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Dietary protein intake, kidney function, and survival in a nationally representative cohort

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ABSTRACT

Background: High-protein diets (e.g., Paleo, Atkins, South Beach, ketogenic) have gained popularity as a means to promote weight loss and avoid excess carbohydrate consumption. Yet in chronic kidney disease (CKD) patients, evidence suggests low dietary protein intake (DPI) leads to attenuation of kidney function decline, although concerns remain for risk of protein-energy wasting.

Objectives: To examine associations of DPI with mortality in a nationally representative cohort of US adults, stratified by kidney function.

Methods: We examined the association between daily DPI scaled to actual body weight (ABW), ascertained by 24-h dietary recall, with all-cause mortality among 27,604 continuous NHANES adult participants (1999–2010), stratified according to impaired versus normal kidney function (estimated glomerular filtration rates <60 compared with ≥60 ml/min/1.72 m^2, respectively), using multivariable Cox models. We also examined the relation between high biological value (HBV) protein consumption with mortality.

Results: In participants with impaired kidney function, a high DPI of ≥1.4 g/kg ABW/day was associated with higher mortality, while lower DPI levels were not associated with mortality (reference, 0.6 to <1.0 g/kg ABW/day): the adjusted HRs (aHRs) were 1.09 (95% CI: 0.90, 1.32), 1.03 (95% CI: 0.82, 1.29), and 1.37 (95% CI: 1.02, 1.85) for DPI <0.6, 1.0 to <1.4, and ≥1.4 g/kg ABW/day, respectively. Yet in participants with normal kidney function, a low DPI of <0.6 g/kg ABW/day was associated with higher mortality, whereas higher DPI levels were not associated with death: the aHRs were 1.18 (95% CI: 1.04, 1.34), 0.92 (95% CI: 0.81, 1.04), and 0.99 (95% CI: 0.85, 1.16) for DPI <0.6, 1.0 to <1.4, and ≥1.4 g/kg ABW/day, respectively. The highest 2 tertiles of HBV consumption were associated with higher mortality in participants with impaired kidney function.

Conclusions: Among participants with impaired kidney function, a higher DPI and greater HBV consumption were associated with higher mortality, whereas a lower DPI was associated with higher mortality in those with normal kidney function. Further studies are needed to elucidate the specific pathways between higher DPI and mortality in CKD. *Am J Clin Nutr* 2021;114:303–313.

Keywords: dietary protein, chronic kidney disease, kidney function, mortality, survival, NHANES

Introduction

There has been increasing interest in dietary protein intake (DPI) as an important modulator of health and survival in both the chronic kidney disease (CKD) and non-CKD populations (1–4). In the general population, consumption of high dietary protein diets (e.g., Paleo, Atkins, ketogenic) has been widely popularized as a means to build muscle with resistance training (5), maintain muscle mass with aging (6), and promote weight loss during

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Supplemental Tables 1–10 and Supplemental Figures 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: ABW, actual body weight; aHR, adjusted hazard ratio; AMPM, Automated Multiple-Pass Method; CKD, chronic kidney disease; CVD, cardiovascular disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; HBV, high biological value; KDOQI, Kidney Disease Outcomes Quality Initiative; NCHS, National Center for Health Statistics; NDD-CKD, non–dialysis dependent CKD; NKF, National Kidney Foundation; UACR, urine albumin-to-creatinine ratio.

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energy restriction (7–9), particularly in those with obesity and diabetes.

However, growing evidence suggests that higher levels of DPI have adverse impact upon kidney health outcomes (10). Experimental models and clinical data have shown that a higher DPI leads to increased glomerular filtration, resulting from augmentation in renal blood flow and intra-glomerular pressure in order to excrete protein-derived nitrogenous waste products (11–13). In contrast, longitudinal studies of CKD have shown a linear relation between lower DPI and reductions in glomerular hyperfiltration, proteinuria, and CKD progression over time (14). Consequently, in non–dialysis dependent CKD (NDD-CKD) patients, low-protein diets (defined as diets with DPI of 0.6–0.8 g/kg/d in patients with diabetes and DPI of 0.55–0.60 g/kg/d in patients without diabetes) have been recommended by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) Nutritional Management of CKD guidelines (15, 16) in order to ameliorate the progression of CKD towards end-stage renal disease (10). However, concern exists that a chronic reduction in DPI below minimum requirements may be harmful in both the CKD and non-CKD populations.

Additionally, wide debate continues regarding the impact of the source of DPI (i.e., animal compared with plant protein) upon kidney health outcomes due to mixed data in both the CKD and non-CKD populations. Some (17, 18) but not all (19) studies have shown that greater consumption of animal proteins and lower consumption of plant proteins are associated with higher mortality risk. In patients with NDD-CKD, clinical practice guidelines advise that ≥50% of DPI should be from high biological value (HBV) proteins, which have amino acid compositions similar to human protein (i.e., containing the full spectrum of essential amino acids) and are more likely to be from animal proteins (20). Yet this stands in contradistinction to growing data suggesting the health benefits of plant-based diets in the CKD (21–23) and non-CKD populations (24–26).

Thus, to address these knowledge gaps, we aimed to examine the association of DPI with all-cause mortality risk in a nationally representative cohort of US adults stratified by kidney function. In addition, we examined the impact of dietary protein source (i.e., HBV proteins) upon survival in this population.

Methods

Source population

We conducted a retrospective cohort study using data from NHANES, a survey executed by the National Center for Health Statistics (NCHS) to provide national estimates of the health and nutritional status of US children and adults, over the period of 1999–2010. The survey employed a complex, multistage, stratified, clustered sampling design in which children, elderly, black, Mexican-American, and low-income white American participants were oversampled to enable precise estimations within these subgroups (27, 28). Study participants underwent standardized personal interviews, followed by physical examinations and laboratory tests, in a mobile examination center. Data collection was administered by highly trained medical personnel to collect information on socio-demographics, dietary intake, and health-related questions; medical, dental, and physiological measurements; and laboratory data.

In the present study, participants were excluded if they *1*) were <18 y of age; *2*) did not have reliable 24-h dietary recall data; *3*) did not have available follow-up data on mortality status (i.e., due to inadequate data needed for linkage to the National Death Index); *4*) had missing serum creatinine data; *5*) had missing body weight data; *6*) had missing body height data; *7*) were pregnant; or *8*) had an outlier estimated glomerular filtration rate (eGFR) value, defined as an eGFR >170 ml/min/1.73 m^2, as calculated using the CKD Epidemiology Collaboration equation (**Supplemental Figure 1**) (29).

