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Original article

Dietary zinc intake and incident chronic kidney disease

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SUMMARY

Background & aims: Previous studies have shown that dietary zinc intake is closely related to cardiovascular complications and metabolic derangements. However, the effect of dietary zinc intake on renal function is not fully elucidated.

Methods: Data from the Korean Genome and Epidemiology Study were used. Dietary zinc intake was assessed by a Food Frequency Questionnaire and dietary zinc density was calculated as absolute zinc intake amount per daily energy intake (mg/1000 kcal day). The participants were categorized into quartiles according to dietary zinc density. The primary end point was incident chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2.

Results: A total of 7735 participants with normal renal function was included in the final analysis. The mean age was 52.0 ± 8.8 years, 47.5% were male, and mean eGFR was 92.1 ± 16.1 ml/min/1.73 m^2. The mean daily zinc intake and zinc intake density were 8.6 ± 3.4 mg and 4.4 ± 0.9 mg/1000 kcal, respectively. During a median follow up of 11.5 (1.7–12.5) years and 70,617 person-years of observation, CKD developed in 1409 (18.2%) participants. Multivariable cox hazard analysis revealed that risk for CKD development was significantly higher in the quartile with a mean zinc intake density of 3.6 ± 0.2 mg/1000 kcal compared with the quartile with a mean zinc intake density of 5.6 ± 1.0 mg/1000 kcal (Hazard ratio; 1.36; 95% Confidence Interval 1.18–1.58; $P < 0.001$). This relationship remained significant even after adjustments for confounding factors.

Conclusion: Low dietary zinc intake may increase the risk of CKD development in individuals with normal renal function.

1. Introduction

Despite widespread treatment of diabetes and hypertension, the two most recognized causes of chronic kidney disease (CKD), the prevalence of CKD continues to rise rapidly worldwide [1,2]. CKD leads to end stage renal disease and predisposition for cardiovascular diseases and premature death [3–5]. Therefore, the increasing number of CKD patients is considered a major public health problem [2,6]. Since established CKD is an irrevocable condition, prevention by identifying modifiable risk factors is important for reducing CKD-related morbidity and mortality.

Zinc is an essential trace element that has critical catalytic, structural, and regulatory functions. Zinc is involved in many catalytic activity of enzymes involved in replication of DNA, cell division, energy metabolism, and growth [7,8]. In addition, zinc plays key roles in maintaining protein structure and stability [9]. It is also an essential component for maintaining cellular membrane structure and function [10]. Recent investigations have also identified key roles for zinc in regulating antioxidant activity and leptin as well as in insulin signaling [11–13]. Accordingly, zinc status has been reported to be associated with several disease conditions

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[14–17]. Low serum zinc level was found to be associated with increased mortality in patients with cardiovascular disease (CVD) [18]. Dietary zinc supplementation has shown beneficial roles in patients with chronic metabolic diseases [19]. Similarly, adequate zinc consumption is associated with reduced blood pressure and glucose control in Chinese diabetes and CVD patients [20]. Collectively, these results suggest a close relationship between zinc intake and metabolic and cardiovascular equanimity.

Despite the similar pathogenic mechanisms of kidney function impairments and cardiovascular and metabolic diseases, the relationship between dietary zinc consumption and kidney function is not well elucidated. Therefore, this study aimed to evaluate the association between dietary zinc consumption and incident CKD development in a prospective community-based cohort consisting of normal renal function participants.

2. Subjects and methods

2.1. Ethical statements

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University Health System Clinical Trial Center (2019-1455-0001).

2.2. Study population

Data were retrieved from the KoGES (Korean Genome and Epidemiology Study), a prospective community-based study. Detailed cohort profiles and methods concerning the development of KoGES have been described elsewhere [21]. In brief, the study cohort comprised middle aged (40–69 years old) participants who reside in Ansan (an urban area) or Ansung (a rural area), cities near Seoul, South Korea. The subjects underwent prearranged anthropometric examinations, laboratory tests, and health-related behavior surveys with an interview or questionnaire at baseline and at biennial visits up to 14 years from study enrollment. For the current study, subjects who had completed the FFQ at baseline were included. Subjects with baseline eGFR <60 ml/min/1.73 m^2, known kidney disease, or proteinuria at baseline were excluded. Participants who reported implausible daily energy intake (<500 kcal/day or ≥5000 kcal/day) were also excluded.

