

Ultraprocessed food consumption and kidney function decline in a population-based cohort in the Netherlands

Qingqing Cai,^{1,2} Ming-Jie Duan,¹ Louise H Dekker,¹ Juan Jesús Carrero,³ Carla Maria Avesani,⁴ Stephan JL Bakker,¹ Martin H de Borst,¹ and Gerjan J Navis¹

¹Department of Internal Medicine, Division of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands;

²Division of Nephrology, Nanfang Hospital, Southern Medical University; National Clinical Research Center for Kidney Disease; State Key Laboratory of Organ Failure Research; Guangdong Provincial Institute of Nephrology; Guangdong Provincial Key Laboratory of Renal Failure Research, Guangzhou, China;

³Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; and ⁴Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

ABSTRACT

Background: Ultraprocessing makes food products more convenient, appealing, and profitable. Recent studies show that high ultraprocessed food (UPF) intake is associated with cardiometabolic diseases.

Objectives: The aim of this study is to investigate the association between UPF consumption and risks of kidney function decline in the general population.

Methods: In a prospective, general population-based Lifelines cohort from Northern Netherlands, 78,346 participants free of chronic kidney disease (CKD) at baseline responded to a 110-item FFQ. We used a multivariable regression analysis to study the associations of the proportion (in grams/day) of UPFs in the total diet with a composite kidney outcome [incident CKD or a $\geq 30\%$ estimated glomerular filtration rate (eGFR) decline relative to baseline] and annual change in eGFR.

Results: On average, 37.7% of total food intake came from UPFs. After 3.6 ± 0.9 years of follow-up, 2470 participants (3.2%) reached the composite kidney outcome. Participants in the highest quartile of UPF consumption were associated with a higher risk of the composite kidney outcome (OR, 1.27; 95% CI, 1.09–1.47; $P = 0.003$) compared with those in the lowest quartile, regardless of their macro- or micronutrient intake or diet quality. Participants in the highest quartile had a more rapid eGFR decline (β , -0.17 ; 95% CI, -0.23 to -0.11 ; $P < 0.001$) compared with those in the lowest quartile. Associations were generally consistent across different subgroups.

Conclusions: Higher UPF consumption was associated with a higher risk of a composite kidney outcome (incident CKD or $\geq 30\%$ eGFR decline) and a more rapid eGFR decline in the general population, independent of confounders and other dietary indices. *Am J Clin Nutr* 2022;116:263–273.

Keywords: ultraprocessed foods, chronic kidney disease, kidney function decline, eGFR change; Lifelines

Introduction

Chronic kidney disease (CKD) is a growing global public health problem that affects 8% to 16% of the population worldwide (1, 2). Lifestyle modification, including a healthy diet, is important to reduce the incidence of CKD and the estimated glomerular filtration rate (eGFR) decline, delay the progression to kidney failure, and reduce the risk of cardiovascular complications (3–8). Adherence to healthy dietary patterns, often rich in plant-based foods, has been associated with a lower risk of developing CKD (9, 10). Conversely, the Western-style diet, characterized by intakes of highly processed and refined foods that contain excessive sugar, salt, and saturated and trans-fatty acids, has been associated with a higher risk of CKD and impaired kidney function (11–13).

The Lifelines initiative has been made possible by subsidies from the Dutch Ministry of Health, Welfare and Sport; the Dutch Ministry of Economic Affairs; the University Medical Center Groningen; Groningen University; and the Provinces in the North of the Netherlands (Drenthe, Friesland, Groningen). This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 754425.

Supplemental Figures 1 and 2 and Supplemental Tables 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/>.

Address correspondence to QC (e-mail: q.cai@umcg.nl).

Abbreviations used: BMR, basal metabolic rate; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EI, energy intake; MDS, Mediterranean diet score; UPF, ultraprocessed food.

Received August 18, 2021. Accepted for publication March 25, 2022.

First published online March 28, 2022; doi: <https://doi.org/10.1093/ajcn/nqac073>.

There has been a global increase in the consumption of ultraprocessed foods (UPFs) during the past decades (14–20). UPFs are usually energy dense; high in saturated fat, sugar, salt, and additives; and low in dietary fiber and vitamins (21). The main purpose of industrial ultraprocessing is to make products convenient (ready-to-eat, -drink, or -heat), hyperpalatable or more appealing (“cosmetic additives”), highly profitable (low-cost ingredients, long shelf-life, emphatic branding), and attractive by packaging (21). Examples of typical UPFs include savory snacks, soft drinks, sweets, ready-to-eat meals, refined starchy food, and reconstituted meat products.

The NOVA system classifies UPFs based on the nature, extent, and purpose of industrial food processing rather than on the nutrient composition, and this system is being increasingly applied in epidemiological studies to understand the impacts of modern industrial food systems on human health (21–23). Studies have consistently found associations between the consumption of UPFs and the risk of cardiometabolic diseases (obesity, diabetes, hypertension, dyslipidemia, and cardiovascular disease) (24–29), cancer (30), and premature death (31). A recent small-scale study shows that higher UPF consumption is associated with a higher risk of kidney function decline in community-dwelling adults >60 years in Spain (32). Whether a high UPF consumption is associated with the risk of kidney function decline in the general population is unknown. In this study, we use a contemporary, large, general-population cohort to evaluate the association of the amount of UPF in the diet with the risk of a composite kidney outcome (incident CKD or eGFR decline $\geq 30\%$) and annual change in eGFR.

Methods

Study population

Lifelines is a multidisciplinary, prospective, population-based cohort study examining, in a unique 3-generation design, the health and health-related behaviors of 167,729 participants living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioral, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. Participants were enrolled from 2006 and 2011 through invitation by their general practitioners. From 2014 to 2019, all participants were invited to a second assessment. The Lifelines cohort is representative of the adult population in the Northern Netherlands (33). Detailed information about the Lifelines cohort has been described previously (34). All participants provided informed consent. The Lifelines Cohort Study is conducted according to the principles of the Declaration of Helsinki and was approved by the medical ethical review committee of the University Medical Center Groningen.

Among 152,728 adult participants, 100,648 returned for the second assessment. We excluded participants with CKD [defined as having an eGFR < 60 mL/min/1.73 m² using the Chronic Kidney Disease Epidemiology Collaboration equation (35)] at baseline ($n = 1916$) and those with missing values of dietary intake information ($n = 2064$) or serum creatinine ($n = 7436$). To evaluate potential errors in dietary reporting, we calculated the ratio between energy intake (EI) and the basal metabolic rate

[BMR, based on the Schofield equation (36)] and applied the Goldberg cutoff (37, 38). Briefly, EI/BMR values <0.5 and >2.75 were considered implausible and represented an additional exclusion criterion. After excluding 10,886 participants with implausible energy intakes, 78,346 participants (45,751 females and 32,595 males) were included in the study (Supplemental Figure 1).

