Adverse Childhood Experiences and Decreased Renal Function: Impact on All-Cause Mortality in U.S. Adults

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Introduction: Evidence suggests that individuals with a history of adverse childhood experiences have higher odds of developing kidney disease than individuals with no adverse childhood experiences. However, no study has examined the influence of coexisting adverse childhood experiences and kidney disease on mortality risk. This study uses a longitudinal survey of adults to examine the influence of coexisting adverse childhood experiences and decreased renal function on all-cause mortality in a sample of U.S. adults.

Methods: A total of 1,205 adults participating in the Midlife Development in the United States series between 1995 and 2014 were used for this analysis performed in 2019. A total of 6 types of adverse childhood experiences were available in the data set, which were combined to create a dichotomous variable with any adverse experience counted as *yes*. Decreased renal function was defined as an estimated glomerular filtration rate <60 milliliter/minute/1.73 m^2. The main outcome was all-cause mortality. Cox proportional hazards models were performed to examine 4 combinations of adverse childhood experiences and decreased renal function associated with overall survival (neither, adverse childhood experiences only, decreased renal function only, or both) controlling for covariables.

Results: In fully adjusted models, adverse childhood experiences and decreased renal function were associated with increased all-cause mortality relative to neither (hazard ratio=2.85, 95% CI=1.30, 6.25). Decreased renal function only and adverse childhood experiences only were not significantly associated with all-cause mortality (hazard ratio=1.14, 95% CI=0.64, 2.04 and hazard ratio=1.55, 95% CI=0.44, 5.41, respectively). When using decreased renal function as the reference group, coexisting adverse childhood experiences and decreased renal function was associated with a 64% increased risk of all-cause mortality, though this relationship was not statistically significant.

Conclusions: Coexistence of adverse childhood experiences and decreased renal function is associated with higher all-cause mortality than seen in individuals with neither adverse childhood experiences nor decreased renal function and may be associated with higher all-cause mortality than seen in individuals with decreased renal function alone. Future research is needed to better understand this potential association.
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INTRODUCTION

Chronic kidney disease (CKD), defined as abnormal kidney function present for more than 3 months, affects 37 million U.S. adults.[1,2] CKD, one of the leading causes of death in the U.S. and worldwide, is commonly caused by diabetes and hypertension.[2,3] Management of CKD is complex and challenging because it is often focused on managing concordant comorbid diseases such as diabetes and hypertension to prevent complications, progression of the disease, and mortality. Though risk factors for CKD include diabetes, hypertension, and heart disease, there is increasing evidence supporting the role of social determinants of health on CKD risk and outcomes.[4,5]

Social determinants of health are conditions in which people are born, grow, live, work, and age, which include socioeconomic factors, psychosocial factors, neighborhood and built environment, political, economic, and cultural factors.[6,7] Social determinants of health exert an influence on adult health through both distal and proximal factors and are particularly salient for understanding chronic disease burden from a life-course perspective.[8] Evidence suggests that social determinants of health have a unique interplay with biological factors that may predispose individuals to have worse health outcomes,[9,10] including diabetes outcomes,[11] hypertension,[12] and kidney disease.[4,5] For example, adverse childhood experiences (ACEs) are social determinants of health that have been shown to confer risk for adult morbidity and early mortality.[7,13−19] The relationship between ACEs and mortality is thought to be related to exposure to adverse events during a sensitive developmental period lending to a toxic stress response.[13,20] This ensuing toxic stress response is central to chronic disease development[21,22] and psychological distress such as self-harm[23] and health risk behaviors,[14] ultimately increasing risk for early mortality.[24]