2.3. Data collection

Details on data collection are described in the Supplemental methods. Serum creatinine level was measured using the Jaffé method throughout the study period. For the main analysis eGFR was calculated using the MDRD equation [22]. For the sensitivity analysis, eGFR calculated through the CKD Epidemiology Collaboration (CKD-EPI) equation was used [23]. The creatinine levels were reduced by a calibration factor of 5% for standardization to isotope dilution mass spectrometry reference method values for CKD-EPI equation substitution [24,25]. Urine protein amounts were determined as absent, trace, 1+, 2+, or 3+, which approximately correlate with urine protein levels of <10, 10–20, >30, >100, and >500 mg/dL, respectively. The presence of proteinuria was considered for a urinalysis result higher than trace level.

2.4. Dietary zinc measurements

Single-day dietary data for nutrients including zinc (mg) and total calorie (kcal) intake were estimated based on semi quantitative FFQ that was collected with the assistance of trained interviewers by computer-based questionnaire programs or questionnaire booklets [26]. The questionnaire consisted of a food list that was leveled for nine intake frequencies and 3 intake amounts. The FFQ was composed of 103 items selected from the 1998 Korean Health and Nutrition Examination Survey, a nationwide dietary survey representing the entire South Korean population. For each food item questionnaire, the participant was asked to select frequency ranging from “never/seldom” to “3 times per day” for each food/dish or to “5 times or more per day” for beverages, as well as the amount, ranging from “small” to “large,” of food they consumed on average over the past year. A picture of each food/dish was provided in the questionnaire so that the subject could easily respond to the daily intake of each food item. Data were entered into the cohort epidemiology information system, analyzed by a nutrient database for each connected item, and systemically designed to calculate nutrient and food intakes for each participant. Total dietary nutrient component and calorie of each food item were calculated based on the seventh edition of the Food Composition Tables of the Korean Nutrition Society [27]. The validity and reproducibility for dietary zinc in this FFQ has been verified previously elsewhere [26,28]. Dietary zinc density was calculated as absolute zinc intake amount per daily energy intake (mg/1000 kcal day).

2.5. Outcome measurement

The primary endpoint was incident CKD development, which was defined as eGFR <60 ml/min/1.73 m^2 during the follow-up period.

2.6. Statistical analysis

Baseline characteristics were stratified based on dietary zinc density quartile. Cox proportional-hazards regression analysis was used to evaluate the relationship between dietary zinc intake and incident CKD development. To test the non-linearity relationship between dietary zinc intake and incident CKD risk, restricted cubic spline analyses were conducted with log-transformed zinc intake as a continuous variable due to distribution of dietary zinc density. The annual rate of renal function decline according to zinc intake group was determined by the slope of eGFR obtained from a linear mixed model. For sensitivity analysis, analyses were conducted excluding those who were dropped out within 3 years after enrollment. Evaluations using eGFR calculated through the CKD-EPI equation were also performed as sensitivity analyses. All analyses were performed by STATA (Version 16.1; Stata Corp, Texas, USA) and R language (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria). *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

In total, 7735 participants were included in the final analysis (Supplemental Fig. 1). The baseline characteristics of the participants are shown in Table 1. The mean age was 52.0 ± 8.8 years, and 47.5% were male. The mean estimated glomerular filtration rate (eGFR) was 92.1 ± 16.1 ml/min/1.73 m^2. The mean daily zinc consumption amount and daily energy intake were 8.6 ± 3.4 mg (8.1 ± 3.2 mg for women and 9.0 ± 3.5 mg for men) and 1933 ± 600 kcal/day, respectively. Mean zinc consumption density, calculated as amount of zinc intake per energy intake, was 4.4 ± 0.9 mg/1000 kcal. When stratified into quartiles by dietary zinc density, participants with higher education and income were allocated to the higher zinc consumption group. In contrast,

Table 1
Baseline characteristics according to dietary zinc density quartiles.