Dietary intake assessment and UPF

Dietary intake was evaluated with a self-administered, 110-item FFQ (34). This FFQ was validated previously in the Netherlands (39, 40); it included questions on the consumption frequencies and portion sizes of food items during the last 1 month. Food items were classified according to the NOVA classification (23), as follows: unprocessed or minimally processed foods, processed culinary ingredients, processed foods, and UPFs. In this study, we focused solely on the UPF category. UPFs are industrial formulations with many ingredients that result from a series of industrial processes, which undergo multiple physical, biological, and/or chemical processes, and generally contain food additives (21). They often contain food substances not commonly used in culinary preparation (e.g., hydrogenated oils and hydrolyzed proteins) and various additives (e.g., dyes and other colors, flavors) (21). The NOVA categorization of the food items in this study was confirmed by 4 researchers, among whom 2 are authors of this study (M-JD and LHD) and 2 are senior researchers in the field of nutritional epidemiology (Petra C Vinke and Eva Corpeleijn). The food items considered as UPFs are shown in Supplemental Table 1. The total UPF consumption (in grams/day) was evaluated by the sum of the food items considered as UPFs. The weight ratio was used to estimate the proportion (in grams/day) of UPF consumption from the total weight of the diet. We used a weight ratio instead of an energy ratio to determine the proportion of UPF intake because it accounts for the food that does not provide energy (e.g., artificially sweetened beverages) and nonnutritional factors (e.g., additives, byproducts of processing). The proportions of UPF intake were then divided into sex-specific quartiles for further analyses.

In order to investigate whether the associations between UPF consumption and kidney outcomes were affected by the overall diet quality, we assessed the Mediterranean diet as an indicator of overall diet quality that has been previously associated with kidney function decline (41). We calculated the Mediterranean diet score (MDS) through a 9-point score developed by Trichopoulou et al. (42). Briefly, 9 food groups were included in the MDS: vegetables, legumes, cereal, fruit and nuts, and fish, which were considered to be beneficial components; meats, poultry, and dairy products, which were considered to be detrimental components; and alcohol intake. For beneficial components, participants received 1 point if their intake was above the sex-specific median in grams per day; for detrimental components, the intake below the median was scored 1. For alcohol, a value of 1 was given to males who consumed between 10 and 50 g/day or to females who consumed between 5 and 25 g/day. The MDSs vary between 0 and 9.

Other nutrition indices, such as nutrient intakes, were considered in this study. The total nutrient intakes (total protein intake, total carbohydrate intake, and total fat intake) were positively correlated with total energy intake; therefore, energy-adjusted

nutrient intakes were calculated by the residual method using a linear regression model (43). With this method, nutrient intakes are not correlated with the total energy intake and are directly related to the overall variation in the food composition.

Assessment of other baseline covariates

Self-administered questionnaires were used to assess sociodemographic characteristics and health-related behaviors. Education level was classified into 4 groups (low: never been to school, or elementary school only, or lower vocational or secondary school; middle: intermediate vocational school or intermediate or higher secondary school; high, higher vocational school or university; and unknown or no answer). Smokers referred to current smokers. The validated Short Questionnaire to Assess Health-Enhancing Physical Activity was used to evaluate the time spent on nonoccupational, moderate to vigorous physical activity (minutes/week). BMI was calculated as weight (kg) divided by height squared (m^2). Blood and urine laboratory assessments have been published previously in detail (44). Serum creatinine was measured by an enzymatic method traceable to isotope dilution MS on a Roche Modular analyzer (Roche Diagnostics). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (35). Participants were considered to have diabetes if they had self-reported diabetes, a nonfasting plasma glucose value ≥ 11 mmol/L, a measured glycated hemoglobin value $\geq 6.5\%$, and/or used oral antidiabetics and/or insulin. Cardiovascular disease included self-reported coronary artery disease, heart failure, and/or stroke. Hypertension was defined as blood pressure $> 140/90$ mmHg or the use of antihypertensive medication.

Kidney outcomes

The primary outcome was a composite kidney outcome including a $\geq 30\%$ eGFR decline relative to baseline or incident CKD, defined as a de novo occurrence of an eGFR < 60 mL/min/1.73 m^2 at the second study visit compared with the baseline visit. The secondary outcome of this study was an annual change in eGFR, calculated by subtracting the eGFR at baseline from the eGFR at the second visit and dividing by each follow-up time period, in years.

Statistical analysis

Baseline characteristics are presented according to sex-specific quartiles of UPF consumption. Data are presented as the mean \pm SD, median (IQR), or percentage, as appropriate. The *P* values for trend over the quartiles of UPF consumption were calculated by linear regression analysis for continuous variables or the Cochran-Armitage Trend Test for categorical variables. Linear regression analyses were performed for the continuous annual change in eGFR outcomes and logistic regression analyses were used for the composite kidney outcome, to evaluate their associations with UPF consumption (in categories as quartiles of UPF consumption or as a continuous variable per 10% increment of UPF in the diet), adjusted for the potential confounders. ORs (95% CIs) and β (95% CIs) are reported in 4 incremental, multivariable models: minimally adjusted for age and sex (model 1); further adjusted for baseline eGFR, diabetes, hypertension,

cardiovascular disease, physical activity, smoking, total energy intake, and education level (model 2); further adjusted for MDS as a measure of dietary quality (model 3); and further adjusted for the energy-adjusted protein intake, energy-adjusted carbohydrate intake, and energy-adjusted fat intake (model 4). Furthermore, we investigated potential effect modifications by key baseline variables by adding multiplicative interaction terms to the regression analyses. Subsequently, we analyzed the associations of UPF consumption with the composite kidney outcome and annual eGFR change separately in different strata of the participants. We stratified the participants by age (younger adults under 45 years and older adults over 45 years), sex (male and female), diabetes (yes and no), hypertension (yes and no), cardiovascular disease (yes and no), baseline eGFR (60–90 and > 90 mL/min/1.73 m^2), MDS (scores, 0–3, 4–5, and 6–9), smoker (yes and no), education level (low, middle, and high), and BMI (18.5–24.9, 25–29.9, and ≥ 30 kg/ m^2). The effects of potential interactions between 10% increments of UPF consumption and these stratified variables were tested in the multiple regression analyses separately. Sensitivity analyses were performed using energy-adjusted UPF intakes by the residual method. A 2-tailed *P* value < 0.05 was considered statistically significant, including for multiplicative interaction terms. The statistical analyses were conducted using R version 3.4.2 (RStudio Team (2022), RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA URL <http://www.rstudio.com/>).

Results

Baseline characteristics

Among 78,346 included participants, the mean \pm SD age was 46 ± 13 years (range, 18–90 years), and 58.4% were females. The mean \pm SD proportion (in grams/day) of UPF consumption in the diet was $37.7\% \pm 12.3\%$. Of all UPF groups, staple or starchy food and cereals (22.6%), dairy products except cheese (14.9%), and sugary beverages (14.5%) were the main contributors to total UPF consumption (median percentages of all UPF groups; **Supplemental Figure 2**). The baseline characteristics, according to sex-specific quartiles of the proportion of UPF consumption in the diet, are summarized in **Table 1**. Participants in the highest quartile of UPF consumption tended to be younger, with a higher baseline eGFR and a lower prevalence of comorbidities, compared with those in the lowest quartile. However, participants in the highest quartile of UPF consumption had a lower level of attained education, were more often smokers, were less physically active, and had a worse triglyceride blood profile. Across increasing quartiles of UPF consumption, the MDS score (representing overall dietary quality) and total alcohol intake decreased, whereas total energy intake, total protein intake, total fat intake, and total carbohydrate intake increased.