Exposure ascertainment

Our primary exposure of interest was the daily DPI scaled to actual body weight (ABW) (30), categorized as <0.6, 0.6 to <1.0, 1.0 to <1.4, and ≥1.4 g/kg ABW/day. In secondary analyses, we examined the: *1*) daily absolute DPI (g/d), categorized as quartiles; *2*) DPI density (percentage of total kilocalories from protein intake), categorized as <10%, 10% to <15%, 15% to <20%, and ≥20%; and *3*) daily proportion of DPI from HBV protein sources (percentage; i.e., protein from meat, fish, poultry, or dairy products) (30), categorized by tertiles.

DPI was ascertained by trained interviewers during an in-person 24-h dietary recall using the USDA's Automated Multiple-Pass Method (AMPM), a 5-step multiple-pass process to enhance complete and accurate data collection. Reliable dietary recall data were defined as those in which: *1*) the first 4 steps of the AMPM were completed; and *2*) foods consumed for each reported meal were identified. In primary analyses, we used DPI information from a single first 24-h dietary recall, and in secondary analyses we considered a second 24-h dietary recall that was collected within 3–10 d after the first recall in a subcohort of NHANES participants on or after 2003.

Outcome ascertainment

The primary outcome of interest was all-cause mortality. Mortality data were obtained through a linkage of NHANES data to death certificate data from the National Death Index, which is a centralized database of death records compiled by the NCHS using identifying information, such as an individual's Social Security number. Participants were followed for the outcome of interest, the day after 24-h dietary recall data collection, and were censored for death or at end of the follow-up period (31 December, 2010).

Socio-demographic, comorbidity, physical activity, and supplement use covariates

Information on socio-demographics, alcohol status, cigarette smoking, comorbidities, physical activity, and dietary supplement use status were self-reported by participants during the interview portion of the survey (31). Race/ethnicity was categorized as *1*) Hispanic (defined as Mexican-American and other Hispanic); *2*) non-Hispanic white; *3*) non-Hispanic black; and *4*) other (including multiracial participants). The poverty income ratio was categorized as *1*) low family income (0.000–1.300); *2*) middle family income (1.301–3.500); and *3*) high

family income (3.501 and above). Diabetes status was ascertained using participants' self-reported information, in which they were queried, "other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" Hypertension status was also ascertained using participants' self-reported information, in which they were queried, "have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" Physical activity status was examined as a dichotomous variable that was ascertained using participants' self-reported information using the Global Physical Activity Questionnaire. Dietary supplement use was defined as a dichotomous variable in which participants were queried if they used supplements in the past month, including vitamins, minerals, fish oils, and/or protein supplements.

Statistical methods

Baseline characteristics between exposure groups were compared as mean ± SD or median (IQR) values using chi-squared, ANOVA, and Kruskal-Wallis tests as dictated by data type. We first estimated the association between DPI and all-cause mortality using Cox proportional hazard regressions in 3 incremental models with the following covariates:

(*1*) Unadjusted analyses: no adjustment for covariates within model;
(*2*) Case mix–adjusted analyses: model adjusted for age, sex, race/ethnicity, family income status, education status, and marital status; and
(*3*) Expanded case mix–adjusted analyses: model adjusted for case-mix covariates plus smoking status, alcohol use status, cardiovascular disease (CVD), cancer, diabetes, hypertension, and BMI.
We a priori defined the expanded case-mix model as our primary model. To account for the possibility that kidney function, health behaviors, and protein-energy wasting may be confounders rather than pathway intermediate of low DPI–mortality associations, we also conducted exploratory analyses that incrementally adjusted for eGFR, dietary intake, physical activity, and markers of nutritional status, using the following models:
(*4*) Expanded case mix + eGFR–adjusted analyses: model adjusted for expanded case-mix covariates plus eGFR;
(*5*) Expanded case mix + eGFR + dietary intake–adjusted analyses: model adjusted for expanded case-mix + eGFR covariates plus dietary energy intake and dietary sodium intake. Additionally, we added DPI only for analysis of HBV or DPI (% of kcal)–mortality associations; and
(*6*) Expanded case mix + eGFR + dietary intake + health behavior + nutritional status–adjusted analyses: model adjusted for expanded case-mix + eGFR + dietary-intake covariates plus physical activity status, supplement status, and serum albumin.

We sought to determine the impact of key confounders highlighted in prior literature upon estimates of the DPI–mortality association, namely *1*) dietary potassium and phosphorus intake; and *2*) urine albumin-to-creatinine ratio (UACR). To do so, we also examined 2 additional models that separately adjusted for these covariates in addition to expanded case-mix + eGFR + dietary intake + health behavior + nutritional status covariates. Effect modification of DPI–mortality associations on the basis of socio-demographics, comorbidities, health behaviors, and nutritional status were explored through the addition of 2-way interaction terms with DPI (separately), using likelihood ratio testing. There were no missing values for age, sex, race/ethnicity, marital status, smoking status, alcohol use, comorbidities, BMI, health behavior indicators, and serum albumin. The remaining covariates ascertained at baseline had <10% missing data, including education (8%) and family income (6%). For the aforementioned covariates, missing data were addressed using multiple imputation with 15 imputed data sets. Statistical analyses were conducted and figures were created using STATA version 13.1 (Stata Corp.) and SigmaPlot version 13 (Systat Software).

Results

Study population

The final study population consisted of 1994 versus 25,605 adults with impaired versus normal kidney function, respectively (eGFRs <60 compared with ≥60 ml/min/1.73 m^2, respectively; Supplemental Figure 1). In participants with impaired kidney function, the mean ± SD, median (IQR), and minimum–maximum of daily DPI scaled to ABW were 0.8 ± 0.4, 0.8 (0.5–1.0), and 0.1–3.4 g/kg ABW/day, respectively. In participants with normal kidney function, the mean ± SD, median (IQR), and minimum–maximum of daily DPI normalized to ABW were 1.1 ± 0.6, 0.9 (0.7–1.3), and 0.0–10.6 g/kg ABW/day, respectively.

Table 1 shows baseline characteristics of the cohort, stratified by *1*) DPI scaled to ABW; and *2*) kidney function. Among participants with normal and impaired kidney function, those with the highest category of DPI intake scaled to ABW (>1.4 g/kg ABW/day) tended to be younger and male; were more likely to be Hispanic; were more likely to have completed higher levels of education (i.e., more than college degree); were more likely to consume alcohol; were less likely to have CVD, diabetes, and hypertension; were more likely to be physically active; had lower BMI and higher eGFR levels; and had higher dietary energy and sodium intake. Notably, in both participants with normal and impaired kidney function, differences in mean serum albumin levels across DPI groups were statistically significant but not biologically meaningful. Baseline characteristics, stratified by absolute DPI, DPI density, and HBV protein consumption, as well as kidney function, are shown in **Supplemental Tables 1**, **2**, and **3**.