	Total (N = 7735)	Quartiles of Zinc density				*P*
		Q1 (N = 1934)	Q2 (N = 1934)	Q3 (N = 1934)	Q4 (N = 1933)	
Zinc consumption						
Absolute intake amount, mg	8.6 ± 3.4	6.6 ± 2.3	7.7 ± 2.4	8.8 ± 2.5	11.2 ± 4.0	<0.001
Intake density, mg/1000 kcal	4.4 ± 0.9	3.6 ± 0.2	4.0 ± 0.1	4.5 ± 0.1	5.6 ± 1.0	<0.001
Daily energy intake, kcal/day	1933 ± 600	1847 ± 623	1910 ± 581	1961 ± 564	2015 ± 616	<0.001
Vitamin & mineral supplement use	1487 (19.2)	269 (13.9)	367 (19.0)	414 (21.4)	437 (22.6)	<0.001
Demographic data						
Age, yr	52.0 ± 8.8	53.5 ± 9.0	52.3 ± 8.9	51.5 ± 8.5	50.8 ± 8.4	<0.001
Male	3676 (47.5)	855 (44.2)	861 (44.5)	916 (47.4)	1044 (54.0)	<0.001
Education						<0.001
Low	4332 (56.0)	1336 (69.1)	1154 (59.7)	1017 (52.6)	825 (42.7)	
Mid	2635 (34.1)	503 (26.0)	634 (32.8)	682 (35.3)	816 (42.2)	
High	768 (9.9)	95 (4.9)	146 (7.5)	235 (12.2)	292 (15.1)	
Income per month, KRW						<0.001
Low (<1 million)	3942 (51.0)	1303 (67.4)	1045 (54.0)	866 (44.8)	728 (37.7)	
Mid (1–2 million)	2440 (31.5)	449 (23.2)	610 (31.5)	682 (35.3)	699 (36.2)	
High (2 million)	1353 (17.5)	182 (9.4)	279 (14.4)	386 (20.0)	506 (26.2)	
Married	6976 (90.2)	1683 (87.0)	1743 (90.1)	1761 (91.1)	1789 (92.6)	<0.001
Smoking						<0.001
Never	4561 (59.0)	1171 (60.5)	1178 (60.9)	1159 (59.9)	1053 (54.5)	
Ever	1266 (16.4)	283 (14.6)	297 (15.4)	327 (16.9)	359 (18.6)	
Current	1908 (24.7)	480 (24.8)	459 (23.7)	448 (23.2)	521 (27.0)	
Current drinker	3683 (47.6)	778 (40.2)	896 (46.3)	944 (48.8)	1065 (55.1)	<0.001
Daily physical activity, MET h	1446.9 ± 893.3	1597.3 ± 961.0	1451.2 ± 885.6	1415.0 ± 878.4	1327.3 ± 824.0	<0.001
BMI, kg/m^2	24.6 ± 3.1	24.6 ± 3.3	24.5 ± 3.1	24.6 ± 3.0	24.6 ± 3.1	0.74
SBP, mmHg	120.4 ± 18.8	123.0 ± 19.3	120.2 ± 19.1	119.9 ± 18.3	118.7 ± 18.1	<0.001
DBP, mmHg	79.8 ± 12.1	80.9 ± 11.9	79.6 ± 12.0	79.4 ± 12.1	79.2 ± 12.1	<0.001
Comorbidities						
Hypertension	2911 (37.6)	759 (39.2)	715 (37.0)	755 (39.0)	682 (35.3)	0.03
Diabetes	1999 (25.8)	467 (24.1)	503 (26.0)	522 (27.0)	507 (26.2)	0.22
CVD	227 (2.9)	61 (3.2)	64 (3.3)	45 (2.3)	57 (2.9)	0.29
Laboratory parameters						
eGFR, ml/min/1.73 m^2	92.1 ± 16.1	92.9 ± 15.6	92.7 ± 16.2	91.6 ± 16.0	91.1 ± 16.4	<0.001
Glucose, mg/dL	86.8 ± 20.4	85.0 ± 16.8	86.3 ± 19.2	87.5 ± 24.0	88.6 ± 20.7	<0.001
Albumin, g/dL	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	<0.001
BUN, mg/dL	14.2 ± 3.5	14.0 ± 3.5	14.2 ± 3.6	14.2 ± 3.5	14.4 ± 3.4	0.03
Total cholesterol, mg/dL	190.8 ± 35.1	189.0 ± 34.6	189.3 ± 35.0	191.8 ± 35.6	193.1 ± 34.9	<0.001
HDL-C, mg/dL	44.0 (38.0–50.0)	43.0 (38.0–50.0)	43.5 (37.0–50.0)	44.0 (38.0–50.0)	43.0 (38.0–50.0)	0.29
Triglyceride, mg/dL	160.5 ± 102.8	161.7 ± 105.2	158.9 ± 98.8	161.3 ± 104.7	160.0 ± 102.3	0.82
CRP, mg/l	0.14 (0.06–0.24)	0.14 (0.06–0.25)	0.14 (0.06–0.24)	0.14 (0.06–0.23)	0.14 (0.07–0.24)	0.37
HBA1c, %	5.8 ± 0.9	5.7 ± 0.8	5.8 ± 0.9	5.8 ± 1.0	5.8 ± 0.9	0.19
HOMA-IR score	1.8 ± 1.4	1.8 ± 1.4	1.8 ± 1.7	1.7 ± 1.3	1.8 ± 1.1	0.80

