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The Prognostic Significance of Body Mass Index and Metabolic Parameter Variabilities in Predialysis CKD: A Nationwide Observational Cohort Study

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ABSTRACT

Background The association between variabilities in body mass index (BMI) or metabolic parameters and prognosis of patients with CKD has rarely been studied.

Methods In this retrospective observational study on the basis of South Korea's national health screening database, we identified individuals who received ≥3 health screenings, including those with persistent predialysis CKD (eGFR <60 ml/min per 1.73 m^2 or dipstick albuminuria ≥1). The study exposure was variability in BMI or metabolic parameters until baseline assessment, calculated as the variation independent of the mean and stratified into quartiles (with Q4 the highest quartile and Q1 the lowest). We used Cox regression adjusted for various clinical characteristics to analyze risks of all-cause mortality and incident myocardial infarction, stroke, and KRT.

Results The study included 84,636 patients with predialysis CKD. Comparing Q4 versus Q1, higher BMI variability was significantly associated with higher risks of all-cause mortality (hazard ratio [HR], 1.66; 95% confidence interval [95% CI], 1.53 to 1.81), *P* [for trend] <0.001), KRT (HR, 1.20; 95% CI, 1.09 to 1.33; *P*<0.001), myocardial infarction (HR, 1.19; 95% CI, 1.05 to 1.36, *P*=0.003), and stroke (HR, 1.19; 95% CI, 1.07 to 1.33, *P*=0.01). The results were similar in the subgroups divided according to positive or negative trends in BMI during the exposure assessment period. Variabilities in certain metabolic syndrome components (*e.g.*, fasting blood glucose) also were significantly associated with prognosis of patients with predialysis CKD. Those with a higher number of metabolic syndrome components with high variability had a worse prognosis.

Conclusions Higher variabilities in BMI and certain metabolic syndrome components are significantly associated with a worse prognosis in patients with predialysis CKD.

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CKD is a major morbidity that is associated with a substantial socioeconomic burden.[1] Patients with CKD suffer from high risks of cardiovascular disease and mortality. The prevalence of CKD is projected to increase, due to the global trend of aging populations and increasing rates of obesity.

Because the development and prognosis of CKD is largely associated with hypertension and diabetes,[2] body mass index (BMI), which is closely related to these two metabolic disorders, has been considered an important clinical factor with prognostic

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significance in the CKD population. Because BMI and metabolic syndrome status change dynamically in the general population, recent population-scale evidence has shown the variability in BMI and metabolic syndrome components has distinct prognostic significance for various adverse outcomes, including kidney function impairment.[3,4] Higher BMI variability, or weight cycling, has been reported to increase fat components or reflect metabolic instability and has further been associated with higher risks of cardiovascular diseases and mortality.[5] However, there have been few large-scale studies including patients with CKD that have investigated the prognostic significance of BMI or metabolic parameter variability in the context of important health outcomes. Such evidence would encourage health care providers to pay attention to recent trends in BMI and metabolic status, which could help clinicians appropriately interpret important clinical parameters in the growing CKD population. In particular, because higher baseline BMI is associated with a better prognosis in patients with CKD (*i.e.*, "the obesity paradox"),[6] which conflicts with the idea that a higher BMI increases the risk of adverse outcomes in the general population,[7] additional investigation of the prognostic significance of another BMI parameter, BMI variability, is warranted.

In this study, we aimed to investigate the association between BMI and metabolic syndrome component variability and risks of adverse outcomes in patients with predialysis CKD in a nationwide health screening database linked to claims information in South Korea. We studied the risks of all-cause mortality, myocardial infarction, stroke, and progression to the state requiring maintenance KRT, with consideration of the trends in BMI. We further extended our assessment to the variability of various metabolic syndrome components, which also reflect fluctuations in metabolic status. We hypothesized that a higher BMI or metabolic parameter variability would be associated with higher risks of adverse outcomes in patients with CKD, independent of baseline metabolic parameters.

Significance statement

The prognostic significance of variabilities in body mass index (BMI) or metabolic parameters in patients with CKD is uncertain. In this observational cohort study of 84,636 patients with predialysis CKD in South Korea, the authors analyzed the association between variability of BMI or various metabolic parameters and risks of all-cause mortality and incident myocardial infarction, stroke, and requirement for KRT. They found that elevated variability in BMI or certain metabolic parameters was associated with higher risks of adverse outcomes, independent of baseline metabolic status. These findings may encourage clinicians in the nephrology field to carefully assess not only baseline BMI or metabolic status in patients with CKD, but also the fluctuating status of metabolic parameters, due to their potential prognostic significance in such patients.

METHODS

Ethics Considerations

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board of Seoul National University Hospital (E-2001–112–1096). The investigation of the Korea National Health Insurance Service (NHIS) database was approved by the relevant government organization (REQ000034394). The need to obtain informed consent was waived by the above organizations, because the study was observational and investigated anonymous public databases.