As they occur before the age of 18 years and can be direct (sexual, physical, or verbal abuse and neglect) or indirect (household dysfunction such as substance abuse, incarcerated relative, mental illness, mother treated violently, and household challenges such as family instability and financial strain), ACEs are considered distal influences on adult health.[20,25] Though occurring during childhood, ACEs can have detrimental effects on adult health.[13,14,16,21] The literature is well-established on the association between ACEs and a number of the leading causes of death in the U.S., namely diabetes, hypertension, chronic respiratory disorders, stroke, kidney disease, and heart disease.[13,14,16,21] In addition to being associated with the leading causes of death, recent evidence shows that individuals who have a history of ACEs and are living with a chronic disease in adulthood

such as diabetes may have a greater mortality risk than individuals who have not experienced ACEs and do not have a chronic disease.[19] For example, a recent study examining the effect of co-occurring ACEs and diabetes on mortality found that during a 20-year follow-up period, individuals reporting a history of ACEs, who also had a diagnosis of diabetes, had a twofold increased risk of early mortality compared with individuals who did not have a history of ACEs but had diabetes.[19] As diabetes is one of the leading causes of CKD, understanding whether ACEs confer similar mortality risk among individuals with CKD is greatly needed.

Overall, the relationship between ACEs and CKD is a widely understudied area.[15] Although evidence suggests that prevalence as well as risk of kidney disease are higher among those who experience ACEs,[13,26] no study has examined the influence of coexisting ACEs and CKD on mortality risk in individuals with kidney disease.[15] Therefore, the aim of this study is to examine the influence of coexisting ACEs and decreased renal function (DRF) on all-cause mortality in a nationally representative sample. The first hypothesis is that the coexistence of ACEs and DRF is associated with an increased risk of all-cause mortality compared with the all-cause mortality in individuals with neither conditions after adjusting for relevant confounders. In addition, the second hypothesis is that the coexistence of ACEs and DRF is associated with an increased risk of mortality compared with mortality in individuals with only DRF.

METHODS

Study Population

Data from the national survey of Midlife Development in the United States (MIDUS) was used for this study.[27] The collective aim of MIDUS is to investigate the role of behavioral, psychological, and social factors in age-related variations in health and well-being in a national sample of U.S. adults. Owing to the success of MIDUS 1 (1995−1996), the National Institute on Aging awarded a grant to the Institute on Aging at the University of Wisconsin-Madison in 2002−2006 to carry out a longitudinal follow-up of MIDUS 1 respondents. The objectives of this research were to repeat the comprehensive assessments obtained in all the original content areas and launch new areas of biological and neurologic assessment. The study was extended for a third round of funding (2011−2016) with the objective of expanding the MIDUS sample. All 3 waves of the longitudinal MIDUS study were used for this study because different variables were collected in each wave. Only those with serum creatinine data collected during Wave 2 comprehensive biomarker assessment project were included in the cohort as determination of whether an individual had decreased estimated glomerular filtration rate (eGFR). ACE variables were collected in Waves 1 and 2, and mortality was collected in Wave 3. Data analysis took place in 2019, and the data are publicly available through the Inter-University Consortium for

Political and Social Research. A total of 50 participants without complete ACE information were excluded. The final cohort for this study was 1,205 (Appendix Figure 1, available online).

Measures

The ACEs Study Questionnaire[21] was used to identify measures of adverse events experienced during childhood. The MIDUS study collected information on a number of possible ACEs included in the Felitti et al.[21] definition of ACEs, as well as additional questions available in MIDUS to examine family instability and financial strain found in the extant literature using MIDUS to examine ACEs.[28−30] Therefore, a combined set of ACEs categories was created, which included emotional abuse, physical abuse, sexual abuse, substance abuse by parents during childhood, family instability, and financial strain. Self-reported questions used to create individual ACE categories are shown in Table 1. Each type of ACE was then dichotomized to indicate exposure. A final dichotomized ACE variable was created to indicate *yes* if an individual responded positively to any of the 6 categories and *no* if they responded negatively to all 6 categories.

In this study, DRF was defined as an estimated eGFR <60 milliliter/minute/1.73 m^2 and was calculated using the CKD Epidemiology Collaboration,[31] the recommended formulas per the Kidney Disease Improving Global Outcomes guidelines. Serum creatinine was used to calculate eGFR, a one-time collection in the biomarker project. The biomarker project did not collect urine albumin; therefore, urine albumin to creatinine ratio was not calculated.