UPF consumption and kidney outcomes

During a mean \pm SD follow-up time of 3.6 ± 0.9 years, 2470 (3.2%) participants reached the composite kidney outcome, and the median annual eGFR change was -2.23 (IQR, -3.96 to -0.80) mL/min/1.73 m^2 . Results of the associations between the composite kidney outcome and UPF consumption are

TABLE 1 Baseline characteristics of participants according to the sex-specific quartiles of UPF consumption in the Lifelines cohort¹

	Quartiles of UPF consumption					P for trend
	Total (n = 78,346)	Q1 (n = 19,587)	Q2 (n = 19,587)	Q3 (n = 19,585)	Q4 (n = 19,587)	
Demographics						
Age, years	45.8 ± 12.6	52.0 ± 11.5	48.4 ± 11.6	44.7 ± 11.4	38.3 ± 11.8	<0.001
Sex, %, female	58.4	58.4	58.4	58.4	58.4	—
Food intake						
Proportion of UPF in the diet, % of grams/day	37.7 ± 12.3	23.9 ± 4.8	32.7 ± 3.2	40.2 ± 3.4	54.1 ± 8.5	<0.001
Range of UPF proportion in the diet, %						
Female	0.1–99.9	0.1–27.0	27.0–34.2	34.2–42.9	42.9–99.9	<0.001
Male	0.1–94.5	0.1–32.1	32.1–39.2	39.2–47.3	47.3–94.5	<0.001
Mediterranean diet score	4.2 ± 1.7	4.8 ± 1.6	4.3 ± 1.6	4.0 ± 1.6	3.6 ± 1.5	<0.001
Total energy intake, kcal/day	2075.6 ± 606.8	1825.4 ± 520.4	2050.3 ± 552.9	2165.2 ± 592.2	2261.8 ± 663.0	<0.001
Total protein intake, g/day	75.9 ± 20.3	71.1 ± 18.8	76.5 ± 19.2	78.4 ± 20.2	77.8 ± 22.1	<0.001
Total fat intake, g/day	82.4 ± 29.3	70.2 ± 24.6	81.4 ± 26.7	87.2 ± 28.9	90.7 ± 32.2	<0.001
Total carbohydrate intake, g/day	232.7 ± 72.9	201.6 ± 63.8	227.5 ± 66.0	242.0 ± 69.9	259.6 ± 78.5	<0.001
Total alcohol intake, g/day	4.0 (0.9–10.4)	5.8 (1.2–11.7)	5.2 (1.2–10.8)	3.9 (0.9–10.1)	3.2 (0.7–9.7)	<0.001
Clinical factors						
eGFR, mL/min/1.73 m ²	95.9 ± 14.3	92.0 ± 13.3	94.0 ± 13.5	96.4 ± 14.0	101.2 ± 14.7	<0.001
BMI, kg/m ²	26.0 ± 4.2	26.0 ± 3.9	26.0 ± 3.9	26.0 ± 4.2	26.0 ± 4.6	0.224
Cholesterol, mmol/L	5.12 ± 1.00	5.27 ± 1.01	5.20 ± 1.00	5.10 ± 0.99	4.91 ± 0.97	<0.001
Triglycerides, mmol/L	1.17 ± 0.78	1.14 ± 0.75	1.16 ± 0.75	1.17 ± 0.77	1.20 ± 0.86	<0.001
Diabetes, %	3.1	3.9	3.2	3.0	2.3	<0.001
Hypertension, %	22.0	26.7	23.1	21.1	17.2	<0.001
Cardiovascular disease, %	2.6	4.0	2.7	2.3	1.6	<0.001
Health-related behaviors						
Physical activity, minutes/week	190 (60–365)	240 (90–420)	210 (80–375)	180 (60–360)	170 (60–345)	<0.001
Smoker, %	16.6	13.9	15.1	16.7	20.5	<0.001
Education, %						
Low	28.7	29.8	29.1	28.4	27.4	<0.001
Middle	39.9	34.4	38.0	40.8	46.5	—
High	31.0	35.2	32.4	30.5	25.8	—
Unknown/no answer	0.4	0.6	0.5	0.4	0.3	—

¹Data are presented as mean ± SD, median (IQR) or percentage, as appropriate. Mediterranean diet scores vary between 0 and 9, eGFR, estimated glomerular filtration rate; Q, quartile; UPF, ultraprocessed food.

shown in **Table 2**. Participants in the highest quartile of UPF consumption had a higher risk of incident CKD or a $\geq 30\%$ eGFR decline (OR, 1.27; 95% CI, 1.09–1.47; $P = 0.003$) compared with those in the lowest quartile in the fully adjusted analysis. The same association was seen between the annual change in eGFR and UPF consumption (**Table 3**). Participants in the highest quartile of UPF consumption had a more rapid eGFR decline (β , -0.17 ; 95% CI, -0.23 to -0.11 ; $P < 0.001$) compared with those in the lowest quartile. Similar dose-response associations were observed per 10% increment of UPF consumption. In fully adjusted analyses, every 10% increase in the amount of UPF consumed in the diet was associated with an 11% higher risk of the composite outcome (OR, 1.11; 95% CI, 1.06–1.17; $P < 0.001$; **Table 2**) and an eGFR decline that was 0.06 mL/min/1.73 m² per year (β , -0.06 ; 95% CI, -0.08 to -0.04 ; $P < 0.001$) faster (**Table 3**). In sensitivity analyses, energy-adjusted consumption of UPF yielded a similar effect size and did not substantially change the results (**Supplemental Tables 2 and 3**).

Subgroup analyses

We observed significant interactions of UPF consumption with the baseline eGFR, age, sex, and education for the composite kidney outcome. The association between UPF consumption and the composite kidney outcome remained significant in both subgroups in younger compared with older individuals, was only significant in subgroups with women, was only significant in subgroups with eGFRs > 90 mL/min/1.73 m², and was significant in subgroups with middle and high education levels. We found no effect modifications by diabetes, hypertension, cardiovascular disease history, MDS, smoking, or BMI (**Figure 1**).

The interaction analysis indicated an effect modification for the association between UPF consumption and the annual change in eGFR by the baseline cardiovascular disease history (P for interaction = 0.007; **Figure 2**). The association between UPF consumption and the annual eGFR change was present in individuals without a cardiovascular disease history, but not in those with a cardiovascular disease history. We also observed a significant interaction by baseline eGFR and BMI categories, but the associations remained significant in all subgroups. We found no effect modification by age, sex, diabetes, hypertension, MDS, smoking, or education (P for interaction > 0.05).