Dietary protein intake scaled to actual body weight and mortality risk

Participants with impaired kidney function contributed a total of 9798 person-years of follow-up, during which 619 death events were observed (crude mortality rate, 63 deaths per 1000 person-years), while those with normal kidney function contributed a total of 160,289 person-years of follow-up, during which 1728 death events were observed (crude mortality rate, 11 deaths per 1000 person-years). Median follow-up times were 3.8 (IQR: 1.9–5.8) versus 4.7 (IQR: 2.4–7.3) y

TABLE 1 Baseline characteristics of participants according to DPI scaled to ABW, stratified by eGFR[1]

	eGFR < 60 ml/min/1.73 m^2						eGFR ≥ 60 ml/min/1.73 m^2					
		DPI scaled to ABW, g/kg ABW/day						DPI scaled to ABW, g/kg ABW/day				
	Overall	<0.6	0.6 to <1.0	1.0 to <1.4	≥1.4	*P*	Overall	<0.6	0.6 to <1.0	1.0 to <1.4	≥1.4	*P*
Participants, *n*	1994	1069	592	224	109	N/A	25,605	9447	8113	4380	3665	N/A
Age, y	72 ± 11	72 ± 11	72 ± 11	71 ± 12	70 ± 13	0.05	46 ± 19	49 ± 19	48 ± 19	44 ± 18	38 ± 17	<0.001
Male, %	44	39	47	50	56	<0.001	51	42	52	59	66	<0.001
Race/ethnicity, %	—	—	—	—	—	<0.001	—	—	—	—	—	<0.001
Hispanic	14	15	11	11	20		28	26	28	30	31	
Non-Hispanic white	68	65	74	75	58		48	45	51	48	45	
Non-Hispanic black	15	18	12	11	17		20	25	17	16	18	
Other/missing	3	3	3	4	6		4	4	4	5	5	
Family income, %	—	—	—	—	—	<0.001	—	—	—	—	—	<0.001
Low income	27	29	25	22	29		28	31	25	27	29	
Middle income	41	42	37	42	44		35	36	35	33	34	
High income	24	20	30	27	22		29	26	32	33	29	
Education completion, %	—	—	—	—	—	0.003	—	—	—	—	—	<0.001
Less than 9th grade	18	20	15	14	15		12	14	12	11	9	
9–11th grade (includes 12th grade with no diploma)	18	20	16	17	15		15	17	13	13	15	
High school graduate/GED or equivalent	27	27	27	28	30		22	23	21	21	20	
Some college or AA degree	22	20	26	19	19		25	25	26	24	23	
College graduate or above	15	13	16	21	20		18	15	21	21	18	
Married/living with partner, %	52	51	52	55	53	0.70	57	55	59	59	53	<0.001
Alcohol use (≥12 alcohol drinks/year), %	55	51	59	59	62	0.001	62	58	65	66	64	<0.001
Smoking status (≥100 cigarettes in lifetime), %	52	51	53	50	59	0.35	44	45	44	44	44	0.48
Comorbidity status, %												
CVD	35	37	34	33	22	0.01	8	10	7	6	4	<0.001
Cancer	22	20	24	22	23	0.36	7	9	8	6	4	<0.001
Diabetes	27	31	25	19	20	<0.001	9	11	9	7	4	<0.001
High blood pressure	72	75	71	65	62	0.002	29	36	29	22	15	<0.001
Physical activity (vigorous/moderate activity for ≥10 min), %	37	32	41	45	47	<0.001	56	50	57	60	62	<0.001
Supplement use (any taken in past 30 d), %	63	62	64	64	65	0.82	46	44	49	46	42	<0.001
BMI, kg/m^2	29.1 ± 6.3	30.7 ± 6.7	28.2 ± 5.5	26.5 ± 4.5	24.7 ± 4.5	<0.001	28.4 ± 6.5	31.1 ± 7.3	28.2 ± 5.7	26.2 ± 5.0	24.5 ± 4.4	<0.001
eGFR, ml/min/1.73 m^2	47 ± 12	46 ± 12	48 ± 12	49 ± 12	48 ± 12	<0.001	100 ± 23	99 ± 23	99 ± 23	102 ± 23	105 ± 23	<0.001
Serum albumin, g/dl	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	4.2 ± 0.3	4.1 ± 0.4	0.004	4.3 ± 0.3	4.2 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	4.4 ± 0.3	<0.001
Dietary energy intake, kcal/d	1518 (1141– 2005)	1240 (956–1566)	1763 (1442–2191)	2060 (1726–2545)	2594 (2107–3330)	<0.001	1982 (1460–2671)	1432 (1086–1835)	2038 (1640–2522)	2,477 (1994–3067)	3,237 (2571–4096)	<0.001
Dietary sodium intake, mg/d	2450 (1751–3369)	1980 (1441–2621)	2818 (2209–3728)	3370 (2694–4571)	4285 (3184–5430)	<0.001	3074 (2141–4292)	2164 (1524–2900)	3184 (2426–4097)	3922 (3012–4966)	5166 (3929–6748)	<0.001
Dietary phosphorus intake, mg/d	976 (710–1297)	753 (568–961)	1138 (951–1395)	1513 (1227–1821)	1935 (1466–2297)	<0.001	1203 (863–1650)	808 (601–1031)	1242 (1016–1527)	1580 (1288–1911)	2087 (1702–2622)	<0.001
Dietary potassium intake, mg/d	2171 (1543–2890)	1760 (1285–2250)	2528 (1990–3117)	3059 (2459–3647)	3596 (3161–4617)	<0.001	2455 (1751–3330)	1751 (1254–2316)	2535 (1982–3191)	3053 (2420–3856)	3856 (3063–4918)	<0.001

[1]Continuous variables are presented as means ± SDs or medians (IQRs), as dictated by data type, and categorical variables are presented as column percentages. Baseline characteristics between exposure groups were compared using chi-squared, ANOVA, and Kruskal-Wallis tests, as dictated by data type. AA, Associates of Arts; ABW, actual body weight; CVD, cardiovascular disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; GED, General Education Development.