Demographic variables included sex, age (dichotomized as 35−59 years and 60−86 years based on the mean age), and race (dichotomized as white and ethnic minority). Comorbidity was based on self-reported medical conditions collected during the biomarker project. Participants were asked the following questions: *Have you ever had any of the following conditions/illnesses? And If yes, was it diagnosed by a physician?* To conserve power in the model, comorbidities could not be added individually. Instead, comorbidity burden was investigated on the basis of a count of 6 self-reported clinically relevant comorbidities in the data set: hypertension, diabetes,

Table 1. ACEs Measures

ACEs category	Values, %	Definition
Emotional abuse	26.6	Wave 1/AA Childhood family background questions: your childhood how often did your mother, father, brothers, sisters, or anyone else insulted you or swore at you; sulked or refused to talk to you; stomped out of the room; did or said something to spite you; threatened to hit you; smashed or kicked something in anger.
		Wave 2 Biomarker project CTQ: family called me names; thought parents wished I had never been born; felt family member hated me; family said hurtful or insulting things to me; believe I was emotionally abused
Physical abuse	22.2	Wave 1/AA Childhood family background questions: during your childhood how often did your mother, father, brothers, sisters, or anyone else pushed, grabbed, or shoved you; slapped you; threw something at you; kicked, hit, or hit you with a fist; hit or tried to hit you with something; beat you up
		Wave 2 Biomarker project CTQ: family hit hard, I had to see doctor; family hit hard, left with bruises or marks; punished with belt or hard object; believe I was physically abused; hit so hard, people noticed
		Wave 2/AA SAQ: Ever physically assaulted before age 18
Sexual abuse	17.8	Wave 2 Biomarker project CTQ: Someone tried to touch me sexually; Other threaten harm if no sexual acts; Other tried to force do/watch sexual; Someone molested me; Believe I was sexually abused
		Wave 2/AA SAQ: Ever sexually assaulted before age of 18
Parental substance abuse	26.1	Wave 1/AA Childhood background questions: What was the main reason father/mother was not working for pay during most of your childhood years? − Alcohol or drug abuse
		Wave 2 Biomarker project CTQ: My parents were too drunk or high to take care of me
		Wave 2/AA Phone interview: Lived with alcoholic during childhood
		Wave 2/AA SAQ: Ever parent drank caused problems; Ever parent drugs caused problems
Family instability	26.5	Wave 1/AA Childhood background questions: Why didn't live with biological parents, the reason "separated/divorced, death of a parent, adopted or other?
		Wave 1/AA Childhood background questions: Who was the male head of your household for most of your childhood? With answer no male in household
		Wave 2/AA SAQ: Did you live with both of your biological parents up till you were 18?
	35.8	Wave 1/AA Childhood background questions: Receipt of welfare; less than a high school education for father (or mother if no male head)
		Wave 1/AA Childhood family background questions: was your family better off or worse off financially than the average family was at that time, report of being somewhat or a lot 'worse off' than other families.

AA, Milwaukee African American sample; ACE, adverse childhood experience; CTQ, childhood trauma questionnaire; SAQ, self-administered questionnaire.

cardiovascular disease, cancer, cholesterol problems, and depression. Based on the importance of specific comorbidities, high blood pressure, and diabetes, these conditions were included as individual comorbidities in the fully adjusted model.

Mortality status was based on data collected at the time of Wave 3. The mortality status was collected from 3 general source categories: (1) tracing conducted by the University of Wisconsin Survey Center before, during, and after fielding; (2) formal National Death Index searches; and (3) longitudinal sample maintenance.[32] Because the data set did not include the cause of death, the outcome of interest for this study was all-cause mortality. All participants were followed from the date of biomarker data collection until death or end of follow-up date (May 2015, the latest death date available in the mortality data). Mortality data included known month and year of death; the middle of the month (Day 15) was used as the day to construct the date. The average follow-up time was 8.3 (SD=1.6) years.