Discussion

In this large, general population–based cohort, we found that higher UPF consumption was significantly associated with a higher risk of a composite kidney outcome (incident CKD or a $\geq 30\%$ eGFR decline relative to baseline) and with a stronger annual eGFR decline, independent of confounders or other nutrition indices. Results were similar when evaluating UPF consumption as a continuous variable or as categories (quartiles of distribution), and were generally consistent across subgroup analyses. Because the proportion of UPF in the diet was associated with worse kidney outcomes regardless of the macro- or micronutrient intake or diet quality score (MDS), our study suggests that additives and nutrient manipulations during the manufacturing of UPF may adversely affect kidney health.

The main and novel finding is that participants consuming a higher proportion of UPFs in their diets were at higher risk of worse kidney outcomes in the general population. Our findings are in agreement with a recent, small-scale study showing that high UPF consumption is independently associated with an increase in the risk of kidney function decline in Spanish older adults (32). We are not aware of other studies evaluating this in the overall general population, but our results expand previous research linking UPF consumption with risks of other noncommunicable diseases, such as cardiovascular disease (24) and diabetes (25). Our observation is aligned with other studies suggesting that dietary patterns more aligned with the consumption of natural and whole foods (like the Mediterranean diet pattern) are associated with lower risks of CKD development and progression in the general population (45, 46). Conversely, dietary patterns aligned with the consumption of processed foods (like the Western-style diet pattern) have been associated with risks of incident CKD and with a more rapid eGFR decline (11–13). In our study, the quality of the diet (evaluated by adherence to the MDS score) was lower among those with a higher proportion of UPFs consumed. Because associations between UPFs and kidney outcomes persisted after adjustment for MDS values, as well as energy-adjusted micro- or macronutrient intakes, we speculate that additives and nutrient manipulations may exert detrimental effects on kidney health.

We observed significant interactions of UPF consumption with the baseline eGFR, age, sex, and education for the composite kidney outcome. In subgroup analyses, the associations between UPF consumption and the composite outcome were significant among both younger and older participants and among participants with a higher baseline eGFR (**Figure 1**). Moreover, no significant effect modification was found by age, sex, or education for the annual change in the eGFR endpoint, and the effect sizes were similar among participants with higher compared with lower baseline eGFR values (**Figure 2**). The interaction by cardiovascular disease history was only significant for the annual change in the eGFR endpoint (**Figure 2**). A prior study focusing on the relationship between UPF consumption and kidney function declines in elderly individuals found no consistent interaction by several cardiovascular risk factors (hypertension, diabetes, and obesity) (32). Other studies focusing on other dietary exposures in relation to kidney function found similar results. In a previous study, we found significant associations between an eGFR-based dietary pattern and kidney function decline for both men and women in the Lifelines cohort (47). In patients with CKD, adherence to healthy dietary patterns was associated with a lower risk for CKD progression or mortality, without consistent interactions by age, sex, race, diabetes, BMI, or baseline eGFR (48). Studies in other populations reported significant associations between nutrients (sodium and potassium intake) and kidney function declines, but no interaction was found by age, sex, or diabetes status (49, 50). Interestingly, the relationship between UPF consumption and the kidney composite outcome was restricted to participants free from cardiovascular disease at baseline in our study. Individuals with a history of cardiovascular disease are more likely to receive medication and lifestyle modifications for cardiovascular risk management, which may also reduce the risk of CKD progression (51). Interestingly, another study in the Lifelines cohort found that the association of diet quality with all-cause mortality was

TABLE 2 Association between composite kidney outcome and UPF consumption by logistic regression analysis¹

	Sex-specific quartiles of UPF consumption, OR (95% CI)					Per 10% increment of UPF consumption OR (95% CI)	P
	Q1	Q2	Q3	Q4	P for trend		
Events, n (%)	864 (4.4%)	653 (3.3%)	560 (2.9%)	393 (2.0%)	<0.001	—	—
Model 1	1.00	0.99 (0.90–1.11)	1.19 (1.06–1.33)	1.41 (1.23–1.60)	<0.001	1.15 (1.11–1.20)	<0.001
Model 2	1.00	0.99 (0.88–1.11)	1.12 (0.99–1.27)	1.35 (1.17–1.55)	<0.001	1.13 (1.08–1.19)	<0.001
Model 3	1.00	0.98 (0.88–1.10)	1.11 (0.98–1.26)	1.33 (1.15–1.53)	<0.001	1.13 (1.08–1.18)	<0.001
Model 4	1.00	0.97 (0.86–1.08)	1.07 (0.95–1.22)	1.27 (1.09–1.47)	0.003	1.11 (1.06–1.17)	<0.001

¹Model 1 was adjusted for age and sex. Model 2 was adjusted for the variables in model 1 plus baseline eGFR, diabetes, hypertension, cardiovascular disease, physical activity, smoking, total energy intake, and education level. Model 3 was adjusted for the variables in model 2 plus Mediterranean diet score. Model 4 was adjusted for the variables in model 3 plus energy-adjusted protein intake, energy-adjusted carbohydrate intake, and energy-adjusted fat intake. eGFR, estimated glomerular filtration rate; Q, quartile; UPF, ultraprocessed food.

modified by the presence of cardiovascular disease (52). The cardiovascular disease history in Lifelines is based on self-reported questionnaires, which is prone to both under- and overreporting.

There is a need for research on the kidney-related health implications of UPF consumption. UPFs are generally energy dense and rich in saturated fat, added sugar, and salt (21). High intakes of these nutrients have been associated with worse kidney outcomes in epidemiological studies (12, 13), as they can induce dyslipidemia, oxidative stress, or inflammation, which are believed to be risk factors for CKD progression (12). The techniques used for the production of UPFs may result in nutrient degradation (53) or lead to the production of neoformed contaminants (e.g., acrylamide) (54). Previous studies have linked the use of additives and contaminants with alterations in the gut microbiome composition and subsequent inflammation (55). UPFs have higher contents of phosphorus and/or potassium additives and acidity regulators (such as citric acid, sodium diacetate, magnesium chloride, or sodium bicarbonate) than minimally processed or unprocessed foods (56). These additives can worsen metabolic alterations inherent to CKD, such as hyperphosphatemia and hyperkalemia, constituting detrimental effects of UPF consumption on kidney health (57, 58). Increased dietary salt intakes and acid loads are recognized risk factors for CKD progression as well (59, 60).

Data on UPF consumption in the general population in the Netherlands are scarce. Pinho et al. (61) found an average UPF consumption of 17.8% of the total food intake in adults aged > 70 years in the Netherlands. Slimani et al. (15) reported a mean contribution of highly processed foods and beverages of 60% in the Netherlands. In the present study, the average consumption of UPFs was 37.7%, ranging from 23.9% to 54.1% across the quartiles. Our study was based on a large, population-based cohort that is representative of the adult population in the Northern Netherlands (33). Thus, the UPF consumption observed in this study is likely to adequately reflect the habitual diets of the Dutch population in the Northern Netherlands. UPF consumption also varies widely around the world, ranging from 17% to 56% of the total energy intake (62). The popularity and high intakes of UPF can be attributed to their convenience and heavy marketing, and are also associated with widespread availability in the current food environment (63). Pinho et al. (61) found that

closer exposure to food retailers, supermarkets, and restaurants, was associated with somewhat lower consumption of UPFs and higher diet quality in the Netherlands.