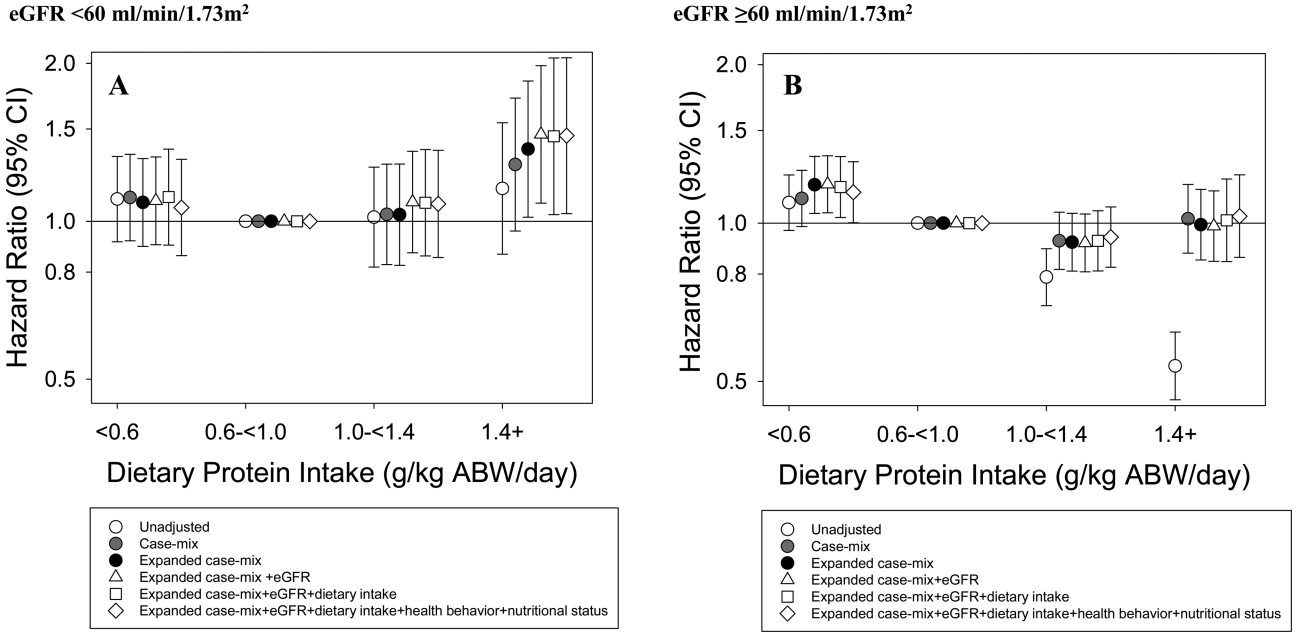

FIGURE 1 Association of DPI scaled to ABW with all-cause mortality risk, stratified by eGFR in participants with (A) impaired kidney function ($n = 1994$) and (B) normal kidney function ($n = 25{,}605$). Each plot shows HRs and their 95% CIs, estimated using Cox regression models incrementally adjusted with the following covariates: *1*) unadjusted analyses; *2*) case mix–adjusted analyses, adjusted for age, sex, race/ethnicity, family income status, educational status, and marital status; *3*) expanded case mix–adjusted analyses, adjusted for case-mix covariates plus smoking status, alcohol status, CVD, cancer, diabetes, high blood pressure, and BMI; *4*) expanded case mix + eGFR–adjusted analyses, adjusted for expanded case-mix covariates plus eGFR; *5*) expanded case mix + eGFR + dietary intake–adjusted analyses, adjusted for expanded case-mix + eGFR covariates plus dietary energy intake and dietary sodium intake; and *6*) expanded case mix + eGFR + dietary intake + health behavior + nutritional status–adjusted analyses, adjusted for expanded case-mix + eGFR + dietary intake covariates plus physical activity status, supplement status, and serum albumin levels. ABW, actual body weight; CVD, cardiovascular disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate.

in participants with impaired versus normal kidney function, respectively.

Among participants with impaired kidney function, expanded case-mix analyses showed that higher levels of DPI scaled to ABW of ≥1.4 g/kg ABW/day were associated with a higher death risk, while lower DPI levels were not associated with mortality (reference, 0.6 to <1.0 g/kg ABW/day): adjusted HRs (aHRs) were 1.09 (95% CI: 0.90, 1.32), 1.03 (95% CI: 0.82, 1.29), and 1.37 (95% CI: 1.02, 1.85) for DPI of <0.6, 1.0 to <1.4, and ≥1.4 g/kg ABW/day, respectively (**Figure 1**A; **Supplemental Table 4**). In analyses that further adjusted for eGFR, dietary intake, health behavior, and nutritional status covariates, associations between the highest (≥1.4 g/kg ABW/day) category of DPI scaled to ABW and mortality risk were robust and amplified (reference, 0.6 to <1.0 g/kg ABW/day): the aHRs were 1.46 (95% CI: 1.08, 1.98), 1.45 (95% CI: 1.03, 2.05), and 1.46 (95% CI: 1.03, 2.05) in analyses adjusted for expanded case mix + eGFR, expanded case mix + eGFR + dietary intake, and expanded case mix + eGFR + dietary intake + health behavior + nutritional status, respectively.

In contrast, among participants with normal kidney function, expanded case-mix analyses showed that lower levels of DPI scaled to ABW of <0.6 g/kg ABW/day were associated with higher mortality, whereas higher DPI levels were not associated with death risk: the aHRs were 1.18 (95% CI: 1.04, 1.34), 0.92 (95% CI: 0.81, 1.04), and 0.99 (95% CI: 0.85, 1.16) for DPI of <0.6, 1.0 to <1.4, and ≥1.4 g/kg ABW/day, respectively (Figure 1B; Supplemental Table 4). These associations were robust with further adjustments for eGFR, dietary intake, health behavior, and nutritional status covariates.

We also conducted additional analyses that *1*) further adjusted for dietary potassium and phosphorus intake; *2*) further adjusted for UACR levels available in a subcohort of participants ($n = 27{,}339$; **Supplemental Figure 2**); and *3*) considered the second 24-h dietary recall collected in a subcohort of participants ($n = 17{,}380$; **Supplemental Figure 3**). Following adjustment for expanded case-mix + eGFR + dietary intake + health behavior + nutritional status + dietary potassium + dietary phosphorus covariates, we observed robust associations between a high DPI and higher mortality in participants with impaired kidney function and a low DPI and higher mortality in those with normal kidney function (Supplemental Table 4). Similarly, after adjustment for expanded case-mix + eGFR + dietary intake + health behavior + nutritional status + UACR covariates, associations between a high DPI and higher mortality in participants with impaired kidney function and a low DPI and higher mortality in those with normal kidney function persisted (Supplemental Table 4). In secondary analyses which used mean values of the two 24-h dietary recall records to define DPI intake scaled to ABW, we observed robust associations between a high DPI and higher mortality in participants with impaired kidney function, whereas the association between a low DPI and higher mortality in those with normal kidney function was attenuated to the null (**Supplemental Table 5**).