Statistical Analysis

The primary independent variable was based on ACEs and DRF definitions to define 4 sample population groups: (1) no ACEs no DRF, (2) ACEs only, (3) DRF only, and (4) ACEs and DRF. Baseline information was compared among these 4 groups using chi-square tests for categorical and ANOVAs for continuous variables.

A univariate Cox proportional hazard model was first developed to examine whether the 4 combinations based on ACEs and DRF coexistence were associated with overall survival. Unadjusted survival curves were then plotted from the univariate Cox model with no ACEs no DRF as the reference category. Furthermore, multivariable Cox proportional hazard models were constructed by first adjusting for demographic variables, including age, sex, and race, and then by adjusting for demographic variables and comorbidities. Finally, the unadjusted and adjusted Cox proportional hazard models were run with DRF as the reference category.

Table 2. MIDUS Biomarker Cohort Description

Variables	All (*n*=1,205)	No ACEs No DRF (*n*=327)	ACEs only (*n*=799)	DRF only (*n*=22)	ACEs and DRF (*n*=57)
Sex					
Male	43.2	48.6	41.2	50.0	38.6
Female	56.8	51.4	58.8	50.0	61.4
Age, years					
35–59	57.6	60.9	60.6	4.5	17.5
60–86	42.4	39.1	39.4	95.5	82.5
Race					
White	79.3	90.8	75.2	77.3	73.2
Minority	20.6	9.2	24.8	22.7	26.8
Comorbidities, % (95% CI)					
Hypertension	36.6 (33.9, 39.3)	27.6 (22.8, 32.5)	37.2 (33.9, 40.6)	63.6 (43.5, 83.7)	69.6 (57.6, 81.7)
Diabetes	12.1 (10.3, 14.0)	9.8 (6.6, 13.0)	12.1 (9.9, 14.1)	28.6 (9.2, 47.9)	19.3 (9.1, 29.5)
Cardiovascular disease	24.5 (22.1, 26.9)	22.6 (18.1, 27.2)	23.2 (20.2, 26.1)	40.9 (20.4, 61.5)	47.4 (34.4, 60.3)
Cancer	13.9 (11.9, 15.8)	11.6 (8.1, 15.1)	13.7 (11.3, 16.0)	27.2 (8.7, 45.9)	24.6 (13.4, 35.7)
Cholesterol problems	42.8 (39.9, 45.6)	36.3 (31.1, 41.5)	43.9 (40.4, 47.3)	59.1 (38.5, 79.6)	58.2 (45.1, 71.2)
Depression	19.8 (17.5, 22.0)	12.6 (9.0, 16.2)	22.4 (19.5, 25.3)	4.6 (0.0, 13.2)	29.8 (17.9, 41.7)
Comorbidity burden					
Mean ± SD (min–max)	1±1 (0–6)	1±1 (0–5)	2±1 (0–6)	2±1 (0–5)	2±1 (0–6)
0–1	55.1	66.4	53.4	36.4	21.1
2+	44.9	33.6	46.6	63.6	78.9
Mean eGFR in mL/minute/1.73 m² (SD)	87.6 (18.2)	88.5 (14.1)	91.1 (15.6)	51.5 (8.4)	47.5 (12.3)
DRF (eGFR <60)	6.6	—	—	—	—
Reported ACEs	71.0	—	—	—	—
ACEs and DRF category					
No ACEs no DRF	27.1	—	—	—	—
ACEs only	66.3	—	—	—	—
DRF only	1.8	—	—	—	—
ACEs and DRF	4.7	—	—	—	—

Note: All values are percentage except when specified.
ACE, adverse childhood experience; DRF, decreased renal function; eGFR, estimated glomerular filtration; Max, maximum; MIDUS, Midlife Development in the United States; Min, minimum; mL, milliliter.