Note: All continuous variables are expressed as mean ± SD, median (interquartile range), or proportion n (percentage).
Abbreviations: KRW, Korean Won; BMI, body mass index; MET, metabolic equivalent of task; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration; BUN, Blood urea nitrogen; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; HBA1c, glycated hemoglobin; HOMA-IR, Homeostatic model assessment-insulin resistance.

individuals in the higher zinc consumption group tended to have a lower eGFR and physical activity. Absolute zinc intake amount increases proportionally with zinc density quartile.

3.2. Development of incident CKD

During a median follow up of 11.5 (1.7–12.5) years and 70,617 person-years of observation, CKD developed in 1409 (18.2%) participants. The overall incidence rate of CKD was 20.0 (95% confidence interval [95% CI], 18.9–21.0) per 1000 person-years. The CKD development rate tended to be lower in subjects with higher dietary zinc density (*P* for trend = 0.001) (Fig. 1).

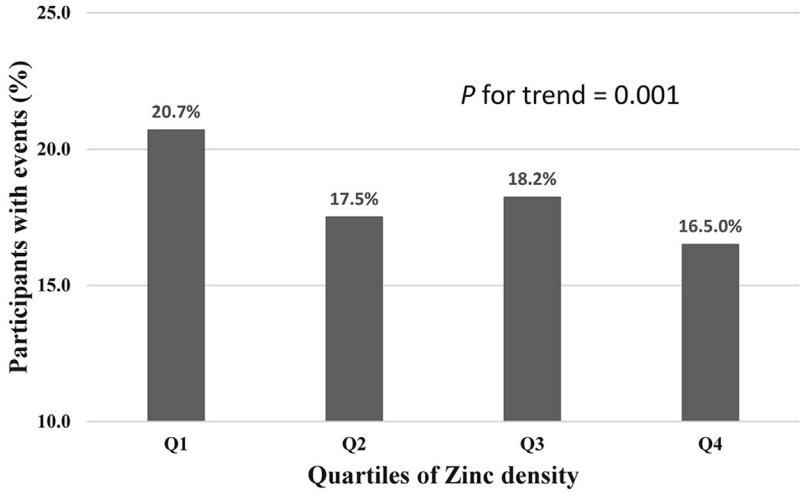
3.3. Impact of dietary zinc consumption on incident CKD development

The association of incident CKD risk and dietary zinc density was assessed using multivariable Cox regression models (Table 2). The risk of CKD development was significantly higher in the lowest zinc consumption group participants compared with the highest quartile group subjects (hazard ratio [HR], 1.36; 95% CI 1.18–1.58, $P < 0.001$). This association was robust even after adjustments for clinical, anthropometric, and laboratory confounding factors (HR, 1.20; 95% CI 1.04–1.40, $P = 0.02$).