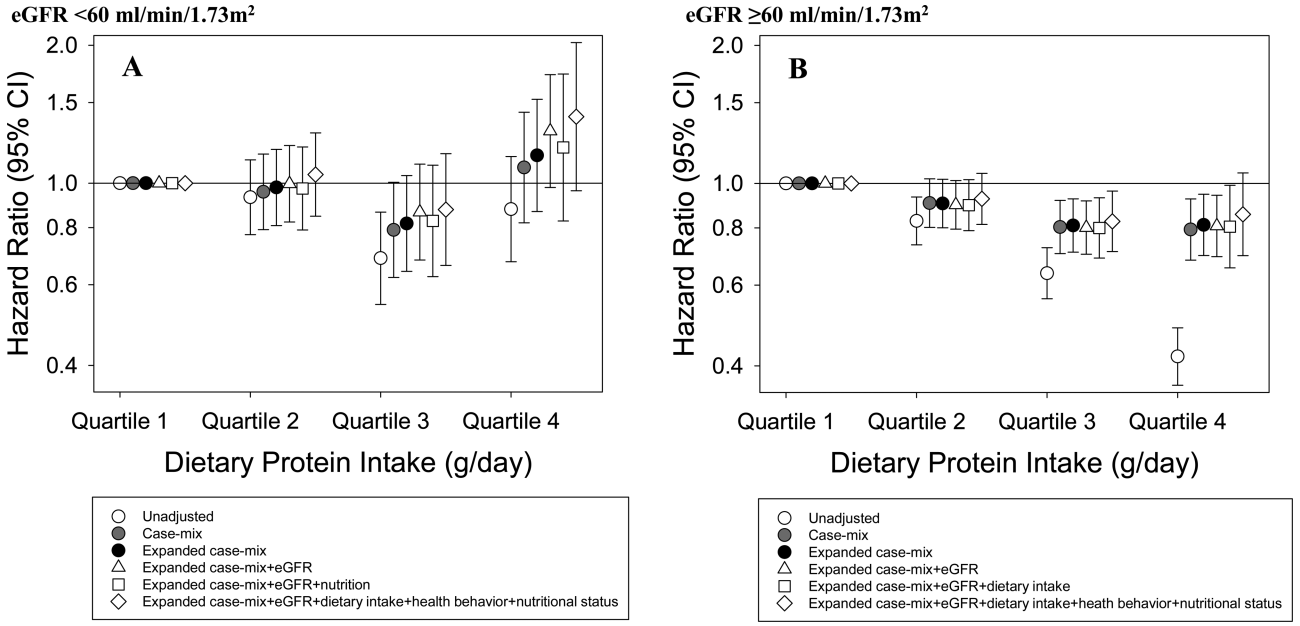

FIGURE 2 Association of absolute DPI with all-cause mortality risk, stratified by eGFR in participants with (A) impaired kidney function (n = 1994) and (B) normal kidney function (n = 25,605). Each plot shows HRs and their 95% CIs, estimated using Cox regression models incrementally adjusted with the following covariates: *1*) unadjusted analyses; *2*) case mix–adjusted analyses, adjusted for age, sex, race/ethnicity, family income status, educational status, and marital status; *3*) expanded case mix–adjusted analyses, adjusted for case-mix covariates plus smoking status, alcohol status, CVD, cancer, diabetes, high blood pressure, and BMI; *4*) expanded case mix + eGFR–adjusted analyses, adjusted for expanded case-mix covariates plus eGFR; *5*) expanded case mix + eGFR + dietary intake–adjusted analyses, adjusted for expanded case-mix + eGFR covariates plus dietary energy intake and dietary sodium intake; and *6*) expanded case mix + eGFR + dietary intake + health behavior + nutritional status–adjusted analyses, adjusted for expanded case-mix + eGFR + dietary intake covariates plus physical activity status, supplement status, and serum albumin levels. DPI quartiles 1, 2, 3, and 4 correspond to DPI of <52, 52 to <73, 73 to <100, and 100–718 g/d, respectively, based on the DPI distribution in the overall cohort. CVD, cardiovascular disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate.

Other dietary protein intake indices and mortality risk

In secondary analyses examining absolute DPI among participants with impaired kidney function, although associations between the highest quartile of intake and survival were not statistically significant, point estimates suggested a higher mortality risk (reference, lowest quartile): the aHR was 1.15 (95% CI: 0.87, 1.52) in an expanded case-mix analysis (**Figure 2**A; **Supplemental Table 6**). However, among participants with normal kidney function, the 2 highest absolute DPI quartiles were significantly associated with lower mortality risk in expanded case-mix analyses: the aHRs were 0.81 (95% CI: 0.71, 0.93) and 0.81 (95% CI: 0.70, 0.95), respectively (Figure 2B; Supplemental Table 6). Incremental adjustments for eGFR and dietary intake showed robust associations between absolute DPI and survival; while associations between the highest DPI quartile and survival were no longer significant after incremental adjustments for health behavior and nutritional status covariates, point estimates suggested lower mortality risk.

Among participants with impaired kidney function, we did not observe a significant association between DPI density and mortality (**Figure 3**A; **Supplemental Table 7**). Yet among participants with normal kidney function, a higher DPI density of ≥10% was associated with a lower death risk: the aHRs were 0.82 (95% CI: 0.69, 0.97), 0.81 (95% CI: 0.69, 0.97), and 0.79 (95% CI: 0.65, 0.95) for DPI densities 10% to <50%, 15% to <20%, and ≥20%, respectively, in expanded case-mix analyses (Figure 3B; Supplemental Table 7). Incremental adjustments for eGFR and dietary intake showed robust associations between DPI density and survival; while associations were no longer significant after incremental adjustments for health behavior and nutritional status covariates, point estimates suggested lower mortality risk.

HBV protein consumption and mortality risk

In secondary analyses examining HBV consumption among participants with impaired kidney function, there was a significant association between the highest tertile of HBV consumption and higher mortality risk in expanded case-mix analyses (reference, lowest tertile): the aHR was 1.24 (95% CI: 1.01, 1.53; **Figure 4**A; **Supplemental Table 8**). While associations were no longer significant after incremental adjustments for eGFR, dietary intake, health behavior, and nutritional status covariates, point estimates suggested lower mortality risk. Among participants with normal kidney function, associations between the highest tertile of HBV consumption and higher mortality risk were not statistically significant in expanded case-mix models: the aHR was 1.08 (95% CI: 0.96, 1.22; Figure 4B; Supplemental Table 8).

Interplay between DPI and physical activity

We also examined the interplay between dietary intake and health behaviors by examining different pairings of DPI and