Risk-adjusted survival curves were plotted from the fitted Cox model using the corrected group prognosis method. In the corrected group prognosis method, survival curves were first calculated for each of the unique combinations of covariates using the fitted Cox model[33]; the average survival was then calculated with weights proportional to the number of individuals at each covariate level.

Results were considered significant for *p*<0.05. All analyses were performed with SAS, version 9.4.

RESULTS

The longitudinal sample included 1,205 adults aged 35−86 years. Table 2 shows sample baseline demographics. The cohort's median age was 57 (IQR, 49−65) years, of which 57% were female and 79% were white. Overall, 71% of the participants reported having ACEs and approximately 7% had DRF. The mean eGFR of the cohort was 87.6 milliliter/minute/1.73 m². A total of 27% of this cohort who reported no history of ACEs did not have DRF (no ACEs no DRF), 66% reported only having a history of ACEs (ACEs only), 2% had DRF without a history of ACEs (DRF only), and 5% reported a history of ACEs and also had DRF (ACEs and DRF).

Table 3 provides information on univariate and multivariable Cox proportional hazard models. In the unadjusted model, compared with individuals who did not have a history of ACEs and also did not have DRF, those who only had a history of ACEs (hazard ratio [HR]=1.10, 95% CI=0.63, 1.92) and those who only had DRF (HR=2.86, 95% CI=0.84, 9.78) were not significantly different in mortality. However, individuals who had a history of ACEs and also had DRF had a fourfold higher mortality risk (unadjusted HR=4.69, 95% CI=2.24, 9.83) than those who did not have a history of ACEs and did not have DRF. In fully adjusted models, individuals with coexisting ACEs and DRF maintained a twofold increase in mortality risk (HR= 2.85, 95% CI=1.30, 6.25). Those who only had DRF and those who only had a history of ACEs did not have a significantly associated all-cause mortality risk (HR=1.14, 95% CI=0.64−2.04 and HR=1.55, 95% CI=0.44, 5.41, respectively). When using DRF as the reference group, those with coexisting ACE and DRF had a 64% increased risk of all-cause mortality, though this relationship was not statistically significant (HR=1.64, 95% CI=0.46, 5.80). This increased risk of mortality remained after adjustment but was not significant (HR=1.72, 95% CI=0.48, 6.11). Figure 1 shows the adjusted survival curves by using the corrected group prognosis method for the 4 groups over time.

DISCUSSION

Consistent with the study hypothesis, this study found that after adjusting for demographics and comorbidities,

Table 3. Cox Proportional Hazard Models for All-Cause Mortality Based on ACEs and DRF Status

Variable	Unadjusted, HR (95% CI)	Adjusted for demographics, HR (95% CI)	Fully adjusted, HR (95% CI)
ACEs and DRF category			
No ACEs no DRF	ref	ref	ref
ACEs only	1.10 (0.63, 1.92)	1.08 (0.61, 1.90)	1.14 (0.64, 2.04)
DRF only	2.86 (0.84, 9.78)	1.46 (0.42, 5.06)	1.55 (0.44, 5.41)
ACEs and DRF	**4.69 (2.24, 9.83)**	**2.78 (1.30, 5.94)**	**2.85 (1.30, 6.25)**
Sex			
Male	ref	ref	ref
Female	0.75 (0.48, 1.18)	0.74 (0.47, 1.17)	0.78 (0.49, 1.23)
Age group, years			
35–59	ref	ref	ref
60–86	**5.59 (3.18, 9.82)**	**4.99 (2.79, 8.93)**	**4.45 (2.45, 8.07)**
Race			
White	ref	ref	ref
Minority	0.96 (0.54, 1.73)	1.18 (0.65, 2.14)	1.00 (0.54, 1.85)
Hypertension			
No	ref		ref
Yes	**2.11 (1.34, 3.31)**		1.16 (0.71, 1.90)
Diabetes			
No	ref		ref
Yes	**2.44 (1.45, 4.09)**		**1.89 (1.10, 3.27)**