Study Setting

This study was a retrospective observational cohort study. The study data comprised nationwide health screening data from the Korea NHIS, which have been previously described.[8,9] In South Korea, a free-of-charge nationwide health screening program is provided to the general adult population that includes clinicodemographic assessments, lifestyle evaluations, and laboratory tests.[2] Health screening is provided annually or biennially, and the quality of health screening centers is monitored and controlled by the NHIS. The data are also linked to the nationwide claims database, which includes information on all insured medical services nationwide. Because national health insurance is provided to all Korean citizens and essential medical services are generally insured, the database has been utilized for many population-scale studies investigating outcomes, including cardiocerebrovascular diseases, ESKD, and mortality.[3,10–12]

In this study, BMI variability was identified on the basis of the BMI calculated at every health screening visit. The health screenings also involve laboratory tests and waist circumference measurements to assess major metabolic syndrome components. Predialysis CKD was identifiable on the basis of serum creatinine levels and dipstick albuminuria, which were measured at every health screening visit with ≥1-year intervals, and insurance codes specified ESKD events. The study outcomes and medical histories were collected from the claims database. A graphical description of the time windows for determining the study population, collecting the covariate data, and identifying the outcomes is presented in Figure 1.[13]

Study Population

The study identified individuals who had undergone baseline health screenings from 2013 to 2014. As multiple health screenings are needed to calculate BMI or metabolic parameter variability, the study included individuals who had ≥3 health screenings before the baseline visit. After excluding those with missing information for the collected variables, those who had persistent predialysis CKD (eGFR <60 ml/min per 1.73 m^2 or dipstick albuminuria ≥1+) in the baseline assessment period were retained in the study population, with the exclusion of patients with ESKD with an eGFR <15 ml/min per 1.73 m^2. Because we aimed to investigate the risks

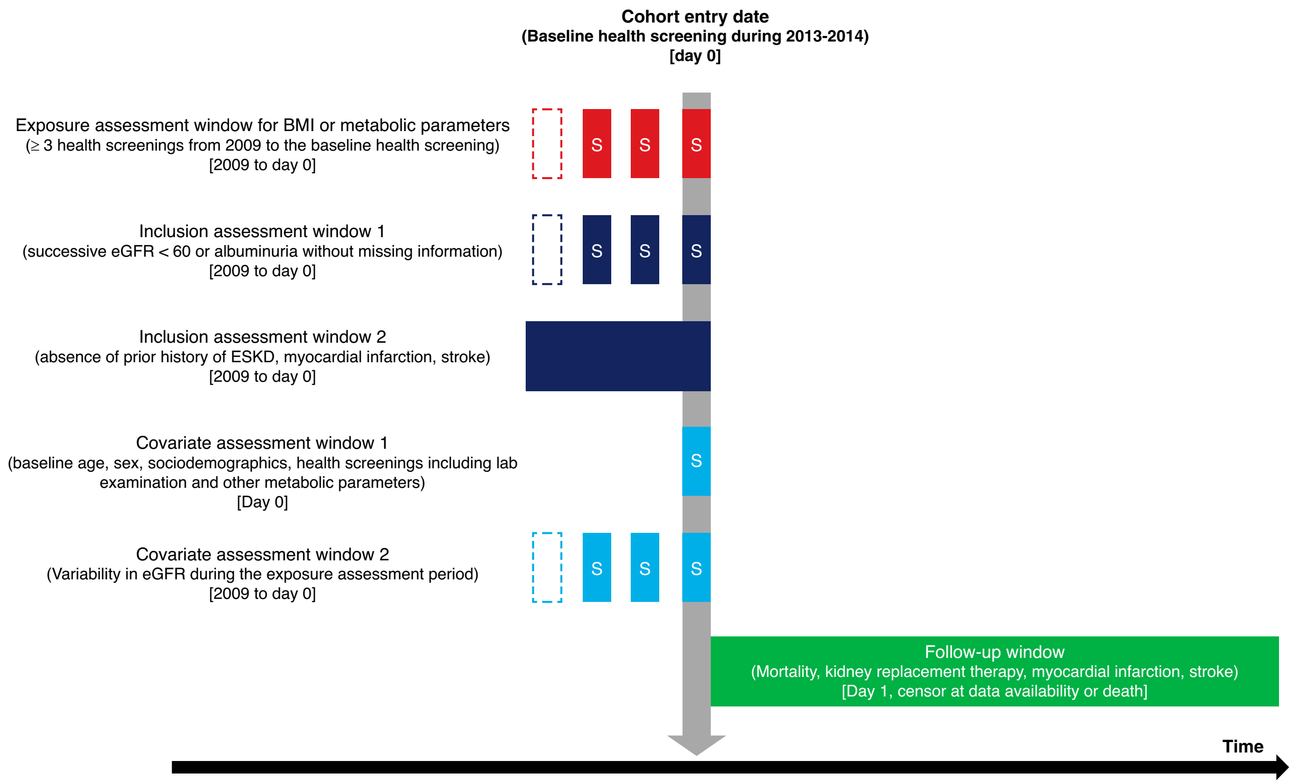


Figure 1. Graphical depiction of the time windows used to determine the studied variables. S indicates the national health screenings that were mostly performed at annual or biennial intervals.

of incident events of myocardial infarction, stroke, and maintenance KRT, those who had a history of the outcomes before follow-up were excluded.