A study strength is the large sample size of a population that is representative of the Northern Netherlands. However, some limitations need to be noted. Our FFQ was self-administrated, and some participants had to be excluded due to unreliable dietary data. Our FFQ was not designed to specifically assess the intake of UPFs, so we acknowledge that our evaluation and adaptation to the NOVA system may have introduced bias. For example, the FFQ in the Lifelines cohort did not distinguish between spreadable and nonspreadable cheeses, and most cheese on the market contains more than 5 ingredients. Therefore, we considered cheese as a UPF in this study. Nevertheless, the definition of a UPF is still under debate, so misclassification might exist. We only had 1 assessment of eGFR at baseline to estimate kidney function; we could not evaluate whether this low kidney function was persistent over time [i.e., no confirmation using another low measurement in 3 months, per the Kidney Disease Improving Global Outcomes recommendation (64)] or whether there was concomitant albuminuria. There were baseline differences among UPF quartiles in the prevalences of diabetes, hypertension, and cardiovascular disease, which may have led to higher health-care surveillance in individuals in the lowest quartile of UPF intake. Even though adjusting for these potential confounders in our multivariable models did not materially change the results and subgroup analyses were generally consistent, we cannot exclude residual confounding. Finally, although we explored the potential nutritional factors driving the relationship between UPF consumption and kidney outcomes, more nutritional factors, such as sodium intake, need to be included in future studies, and the underlying biological mechanisms need to be further explored.

In conclusion, this study provides evidence that high consumption of UPFs increases the risks of incident CKD or a $\geq 30\%$ eGFR decline and is associated with a rapid annual eGFR decline in the general population. The associations between UPF consumption and kidney outcomes were independent of overall diet quality and some macro- or micronutrient intakes. Current dietary guidelines are mainly focused on nutrients or food groups. Our findings support considering UPFs when designing future dietary strategies for the prevention of CKD.

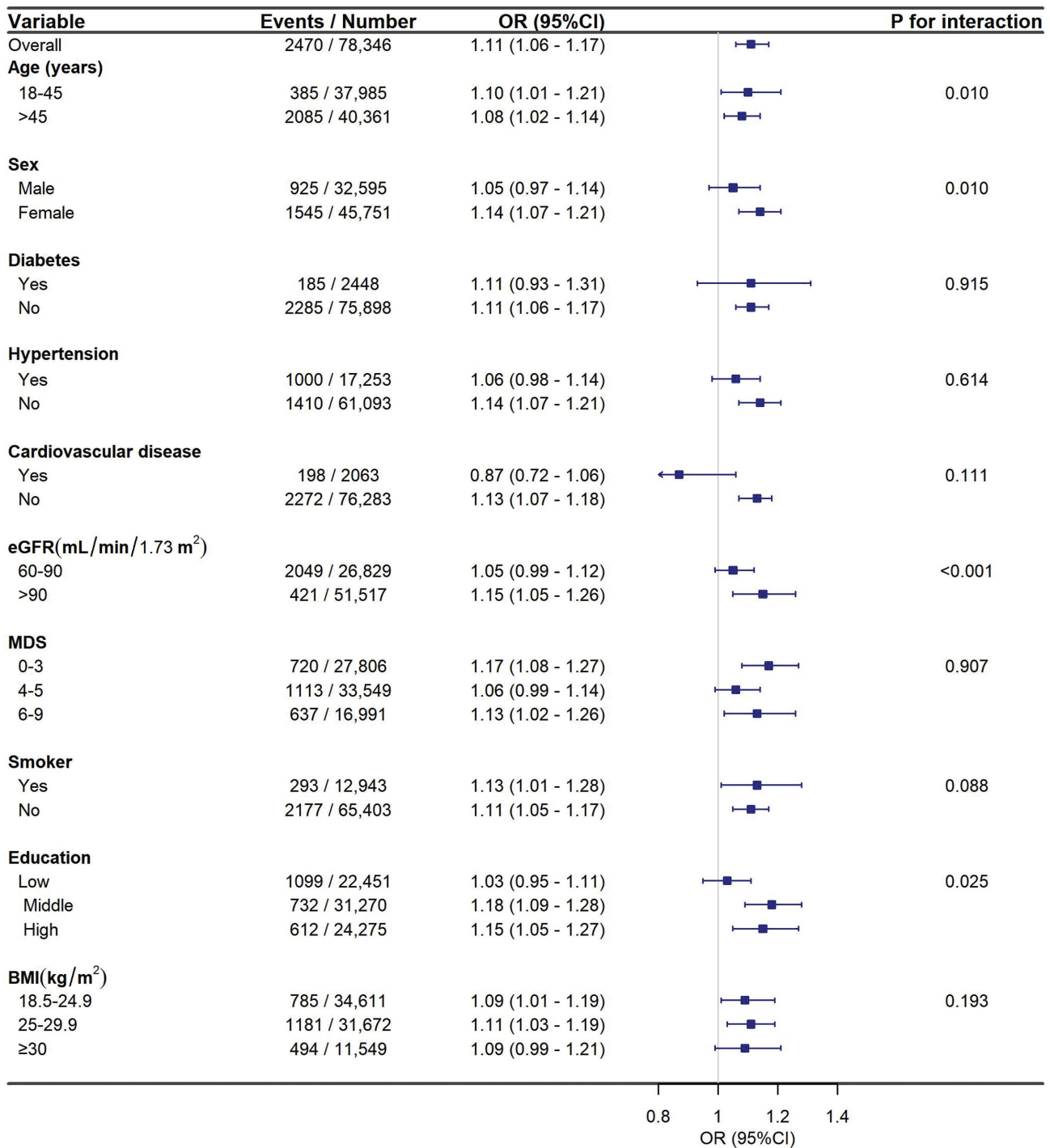


FIGURE 1 Subgroup analyses of the associations between UPF consumption and composite kidney outcomes. ORs are for participants who reached incident CKD or an eGFR decline $\geq 30\%$, per 10% increment of UPF consumption. The multivariable logistic regression model adjusted for age, sex, baseline eGFR, diabetes, hypertension, cardiovascular disease, physical activity, smoking, total energy intake, education level, energy-adjusted protein intake, energy-adjusted carbohydrate intake, energy-adjusted fat intake, and MDS. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDS, Mediterranean diet score; UPF, ultraprocessed food.

We acknowledge the services of the Lifelines cohort study, the contributing research centers delivering data to Lifelines, and all the study participants. We thank Petra C. Vinke and Eva Corpeleijn (senior researchers in the field of nutritional epidemiology from University Medical Center Groningen) for verifying the NOVA categorization of the food item in the Lifelines cohort.