Note: Boldface indicates statistical significance (*p*<0.05).
ACE, adverse childhood experience; DRF, decreased renal function; HR, hazard ratio.
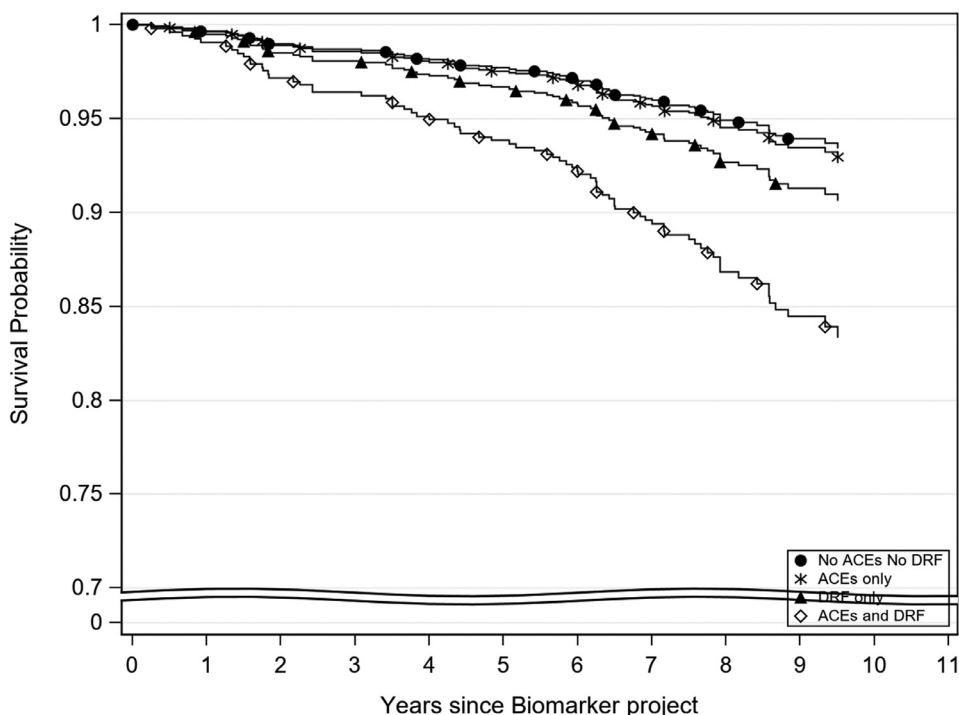
Figure 1. Adjusted overall survival curves based on ACEs and DRF status.
Note: Adjusted survival curves using the corrected group prognosis method. Adjusted by age, sex, and race.
ACE, adverse childhood experience; DRF, decreased renal function.

individuals with coexisting ACEs and DRF had a twofold increased risk of all-cause mortality compared with those with neither. Contrary to the second hypothesis, having coexisting ACEs and DRF was not associated with higher mortality compared with having DRF alone.

Current findings suggest that individuals with coexisting ACEs and DRF have significantly higher mortality risk than individuals with neither ACEs nor DRF. The Kaplan−Meier curve suggests that individuals with coexisting ACEs and DRF may have a more severe drop in survival than individuals in other groups; however, given the preliminary nature of this analysis, additional investigation into this relationship is warranted. Although existing evidence supports the exacerbating impact that ACEs may have on the health status of individuals living with a chronic illness and its association with early mortality, these results serve as preliminary findings highlighting the influence of ACEs on mortality specifically among individuals with kidney disease.[19] Though the mechanisms driving the observed higher mortality rate in individuals with coexisting ACEs and DRF remains unclear, evidence suggests that the prolonged stress response resulting from experiencing ACEs may underlie many biological processes leading to what has been referred to as clustered metabolic risk and increasing the risk for early mortality.[34,35] Coexisting

ACEs and DRF may serve to compound existing health vulnerabilities leading to early mortality; however, more fully powered studies with additional measures are needed to tease out this association and the underlying mechanisms. In addition, evidence suggests that increased risk of early mortality may relate to factors during the embryonic and fetal phases of life.[36,37] The impact of these factors on birth weight and disease susceptibility of an individual during their entire life is a phenomenon known as fetal programming.[36,37] Fetal programming has been shown through a number of epidemiologic studies to have an influence on chronic disease incidence and mortality.[36,37] This relationship is another possible mechanism to explain the results of this study.