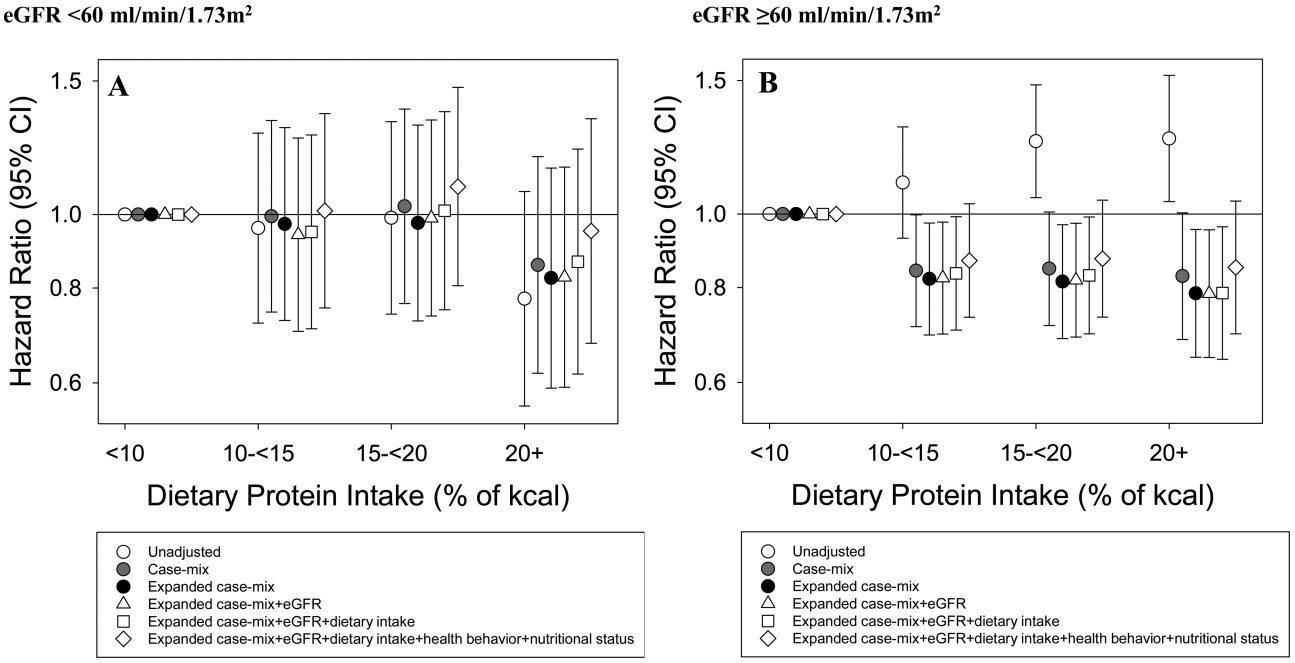

FIGURE 3 Association of DPI as a proportion of total energy intake with all-cause mortality risk stratified by eGFR in participants with (A) impaired kidney function ($n = 1994$) and (B) normal kidney function ($n = 25{,}605$). Each plot shows HRs and their 95% CIs, estimated using Cox regression models incrementally adjusted with the following covariates: *1*) unadjusted analyses; *2*) case mix–adjusted analyses, adjusted for age, sex, race/ethnicity, family income status, educational status, and marital status; *3*) expanded case mix–adjusted analyses, adjusted for case-mix covariates plus smoking status, alcohol status, CVD, cancer, diabetes, high blood pressure, and BMI; *4*) expanded case mix + eGFR–adjusted analyses, adjusted for expanded case-mix covariates plus eGFR; *5*) expanded case mix + eGFR + dietary intake–adjusted analyses adjusted for expanded case-mix + eGFR covariates plus dietary energy intake and dietary sodium intake; and *6*) expanded case mix + eGFR + dietary intake + health behavior + nutritional status–adjusted analyses, adjusted for expanded case-mix + eGFR + dietary intake covariates plus physical activity status, supplement status, and serum albumin levels. CVD, cardiovascular disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate.

physical activity and their associations with survival. Among participants with impaired kidney function, compared to those with lower DPI who were physically active, participants who were physically inactive had a higher mortality risk, with stronger point estimates observed for those with higher DPI in expanded case-mix analyses: the aHRs were 1.70 (95% CI: 1.31, 2.20) and 1.58 (95% CI: 1.27, 1.95) for those with a high DPI versus a low DPI who were physically inactive, respectively (**Supplemental Table 9**).

Among participants with normal kidney function, compared to those with lower DPI who were physically active, participants who were physically inactive had higher mortality risk, with stronger point estimates observed for those with lower DPI in expanded case-mix analyses: the aHRs were 1.53 (95% CI: 1.35, 1.74) and 1.35 (95% CI: 1.16, 1.57) for those with a low DPI versus a high DPI who were physically inactive, respectively (Supplemental Table 9).

DPI and mortality riskacross other clinically relevant subgroups

Among participants with impaired kidney function, we did not detect effect modification on the basis of age, sex, race, income, educational status, smoking status, alcohol use, CVD status, cancer status, diabetes status, BMI level, or serum albumin level (**Figure 5**A; **Supplemental Table 10**). Among participants with normal kidney function, we observed effect modification on the basis of age (P-interaction < 0.001), such that a high DPI scaled to ABW (≥1.4 g/kg ABW/day) was associated with a decreased mortality risk in those of younger age (<65 y old) but not in those of older age (≥65 y old) in expanded case-mix analyses: the aHRs were 0.75 (95% CI: 0.60, 0.94) and 0.89 (95% CI: 0.74, 1.07), respectively (Figure 5B; Supplemental Table 10). We did not detect effect modification on the basis of sex, race, income, educational status, smoking status, alcohol use, CVD status, cancer status, diabetes status, BMI level, or serum albumin level.

Discussion

In this nationally representative cohort of US adults who underwent 24-h dietary recalls, we observed markedly different relations of DPI intake with survival among those with impaired versus normal kidney function. Among participants with impaired kidney function (i.e., eGFR <60 ml/min/1.73 m^2), we observed that higher levels of DPI scaled to ABW (i.e., ≥1.4 g/kg ABW/day) were associated with higher mortality risk independent of socio-demographics and comorbidity status, whereas lower levels of DPI were not associated with death. In contrast, among participants with normal kidney function (i.e., eGFR ≥60 ml/min/1.73 m^2), we found that lower levels of DPI scaled to ABW (i.e., <0.6 g/kg ABW/day) were associated with worse survival, whereas higher DPI levels were not associated with higher mortality risk. These associations were robust and were amplified in further adjusted models that accounted for