The authors' responsibilities were as follows – QC, M-JD, LHD, MHdB, GJN: designed the study; QC, M-JD: analyzed the data; QC: made the figures and drafted the manuscript; M-JD, LHD, JJC, CMA, SJLB, MHdB, GJN: revised the paper; and all authors: read and approved the final manuscript. Some authors (JJC, CMA, SJLB) are members of the European

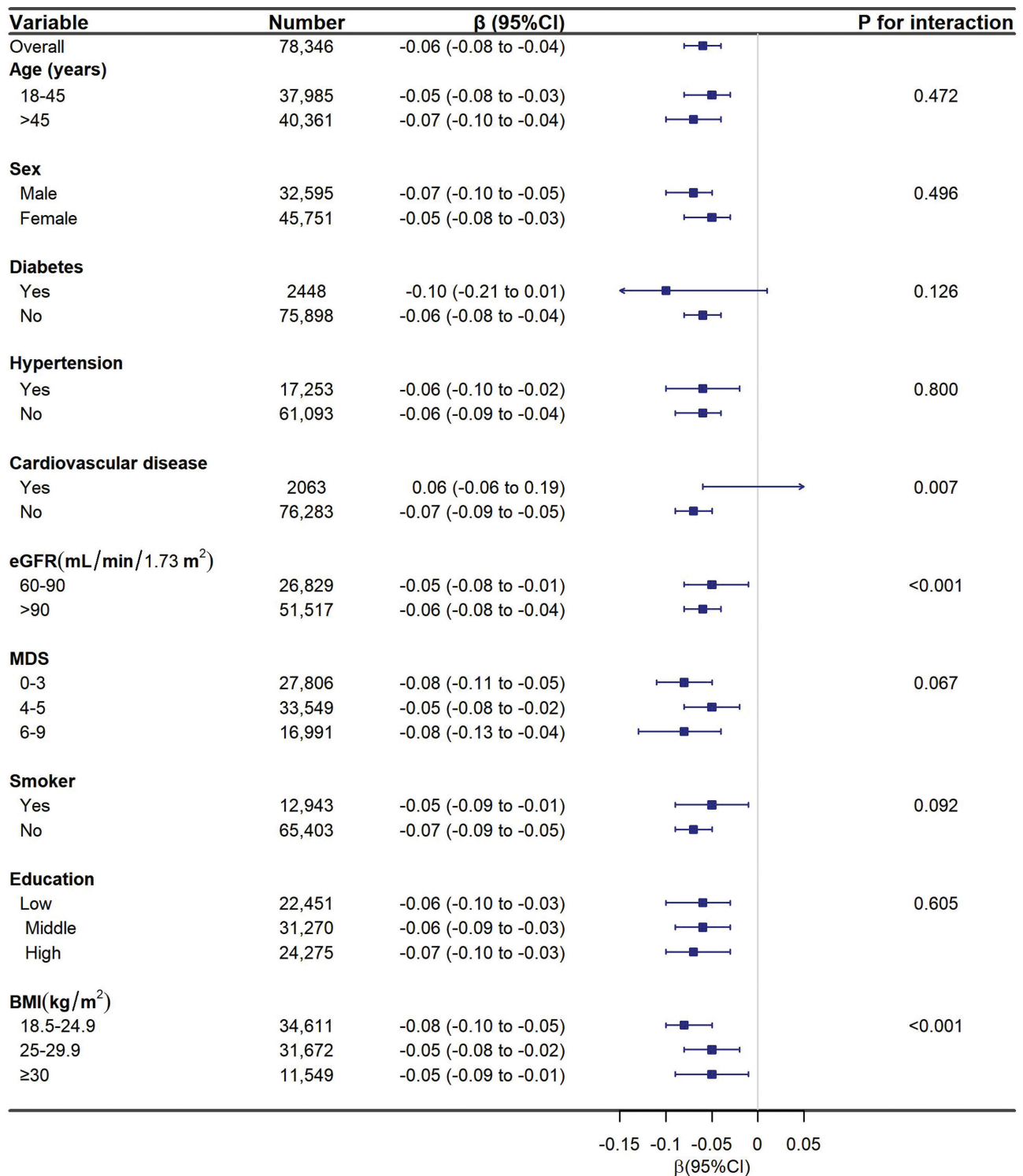


FIGURE 2 Subgroup analyses of the association between UPF consumption and annual change in eGFR. Regression coefficient (β) represents the annual change in eGFR per 10% increment of UPF consumption. Linear regression model adjusted for age, sex, baseline eGFR, diabetes, hypertension, cardiovascular disease, physical activity, smoking, total energy intake, education level, energy-adjusted protein intake, energy-adjusted carbohydrate intake, energy-adjusted fat intake, and MDS. eGFR, estimated glomerular filtration rate; MDS, Mediterranean diet score; UPF, ultraprocessed food.

Renal Nutrition Working Group, an initiative of and supported by the European Renal Association–European Dialysis Transplant Association. Further information on this Working Group and its activities can be found at <https://www.era-edtaworkinggroups.org/en-US/group/european-renalnutrition>. All other authors report no conflicts of interest.

Data availability

Data described in the manuscript, code book, and analytic code will not be made available because data are obtained from a third party and are not publicly available. Researchers can apply to use

TABLE 3 Association between annual change in eGFR and UPF consumption by linear regression analysis¹

	Sex-specific quartiles of UPF consumption, β (95% CI)					P for trend	Per 10% increment of UPF consumption β (95% CI)	P
	Q1	Q2	Q3	Q4	Q4			
Annual change in eGFR, mL/min/1.73 m ²	-2.07 (-3.74 to -0.72)	-2.15 (-3.83 to -0.74)	-2.25 (-3.99 to -0.81)	-2.46 (-4.30 to -0.93)	-2.46 (-4.30 to -0.93)	<0.001	—	—
Model 1	1.00	-0.03 (-0.08 to 0.03)	-0.09 (-0.14 to -0.03)	-0.23 (-0.28 to -0.17)	-0.23 (-0.28 to -0.17)	<0.001	-0.08 (-0.10 to -0.06)	<0.001
Model 2	1.00	-0.08 (-0.13 to -0.02)	-0.16 (-0.21 to -0.10)	-0.29 (-0.34 to -0.23)	-0.29 (-0.34 to -0.23)	<0.001	-0.10 (-0.12 to -0.08)	<0.001
Model 3	1.00	-0.06 (-0.12 to -0.01)	-0.14 (-0.19 to -0.08)	-0.26 (-0.31 to -0.20)	-0.26 (-0.31 to -0.20)	<0.001	-0.09 (-0.11 to -0.07)	<0.001
Model 4	1.00	-0.04 (-0.09 to 0.02)	-0.09 (-0.14 to -0.03)	-0.17 (-0.23 to -0.11)	-0.17 (-0.23 to -0.11)	<0.001	-0.06 (-0.08 to -0.04)	<0.001

¹Model 1 was adjusted for age and sex. Model 2 was adjusted for the variables in model 1 plus baseline eGFR, diabetes, hypertension, cardiovascular disease, physical activity, smoking, total energy intake, and education level. Model 3 was adjusted for the variables in model 2 plus Mediterranean diet score. Model 4 was adjusted for the variables in model 3 plus energy-adjusted protein intake, energy-adjusted carbohydrate intake, and energy-adjusted fat intake. eGFR, estimated glomerular filtration rate; Q, quartile; UPF, ultraprocessed food.

the Lifelines data used in this study. More information about how to request Lifelines data and the conditions of use can be found on their website (<https://www.lifelines.nl/researcher/how-to-apply>).