This study did not find a significant association between early mortality among those who had a history of ACEs only or DRF only. This contrasts with the existing evidence that shows an association between ACEs and early mortality.[24,38,39] Specifically, individuals with a high number of ACEs have been shown to be at risk of premature death.[17] In a study of more than 17,000 adults, cumulative exposure to ACEs was associated with a likelihood of dying 20 years early compared with individuals with no exposure to ACEs.[17] In addition, the relationship between ACEs and premature mortality has

been found independent of adult-mediating factors such as education, social class, BMI, smoking status, and alcohol consumption, where exposure to 2 or more ACEs was associated with 57%−80% increased risk of death.[34] The lack of association seen in this study may relate to the small sample size in the DRF group and large proportion of individuals who reported ACEs in this particular sample, which limits variability, or the broad definition of ACEs, which could lead to very different individuals being categorized together. These findings should be interpreted within the context of previous work on ACEs and suggest that future work in this area is needed.

These study findings have implications for clinical care. Clinically, although ACEs may not be the primary concern of a nephrologist faced with the complex management of concordant comorbid diseases such as diabetes and hypertension,[40] the findings of this study underscore the significance of early recognition of ACEs history in individuals with DRF during healthcare delivery. Early recognition and screening for ACEs have the potential to mitigate the negative impact of ACEs on an individual's life-course health and health outcomes.[41] There is growing evidence to support that social determinants of health such as ACEs impact physical and mental health, increase utilization of health care, and as such increase healthcare costs.[13,14,21,33,42] Furthermore, the existing literature has shown that the presence of ACEs confers risk for poor health behaviors in adulthood as well as morbidity and chronic diseases such as diabetes and hypertension.[43] Consequently, this could increase the risk for kidney disease, the potential for complications, and the progression of the disease.[43] Taken together, for healthcare providers, specifically primary care physicians and nephrologists, an ACE-informed practice may be an important consideration when using patient history and contextual factors of patients' environments to inform management options.[15] In addition, as providers are often uncomfortable screening for conditions without a plan for treatment, it is recommended that ACE screening is accompanied with referral pathways and the provision of evidence-based treatment resources.[41]

Limitations

Despite the novelty of this study, it is not without limitations. First, the study population was middle-aged adults, so prevalence estimates for DRF may be lower than national estimates, which are based on a population level that includes elderly adults known to have the highest prevalence of the disease. Second, based on the variables available in the data set, CKD could not be defined and DRF may not be of the same population. Third, though a large proportion of the sample had ACEs, the group with DRF only was small, so estimates may not be stable. Fourth, 8 years may not be enough time to capture mortality in this study population as DRF could be suggestive of acute kidney injury or future CKD. Fifth, because of the small overall sample and the small sample of individuals in the DRF only group, several covariates could not be included in the models. Sixth, the data set does not have information on parental risk factors, which could potentially affect mortality risk in individuals with DRF. Finally, this data set did not include information on CKD awareness, which is an important factor for disease outcomes. Future studies should investigate a larger population-based sample controlling for additional cofounding factors, following participants for a longer period, investigating specific types of ACEs, and collecting information on awareness of and treatment for the disease. Studies should also collect multiple serum creatinine data over time to allow the investigation of CKD and change in eGFR within a CKD population.

CONCLUSIONS

This longitudinal study of U.S. adults found that the coexistence of ACEs and DRF in individuals was associated with higher all-cause mortality compared with all-cause mortality in individuals having neither ACEs nor DRF. These results serve as preliminary findings to understand the influence of ACEs on health status among individuals with DRF. Future work that would focus on the mechanistic factors driving this relationship as well as the influence of specific ACEs among this population is needed.

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SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2020.04.005.

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