To test the non-linearity association between zinc consumption amount and risk of incident CKD, restrictive cubic spline analyses were further conducted. A significant increase in HR for CKD development was noted when dietary zinc density was less than 4.4 mg/1000 kcal. In addition, the HR gradually increased with a decrease in dietary zinc density (Fig. 2).

3.4. Difference in the annual renal function decline rate among the zinc consumption groups

During the follow-up duration, eGFR declined at an average rate of −1.31 (95% CI, −1.33 to −1.28) ml/min/1.73 m^2 per year. Kidney function declined at a faster rate in the lowest zinc density quartile compared to the highest quartile (−1.43 vs −1.18 ml/min/1.73 m^2 per year, $P < 0.001$) (Table 3).



No. of Participants	1934	1934	1934	1933
No. of Events	400	338	352	319
Incidence rate (per 1000 person-years)	23.1 (20.9-25.4)	19.2 (17.3-21.4)	19.7 (17.8-21.9)	17.9 (16.0-19.9)

Fig. 1. Outcomes according to quartile of dietary zinc density.

Table 2
Risk of chronic kidney disease in quartile groups of dietary zinc consumption.

Models	Dietary zinc density quartile						
	Q1		Q2		Q3		Q4
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	
1	1.36 (1.18–1.58)	<0.001	1.10 (0.94–1.28)	0.25	1.12 (0.96–1.30)	0.15	Reference
2	1.20 (1.03–1.40)	0.02	1.02 (0.87–1.19)	0.83	1.06 (0.91–1.24)	0.42	
3	1.25 (1.07–1.46)	0.005	1.05 (0.90–1.22)	0.56	1.10 (0.94–1.28)	0.25	
4	1.20 (1.04–1.40)	0.02	1.01 (0.87–1.18)	0.87	1.10 (0.94–1.28)	0.92	

***Note*:** model 1: adjusted for age, sex, eGFR, vitamin & mineral supplement use, and total energy intake.
Model 2: model 1 + BMI, systolic blood pressure, education, income, diabetes, and cardiovascular disease.
Model 3: model 2 + C-reactive protein, HDL-C, and HOMA-IR score.
Model 4: model 3 + smoking status, alcohol consumption, and physical activity.
C-reactive protein, HDL-C, and HOMA-IR were log-transformed due to skewed distribution.
***Abbreviations*:** HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; BMI, body mass index; HDL-C, high-density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance.

3.5. Subgroup analysis

The relationship between zinc consumption amount and incident CKD was further evaluated in subgroups stratified by age (<60 or ≥60 years), sex (male or female), BMI (<25 kg/m^2 or ≥25 kg/m^2), diabetes (with or without), and hypertension (with or without). No significant interaction was found in any of the subgroups, suggesting that the relationship between zinc consumption and incident CKD risk was consistently significant across subgroups (Fig. 3).

3.6. Sensitivity analysis

Evaluations excluding subjects with a shorter than 3-year follow-up duration, yielded results consistent with the main analysis (Supplemental Table 1). In addition, evaluations were also made with eGFR values obtained through the CKD-EPI equation. Analyses evaluating CKD incidence, development risk, and renal function decline rate all revealed results similar to the main analysis (Supplemental Figs. 2 and 3, and Supplemental Tables 2 and 3).