Conflicts of interest

The authors of this manuscript have no conflicts of interest.

References

- Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: A systematic analysis for the Global Burden of Disease study 2017. *Lancet North Am Ed* 2020;395(10225):709–33.
- Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: Global dimension and perspectives. *Lancet North Am Ed* 2013;382(9888):260–72.
- Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. *N Engl J Med* 2017;377(18):1765–76.
- Alp Ikizler T, Robinson-Cohen C, Ellis C, Headley SAE, Tuttle K, Wood RJ, et al. Metabolic effects of diet and exercise in patients with moderate to severe CKD: A randomized clinical trial. *J Am Soc Nephrol* 2018;29(1):250–9.
- Packard DP, Milton JE, Shuler LA, Short RA, Tuttle KR. Implications of chronic kidney disease for dietary treatment in cardiovascular disease. *J Ren Nutr* 2006;16(3):259–68.
- Lin J, Hu FB, Curhan GC. Associations of diet with albuminuria and kidney function decline. *Clin J Am Soc Nephrol*. 2010;5(5):836–43.
- Kelly JT, Su G, Zhang L, Qin X, Marshall S, González-Ortiz A, et al. Modifiable lifestyle factors for primary prevention of CKD: A systematic review and meta-analysis. *J Am Soc Nephrol* 2021;32(1):239–53.
- Carrero JJ, González-Ortiz A, Avesani CM, Bakker SJL, Bellizzi V, Chauveau P, et al. Plant-based diets to manage the risks and complications of chronic kidney disease. *Nat Rev Nephrol* 2020;16(9):525–42.
- Bach KE, Kelly JT, Campbell KL, Palmer SC, Khalesi S, Strippoli GFM. Healthy dietary patterns and incidence of CKD: A meta-analysis of cohort studies. *Clin J Am Soc Nephrol*. 2019;14(10):1441–9.
- Kelly JT, Palmer SC, Wai SN, Ruospo M, Carrero JJ, Campbell KL, et al. Healthy dietary patterns and risk of mortality and ESRD in CKD: A meta-analysis of cohort studies. *Clin J Am Soc Nephrol*. 2017;12(2):272–9.
- Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, et al. Origins and evolution of the Western diet: Health implications for the 21st century. *Am J Clin Nutr* 2005;81(2):341–54.
- Odermatt A. The Western-style diet: A major risk factor for impaired kidney function and chronic kidney disease. *Am J Physiol Renal Physiol* 2011;301(5):F919–31.
- Hariharan D, Vellanki K, Kramer H. The Western diet and chronic kidney disease. *Curr Hypertens Rep* 2015;17(3):16.
- Rauber F, da Costa Louzada ML, Steele E, Millett C, Monteiro CA, Levy RB. Ultra-processed food consumption and chronic non-communicable diseases-related dietary nutrient profile in the UK (2008–2014). *Nutrients* 2018;10(5):587.
- Slimani N, Deharveng G, Southgate DAT, Biessy C, Chajès V, van Bakel MME, et al. Contribution of highly industrially processed foods to the nutrient intakes and patterns of middle-aged populations in the European prospective investigation into cancer and nutrition study. *Eur J Clin Nutr* 2009;63(S4):S206–25.
- Monteiro CA, Levy RB, Claro RM, De Castro IRR, Cannon G. Increasing consumption of ultra-processed foods and likely impact on human health: Evidence from Brazil. *Public Health Nutr* 2011;14(1):5–13.
- Baraldi LG, Martinez Steele E, Canella DS, Monteiro CA. Consumption of ultra-processed foods and associated sociodemographic factors in the USA between 2007 and 2012: Evidence from a nationally representative cross-sectional study. *BMJ Open*. 2018;8(3):e020574.
- Moubarac JC, Batal M, Louzada ML, Martinez Steele E, Monteiro CA. Consumption of ultra-processed foods predicts diet quality in Canada. *Appetite* 2017;108:512–20.
- MacHado PP, Steele EM, Levy RB, Sui Z, Rangan A, Woods J, et al. Ultra-processed foods and recommended intake levels of