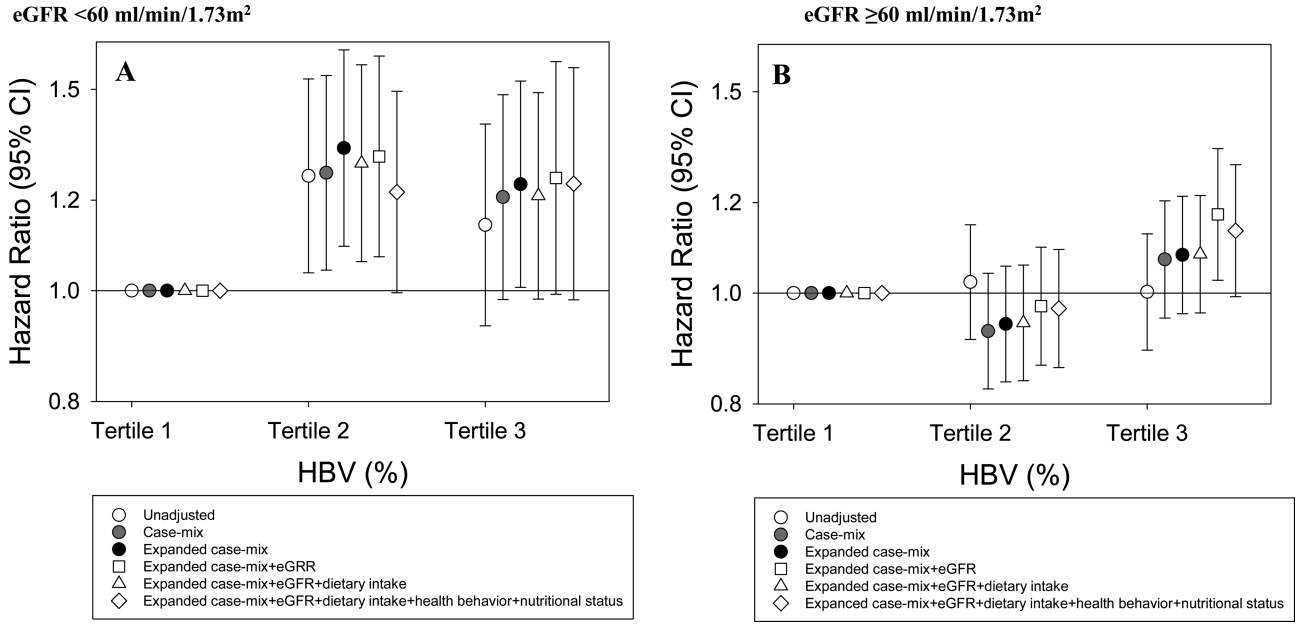

FIGURE 4 Association of proportion of HBV protein intake with all-cause mortality risk, stratified by eGFR, in participants with (A) impaired kidney function ($n = 1994$) and (B) normal kidney function ($n = 25,605$). Each plot shows HRs and their 95% CIs, estimated using Cox regression models incrementally adjusted with the following covariates: *1*) unadjusted analyses; *2*) case mix–adjusted analyses, adjusted for age, sex, race/ethnicity, family income status, educational status, and marital status; *3*) expanded case mix–adjusted analyses, adjusted for case-mix covariates plus smoking status, alcohol status, CVD, cancer, diabetes, high blood pressure, and BMI; *4*) expanded case mix + eGFR–adjusted analyses, adjusted for expanded case-mix covariates plus eGFR; *5*) expanded case mix + eGFR + dietary intake–adjusted analyses, adjusted for expanded case-mix + eGFR covariates plus dietary energy intake and dietary sodium intake; and *6*) expanded case mix + eGFR + dietary intake + health behavior + nutritional status–adjusted analyses, adjusted for expanded case-mix + eGFR + dietary intake covariates plus physical activity status, supplement status, and serum albumin levels. The HBV tertiles 1, 2, and 3 correspond to proportions of HBV protein intake of <47%, 47% to <69%, and 69–100%, respectively, based on HBV protein intake distribution in the overall cohort. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HBV, high biological value.

differences in kidney function, nutritional status, and health behaviors.

To date, there have been few studies that have examined the relation between the total amount of protein intake and the mortality risk across varying levels of kidney function. Among these studies is the Prevention of Renal and Vascular End-Stage Disease (PREVEND) cohort, a community-based study of 8461 adults in the Netherlands who underwent DPI estimations using 24-h urinary urea excretion. While there was no association between the DPI and the rate of kidney function decline, a lower DPI was associated with a higher all-cause mortality risk, yet a higher DPI was linked with a heightened risk of cardiovascular events. Notably, only a small proportion (~9%) of the cohort had impaired kidney function (defined as an eGFR <60 ml/min/1.73 m^2) (32). In a subsequent study of 4679 adults from the Gubbio cohort in Italy, a lower DPI, ascertained by urine urea nitrogen levels, was also associated with a higher death risk in the overall cohort (33). Notably, when the cohort was examined according to the level of kidney function (eGFRs ≥90 compared with <90 ml/min/1.73 m^2), higher levels of DPI were associated with higher death risk in those with eGFRs <90 ml/min/1.73 m^2.

To our knowledge, this is the first study to examine the relation between DPI and mortality risk among participants with impaired versus normal kidney function using established CKD thresholds (i.e., eGFR <60 compared with ≥60 ml/min/1.73 m^2, respectively). While daily DPI levels of <0.6 g/kg ABW/day were associated with worse survival in participants with preserved kidney function, there was no relation between lower DPI and mortality in those with impaired function. Notably, higher levels of DPI of ≥1.4 g/kg ABW/day were associated with higher mortality risk in participants with impaired kidney function, consistent with CKD thresholds. These findings have several important implications for the recommended management of NDD-CKD patients and for current secular practice. First, the most recent NKF KDOQI nutrition guidelines recommend reduced DPI in metabolically stable nondiabetic CKD and diabetic CKD patients (DPI of 0.55–0.6 g/kg/d and 0.6–0.8 g/kg/d, respectively) (15, 34), with a similar endorsement by the Kidney Disease Improving Global Outcomes guidelines (DPI 0.6–0.8 g/kg/d in NDD-CKD patients) (16, 35), as a means to ameliorate CKD progression. However, these recommendations are not widely implemented due to concerns about potential protein-energy wasting in advanced kidney disease patients. Although our study was not specifically designed to examine the impact of DPI on the kidney function trajectory, our observations support a reduction of the KDOQI DPI threshold and may also provide reassurance regarding the safety of DPI restrictions in NDD-CKD patients.

Second, as high-protein diets (e.g., Paleo, Atkins, South Beach, ketogenic) have gained popularity as a means to lose weight and avoid excess carbohydrate consumption in the general population, our observations of high DPI and mortality associations suggest that higher protein intake may be associated with a higher risk in those with NDD-CKD. Indeed, the safety of habitual consumption of excess dietary protein has