4. Discussion

In this study, dietary zinc intake was significantly associated with incident CKD risk among the general population with preserved renal function. The CKD incidence rate was higher in lower dietary zinc consuming participants. In addition, risk of CKD development significantly increased in those whose dietary zinc intake was lower compared with average zinc-consuming individuals. This risk elevation was independent of confounding factors including total energy intake, comorbidities, and body anthropometric features.

Several approaches were used to examine the relationship between dietary zinc and CKD development. Comparing chronic kidney disease incidence among dietary zinc quartiles allows an estimation of the relationship between dietary zinc and kidney function. However, it is difficult to conclude an independent association with incidence comparison alone. On the other hand, Cox regression analysis and annual eGFR decline rate comparison intensifies the independent relationship between dietary zinc and

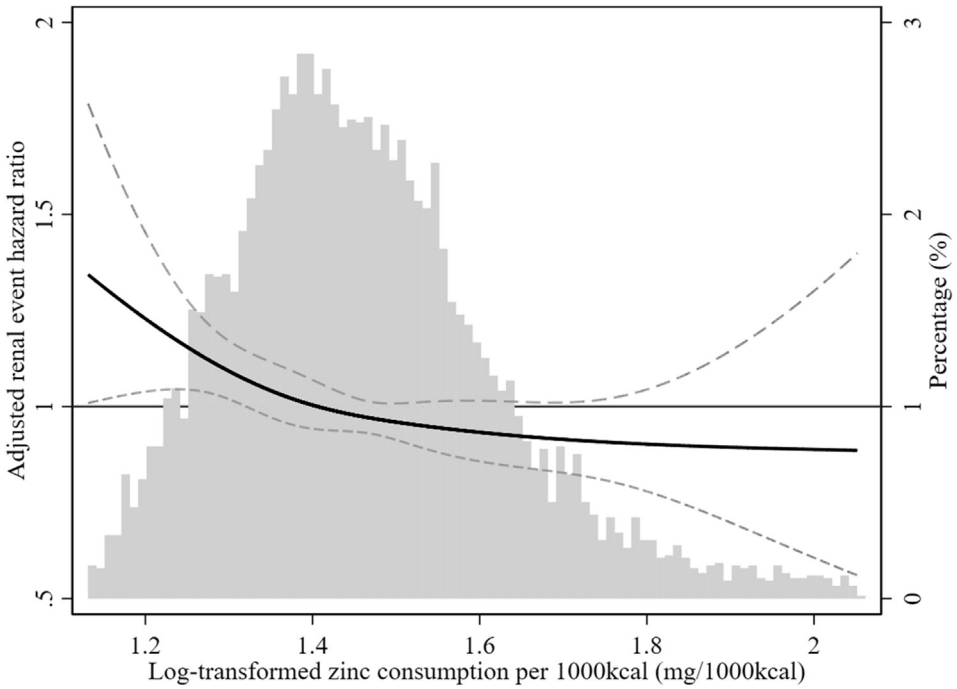


Fig. 2. Restricted cubic spline plot for incident chronic kidney disease according to dietary zinc density. ***Note:*** Adjusted for age, sex, eGFR, BMI, SBP, vitamin & mineral supplement use, education, income, diabetes, CVD, CRP, HDL-C, BMI, smoking status, HOMA-IR score, alcohol consumption, and physical activity. Mean zinc intake amount was considered as reference. ***Abbreviations:*** eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; CVD, cardiovascular disease; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance.

Table 3
Annual rate of renal function decline according to dietary zinc density quartiles.

Zinc density quartile	Slopes of eGFR decline (ml/min/1.73 m^2 per year)	*P*
Quartile 1	−1.43 (−1.48 to −1.38)	<0.001
Quartile 2	−1.37 (−1.42 to −1.32)	<0.001
Quartile 3	−1.25 (−1.30 to −1.20)	0.07
Quartile 4	−1.18 (−1.23 to −1.14)	Reference

Note: Adjusted for age, sex, eGFR, BMI, SBP, vitamin & mineral supplement use, education, income, diabetes, CVD, CRP, HDL-C, BMI, smoking status, HOMA-IR score, alcohol consumption, and physical activity.
Abbreviations: eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; CVD, cardiovascular disease; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance.

kidney function. Cox regression analysis demonstrates that lower dietary zinc consumption increases the risk of CKD development, while the annual eGFR decline rate comparison results show that the actual kidney function decline is steeper which ultimately leads to higher CKD event rates. The cubic spline analysis further visualizes the dietary zinc consumption and CKD development risk.