- nutrients linked to non-communicable diseases in Australia: Evidence from a nationally representative cross-sectional study. *BMJ Open*. 2019;9(8):e029544.
20. Monteiro CA, Moubarac JC, Levy RB, Canella DS, Da Costa Louzada ML, Cannon G. Household availability of ultra-processed foods and obesity in nineteen European countries. *Public Health Nutr* 2018;21(1):18–26.
 21. Monteiro CA, Cannon G, Levy RB, Moubarac JC, Louzada MLC, Rauber F, et al. Ultra-processed foods: What they are and how to identify them. *Public Health Nutr* 2019;22(5):936–41.
 22. Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN decade of nutrition, the NOVA food classification and the trouble with ultra-processing. *Public Health Nutr* 2018;21(1):5–17.
 23. Monteiro CA, Cannon G, Levy R, Moubarac J-C, Jaime P, Martins AP, et al. NOVA. The star shines bright. *World Nutr* 2016;7(1–3):28–38.
 24. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Méjean C, Andrianasolo RM, et al. Ultra-processed food intake and risk of cardiovascular disease: Prospective cohort study (NutriNet-Santé). *BMJ* 2019;365:11451.
 25. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Debras C, Druésne-Pecollo N, et al. Ultraprocessed food consumption and risk of type 2 diabetes among participants of the Nutrinet-Santé prospective cohort. *JAMA Intern Med*. 2020;180(2):283–91.
 26. De Deus Mendonça R, Pimenta AM, Gea A, De La Fuente-Arrillaga C, Martínez-González MA, Lopes ACS, et al. Ultraprocessed food consumption and risk of overweight and obesity: The University of Navarra follow-up (SUN) cohort study. *Am J Clin Nutr* 2016;104(5):1433–40.
 27. De Deus Mendonça R, Souza Lopes AC, Pimenta AM, Gea A, Martínez-González MA, Bes-Rastrollo M. Ultra-processed food consumption and the incidence of hypertension in a Mediterranean cohort: The seguimiento Universidad de Navarra project. *Am J Hypertens* 2017;30(4):358–66.
 28. Montero-Salazar H, Donat-Vargas C, Moreno-Franco B, Sandoval-Insausti H, Civeira F, Laclaustra M, et al. High consumption of ultra-processed food may double the risk of subclinical coronary atherosclerosis: The Aragon Workers' Health Study (AWHS). *BMC Med* 2020;18(1):235.
 29. Donat-Vargas C, Sandoval-Insausti H, Rey-García J, Moreno-Franco B, Åkesson A, Banegas JR, et al. High consumption of ultra-processed food is associated with incident dyslipidemia: A prospective study of older adults. *J Nutr* 2021;151(8):2390–8.
 30. Fiolet T, Srour B, Sellem L, Kesse-Guyot E, Allès B, Méjean C, et al. Consumption of ultra-processed foods and cancer risk: Results from Nutrinet-Santé prospective cohort. *BMJ* 2018;360:k322.
 31. Rico-Campà A, Martínez-González MA, Alvarez-Alvarez I, De Deus Mendonça R, De La Fuente-Arrillaga C, Gómez-Donoso C, et al. Association between consumption of ultra-processed foods and all-cause mortality: SUN prospective cohort study. *BMJ* 2019;365:11949.
 32. Rey-García J, Donat-Vargas C, Sandoval-Insausti H, Bayan-Bravo A, Moreno-Franco B, Banegas JR, et al. Ultra-processed food consumption is associated with renal function decline in older adults: A prospective cohort study. *Nutrients* 2021;13(2):1–13.
 33. Klijs B, Scholtens S, Mandemakers JJ, Snieder H, Stolk RP, Smidt N. Representativeness of the Lifelines cohort study. *PLoS One* 2015;10(9):e0137203.
 34. Scholtens S, Smidt N, Swertz MA, Bakker SJL, Dotting A, Vonk JM, et al. Cohort profile: Lifelines, a three-generation cohort study and biobank. *Int J Epidemiol* 2015;44(4):1172–80.
 35. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150(9):604–12.
 36. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* 1985;39(Suppl 1):5–41.
 37. Goldberg GR, Black AE, Jebb SA, Cole TJ, Murgatroyd PR, Coward WA, et al. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. *Eur J Clin Nutr* 1991;45(12):569–81.
 38. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake: basal metabolic rate. A practical guide to its calculation, use and limitations. *Int J Obes* 2000;24(9):1119–30.
 39. Siebelink E, Geelen A, De Vries JHM. Self-reported energy intake by FFQ compared with actual energy intake to maintain body weight in 516 adults. *Br J Nutr* 2011;106(2):274–81.
 40. Stoppel MT, De Vries JH, Meijboom S, Beekman M, De Craen AJ, Slagboom PE, et al. Relative validity of the food frequency questionnaire used to assess dietary intake in the Leiden Longevity Study. *Nutr J* 2013;12(1):75.
 41. Hansrivijit P, Oli S, Khanal R, Ghahramani N, Thongprayoon C, Cheungpasitporn W. Mediterranean diet and the risk of chronic kidney disease: A systematic review and meta-analysis. *Nephrology* 2020;25(12):913–8.
 42. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med* 2003;348(26):2599–608.
 43. Willett W, Stampfer MJ. Total energy intake: Implications for epidemiologic analyses. *Am J Epidemiol* 1986;124(1):17–27.
 44. Dekker LH, Rijnks RH, Strijker D, Navis GJ. A spatial analysis of dietary patterns in a large representative population in the north of The Netherlands—The Lifelines cohort study. *Int J Behav Nutr Phys Act* 2017;14(1):166.
 45. Khatri M, Moon YP, Scarneas N, Gu Y, Gardener H, Cheung K, et al. The association between a Mediterranean-style diet and kidney function in the Northern Manhattan study cohort. *Clin J Am Soc Nephrol* 2014;9(11):1868–75.
 46. Asghari G, Farhadnejad H, Mirmiran P, Dizavi A, Yuzbashian E, Azizi F. Adherence to the Mediterranean diet is associated with reduced risk of incident chronic kidney diseases among Tehranian adults. *Hypertens Res* 2017;40(1):96–102.
 47. Cai Q, Dekker LH, Bakker SJ, de Borst MH, Navis GJ. Dietary patterns based on estimated glomerular filtration rate and kidney function decline in the general population: The lifelines cohort study. *Nutrients* 2020;12(4):1099.
 48. Hu EA, Coresh J, Anderson CA, Appel LJ, Grams ME, Crews DC, et al. Adherence to healthy dietary patterns and risk of CKD progression and all-cause mortality: Findings from the CRIC (Chronic Renal Insufficiency Cohort) study. *Am J Kidney Dis* 2021;77(2):235–44.
 49. He J, Mills KT, Appel LJ, Yang W, Chen J, Lee BT, et al. Urinary sodium and potassium excretion and CKD progression. *J Am Soc Nephrol* 2016;27(4):1202–12.
 50. Smyth A, Dunkler D, Gao P, Teo KK, Yusuf S, O'donnell MJ, et al. The relationship between estimated sodium and potassium excretion and subsequent renal outcomes. *Kidney Int* 2014;86(6):1205–12.
 51. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: Epidemiology, mechanisms, and prevention. *Lancet North Am Ed* 2013;382(9889):339–52.
 52. Vinke PC, Navis G, Kromhout D, Corpeleijn E. Associations of diet quality and all-cause mortality across levels of cardiometabolic health and disease: A 7.6-year prospective analysis from the Dutch lifelines cohort. *Diabetes Care* 2021;44(5):1228–35.
 53. Sari YW, Mulder WJ, Sanders JPM, Bruins ME. Towards plant protein refinery: Review on protein extraction using alkali and potential enzymatic assistance. *Biotechnol J* 2015;10(8):1138–57.
 54. Virk-Baker MK, Nagy TR, Barnes S, Groopman J. Dietary acrylamide and human cancer: A systematic review of literature. *Nutr Cancer* 2014;66(5):774–90.
 55. Zinöcker M, Lindseth I. The Western diet–Microbiome–host interaction and its role in metabolic disease. *Nutrients*. 2018;10(3):365.
 56. Angélico LR, de Souza GC, Romão EA, Chiarello PG. Alkaline diet and metabolic acidosis: Practical approaches to the nutritional management of chronic kidney disease. *J Ren Nutr* 2018;28(3):215–20.
 57. Picard K. Potassium additives and bioavailability: Are we missing something in hyperkalemia management? *J Ren Nutr* 2019;29(4):350–3.
 58. Uribarri J. Phosphorus additives in food and their effect in dialysis patients. *Clin J Am Soc Nephrol* 2009;4(8):1290–2.
 59. Jones-Burton C, Mishra SI, Fink JC, Brown J, Gossa W, Bakris GL, et al. An in-depth review of the evidence linking dietary salt intake and progression of chronic kidney disease. *Am J Nephrol* 2006;26(3):268–75.
 60. Banerjee T, Crews DC, Wesson DE, Tilea A, Saran R, Rios Burrows N, et al. Dietary acid load and chronic kidney disease among adults in the United States. *BMC Nephrol* 2014;15(1):137.
 61. Pinho MGM, Lakerveld J, Harbers MC, Sluijs I, Vermeulen R, Huss A, et al. Ultra-processed food consumption patterns among older adults

- in the Netherlands and the role of the food environment. *Eur J Nutr* 2021;60(5):2567–80.
62. Lane MM, Davis JA, Beattie S, Gómez-Donoso C, Loughman A, O'Neil A, et al. Ultra-processed food and chronic noncommunicable diseases: A systematic review and meta-analysis of 43 observational studies. *Obes Rev* 2021;22(3): e13146.
63. Monteiro CA, Moubarac JC, Cannon G, Ng SW, Popkin B. Ultra-processed products are becoming dominant in the global food system. *Obes Rev* 2013;14(S2):21–8.
64. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Tamura MK, Feldman HI. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 2014;63(5):713–35.