeted healthcare policies and improvements in infrastructure to enhance survival rates and the quality of life for ESKD patients.

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