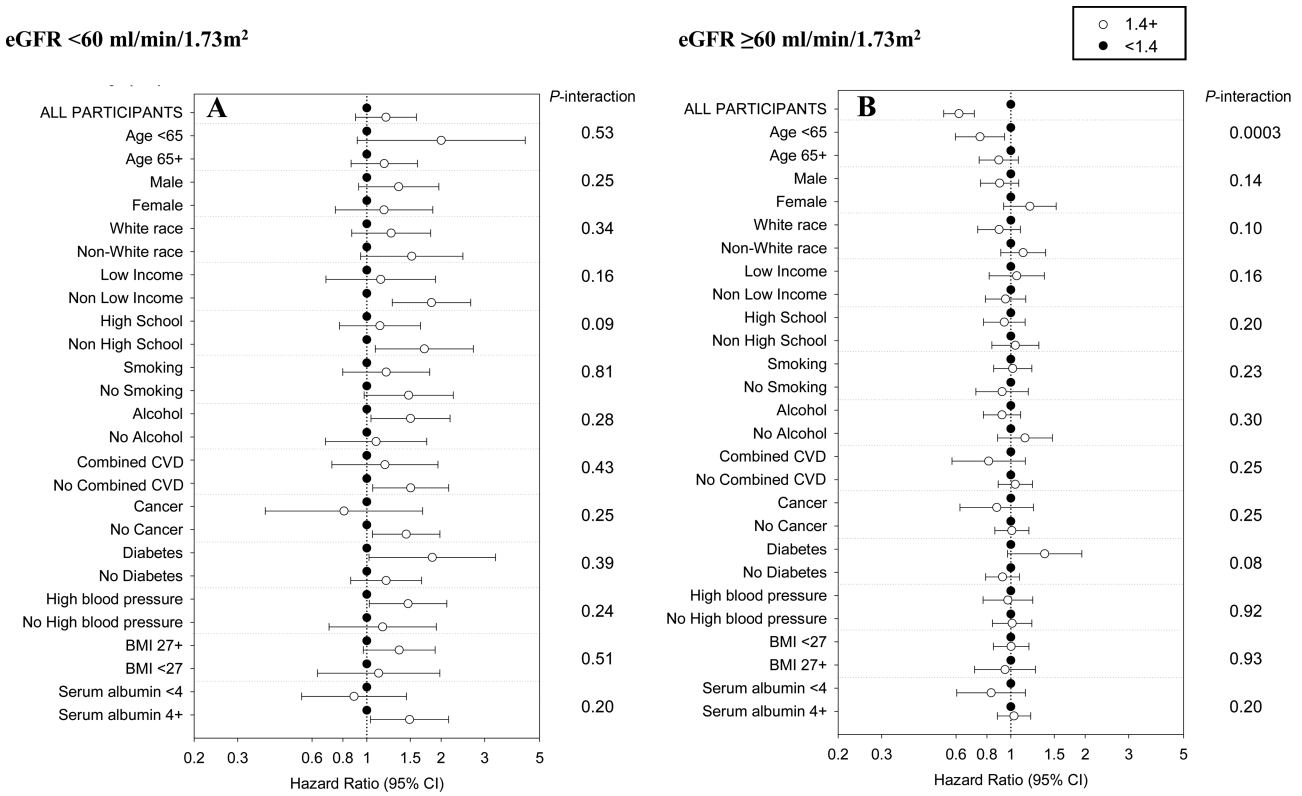

FIGURE 5 Subgroup analyses of the association of DPI scaled to ABW (dichotomized as ≥1.4 compared with <1.4 g/kg ABW/day) with all-cause mortality risk among participants with (A) impaired kidney function ($n = 1994$) and (B) normal kidney function ($n = 25{,}605$). Each plot shows HRs and their 95% CIs, estimated using Cox regression models adjusted for expanded case-mix covariates, including age, sex, race/ethnicity, family income status, education status, marital status, smoking status, alcohol status, CVD, cancer, diabetes, high blood pressure, and BMI. *P*-interactions were explored through the addition of 2-way interaction terms with DPI (separately), using likelihood ratio tests. ABW, actual body weight; CVD, cardiovascular disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate.

been questioned given concerns for subsequent DPI-induced glomerular hyperfiltration, increased urinary albumin excretion, and the development and progression of CKD over time (3, 10, 11). Hence, further studies are needed to clarify the impact of intermediate- and long-term DPI levels upon the health and survival of CKD patients.

Another noteworthy finding of our study was the observation that higher levels of HBV protein consumption were associated with higher death risk in participants with impaired kidney function in expanded case-mix analyses. While associations were no longer significant after incremental adjustments for eGFR, dietary intake, health behavior, and nutritional status covariates, point estimates suggested lower mortality risk. As HBV protein sources tend to be from animal proteins, our findings suggest that plant-based sources of protein may be more favorable in those with NDD-CKD. Indeed, plant-based protein or plant protein–rich diets may confer potential benefits in these patients with respect to their impact on cholesterol metabolism (36, 37), acid-base balance (38, 39), attenuated production of uremic toxins (e.g., *p*-cresyl sulfate, indoxyl sulfate) (40), decreased bioavailability of phosphorus (41–43), and reduced risk of comorbidities that commonly coexist with CKD [e.g., cancer (44), cardiovascular disease (18), hypertension (45), diabetes (46)]. However, while our observational data suggest potential benefits, future interventional studies of plant-based protein consumption in the NDD-CKD population are urgently needed.

In sensitivity analyses, we also found that there was a synergistic relation between DPI and physical activity on survival in participants with and without CKD. Upon examining different pairings of DPI and physical activity, among CKD participants with higher DPI who were physically inactive (i.e., hypothesized as the worst combination in the CKD cohort), we observed the strongest associations for higher death risk, suggesting a synergistic relation between a higher DPI and reduced physical activity. Among non-CKD participants with lower DPI who were physically inactive (i.e., hypothesized as the worst combination in the non-CKD cohort), we observed the most potent point estimates for higher death risk, supporting a synergistic association between a lower DPI and reduced physical activity. Further studies are needed to elucidate the interplay between nutritional intake and health behaviors in those with and without CKD.

The strengths of our study include its examination of a large, nationally representative cohort of US adults; detailed availability of participant-level data on socio-demographics, dietary intake, nutritional status, health behaviors, kidney function, and laboratory results; and examination of multiple validated metrics of DPI (30). However, several limitations of our study bear mention. First, DPI was ascertained using a baseline 24-h dietary

recall measurement collected at a single point in time, which may be prone to recall bias and may not be representative of an individual's long-term DPI and/or habitual dietary intake. However, it should be recognized that alternative metrics of DPI estimation (e.g., 24-h urine urea measurement) are also prone to measurement bias and fluctuations over time, and may not enable either a comprehensive or granular examination of dietary intake (i.e., DPI source, dietary energy and sodium intake) as compared with a 24-h dietary recall. Secondly, NHANES contains very few individuals with advanced CKD; hence, the results may only apply to those with milder degrees of kidney dysfunction. Thirdly, information regarding participants' access to dietitian-led dietary support was not collected within the NHANES study. Finally, as with all observational studies, we cannot confirmation a causal relation between DPI and survival based on these findings.

In conclusion, our study has shown that among participants with impaired kidney function, higher DPI and greater HBV consumption were associated with higher death risk, whereas lower DPI was associated with higher mortality in those with normal kidney function. Future studies are needed to elucidate the specific pathways between higher DPI and mortality in those with NDD-CKD, and interventional studies are needed to examine the impact of the source of protein intake upon health outcomes in this population.

The authors' responsibilities were as follows—YN, CMR: designed the study and wrote the manuscript; YN: conducted the research and performed the statistical analysis; CMR: had primary responsibility for the final content; YO, LWM, ASY, ET, JKI, TM, TN, CPK, DVN, and KK-Z: reviewed and provided feedback on the manuscript; and all authors: read and approved the final manuscript.

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Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval by the corresponding author.

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