Zinc intake is related with development and progression of several chronic metabolic diseases [29–31]. In particular, a close association between insulin resistance and blood pressure has been repeatedly reported [17,20,32]. In a cross-sectional study of 3575 Indian participants, low zinc intake was associated with higher prevalence of coronary artery disease, diabetes, and altered metabolic surrogate markers [17]. Similarly, in 12,028 Chinese participants, adequate zinc consumption was associated with reduced diastolic blood pressure and fasting glucose levels in females [20]. Concordantly, in this study, systolic blood pressure and diastolic blood pressure were significantly higher in those consuming smaller amounts of zinc. In addition, metabolic syndrome was more prevalent among lower zinc-consuming participants, supporting the previously reported link between dietary zinc and metabolic derangement [17].

One of the main strengths of this study is the prospective design. Dietary habits are bound to change when CKD is diagnosed. Therefore, it is noteworthy that the dietary data were collected prior to development of CKD in participants with normal kidney function. In addition, since kidney function decline usually shows an indolent progress, the long follow-up duration is an indispensable advantageous characteristic of the study. Moreover, the population-based cohort, which consisted of relatively healthy participants compared with hospital-based studies, and the considerably large sample size, should also be noticed as a merit.

This study has several limitations. First, food frequency questionnaire (FFQ) was surveyed only at baseline. Therefore, the diet pattern changes over time could not be considered in the analysis. Second, serum zinc concentration level was not available. However, serum zinc level has been found to be a poor surrogate of body zinc homeostasis [33]. This is supported by the fact that serum zinc level is not associated with chronic metabolic disease, although there is an accumulation of reports showing a positive link between dietary zinc and poor outcome. Third, data on zinc supplementation was not available. However, information on vitamin & mineral supplementation in general was included in the analyses which would have

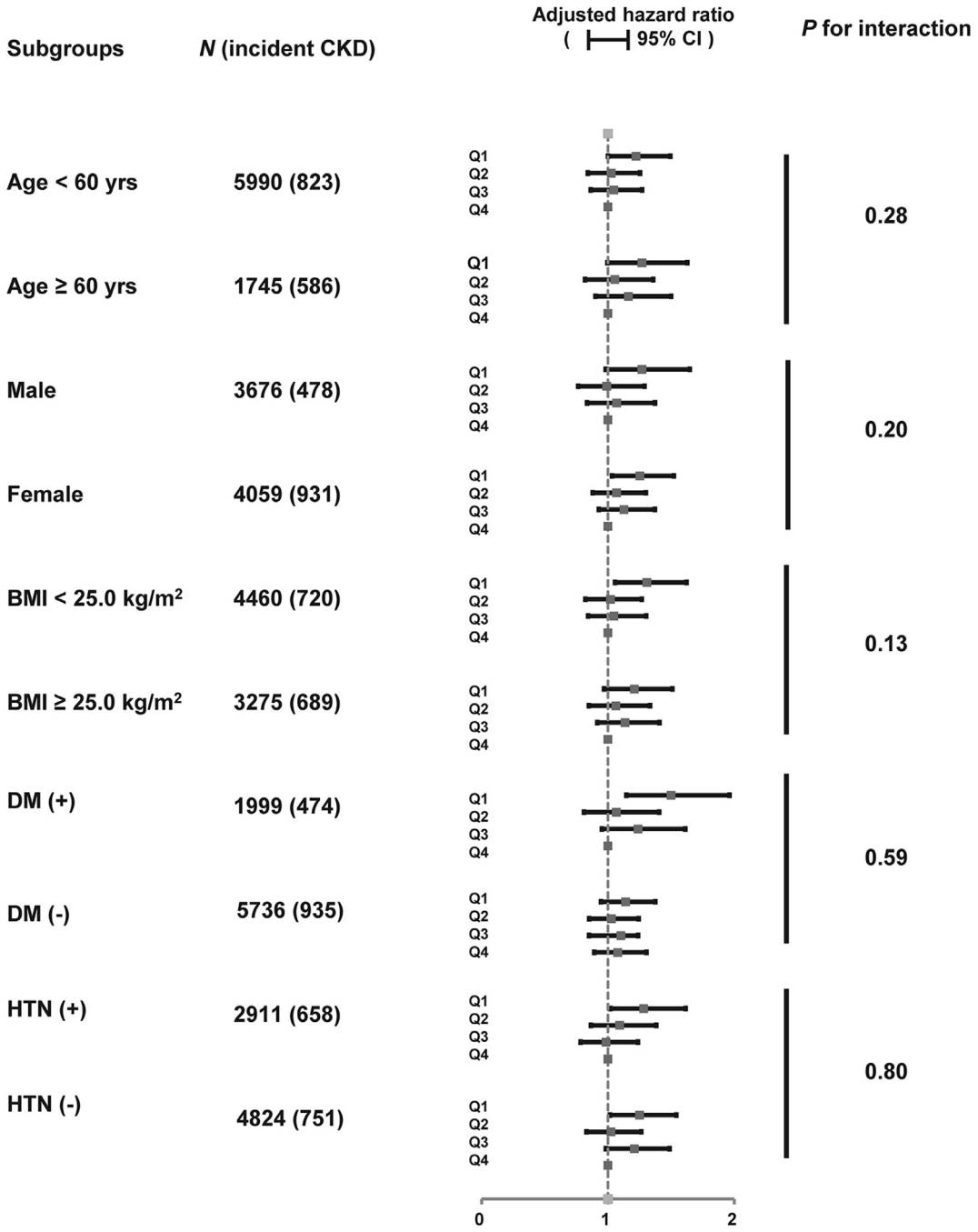


Fig. 3. Forest plots for subgroup analyses of incident CKD development according to quartile of zinc consumption. ***Note:*** Adjusted for age, sex, eGFR, BMI, SBP, vitamin & mineral supplement use, education, income, diabetes, CVD, CRP, HDL-C, BMI, smoking status, HOMA-IR score, alcohol consumption, and physical activity. ***Abbreviations***: CKD, chronic renal disease; CI, confidence interval; BMI; body mass index; DM, diabetes mellitus; HTN, hypertension.

lowered the chances of bias to some extent. Fourth, the participants consisted of an Asian population in a single country. Since dietary habits vary among ethnicity and cultural backgrounds, further investigations including other cultures are needed to generalize the results. In particular, the zinc consumption amount in this study was somewhat lower than that reported in Western countries [34,35]. Nonetheless, the reported amount still corresponds to the Korean Recommended Nutrient Intake (RNI) for zinc [36]. Finally, a clear causal relationship between zinc consumption and incident CKD could not be ascertained due to the observational nature of this study.

In conclusion, in this community-based prospective cohort of participants with preserved renal function, low zinc intake was associated with a significantly increased risk of incident CKD. Further studies are warranted to elucidate the mechanisms underlying this relationship.

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None.

Statement of authorship

Y.S.J., H.W.K and J.T.P. made conception and design of the study; Y.S.J., H.W.K, K.H.N., H.R.Y., S.L., J.H.J., and J.T.P. acquired the data;

Y.S.J., H.W.K., K.H.N., H.R.Y., S.L., J.H.J, S.H.H., T.H.Y., J.T.P., and S.W.K analyzed the data; Y.S.J, H.W.K. and K.H.N. made the figures; Y.S.J. and J.T.P. drafted paper; S.H.H., T.H.Y., and S.W.K. supervised the study; All authors contributed to important intellectual contents during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work were appropriately investigated and resolved.

Conflicts of interest

The authors declare that they have no relevant interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.07.005.

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