Ascertainment of BMI Exposure

BMI values were calculated from the height and weight measured at the health screening visits. BMI variability was primarily determined by variation independent of the mean (VIM).[3] The VIM has advantages over other variability indexes, because the parameter is calculated from a regression model to be independent of the mean level. The other well-known variability indexes were also calculated, including standard deviation; coefficient of variation, which divides the standard deviation by the mean value; and average real variability, calculated as the sum of the differences between adjacent values divided by the number of gaps. The collected exposures were divided into quartiles, and high variability was defined as the highest quartile (Q4) variability level. The baseline BMI was also utilized as a supplemental exposure, to determine whether an inverse association between baseline BMI and the survival of patients with CKD also existed in this cohort.

Ascertainment of Metabolic Syndrome Component Exposure

We extended our assessment to various metabolic parameters, because BMI variability was likely to be closely linked to variabilities in metabolic syndrome components. The assessed metabolic parameters included the components of metabolic syndrome defined in the harmonized criteria[14]: waist circumference, fasting blood glucose, systolic BP, diastolic BP, serum triglycerides, and HDL. We also assessed other cholesterol parameters, including low-density lipoprotein and total cholesterol levels. The VIM was calculated as above and stratified into quartiles.

Construction of Cumulative Metabolic Variability Score

We constructed an ordinal score to reflect the overall burden of metabolic variability. We defined the score by summing the number of high-variability (Q4) metabolic parameters, selecting a component from each metabolic syndrome domain (obesity, impaired glucose tolerance, high BP, and dyslipidemia).[3] BMI, fasting blood glucose, systolic BP, and total cholesterol were included in the ordinal scoring as in a previous study.[3]

Ascertainment of Study Outcomes

The main study outcome was all-cause mortality on the basis of the claims database, which includes nationwide mortality events collected from the death certificates. Additional incident risks of major adverse outcomes in patients with predialysis CKD were collected. Incident KRT was determined by specific insurance coverage codes for “maintenance” KRT in the NHIS data, including hemodialysis, peritoneal dialysis, and transplantation events. As in the previous study,[3] myocardial infarction was recorded if an individual had International Classification of Diseases 10th revision (ICD-10) codes I21 or I22 during hospitalization, or if these codes were issued ≥2 times. Stroke was defined as ICD-10 codes I63 or I64 during hospitalization, with claims information for brain magnetic resonance imaging or brain computerized tomography imaging. Follow-up was initiated after the date of the baseline health screening visit at which the variability exposure assessment was completed (day 1) and was censored on the last date of data availability or at the date of death, to consider the competing risk by mortality (Figure 1).

Collection of the Covariate Data

We aimed to include a range of data, including demographic information, lifestyle factors, baseline kidney function, and various metabolic parameters, as covariates.[3] We collected baseline age, sex, waist circumference, current smoking history, alcohol intake (>0 g of alcohol intake per day), regular physical activity (moderate-intensity physical activity ≥5 days or vigorous-intensity physical activity ≥3 days per week), low-income status (lower quartile of the nation), diabetes mellitus (ICD-10 codes E11–14 with relevant antidiabetes medication history), hypertension (ICD-10 codes I10–13 or I15 with relevant antihypertensive medication history), dyslipidemia (ICD-10 code E78 with relevant dyslipidemia medication history), chronic lung disease (ICD-10 codes J41–44), cancer (specific insurance code for malignancies in the NHIS data), baseline eGFR, presence of dipstick albuminuria (≥1+), fasting glucose, systolic BP, diastolic BP, high-density lipoprotein, low-density lipoprotein, and triglycerides. We also calculated the variability in eGFR during the exposure assessment period, because including the covariates in the multivariable model could adjust the effects of a direct association between BMI variability and eGFR variability.[15] In addition, the number of examinations during the exposure period was also collected as a covariate, because the number of examinations could affect variability parameters or reflect the health-seeking behavior of a subject.

Statistical Analysis

We first assessed the risk of adverse outcomes according to BMI exposure, both ordinal or continuous, by Cox regression analysis. In addition to the univariable model and a model adjusted for age, sex, and the number of exams, a multivariable model including various collected covariates was constructed. To show the cumulative risks of the study outcomes, we plotted adjusted survival curves on the basis of the final multivariable model. We also performed subgroup analyses, with stratification according to sex, baseline BMI ≥25 kg/m^2, the presence of diabetes, and baseline eGFR <60 ml/min per 1.73 m^2. Furthermore, we assessed interactions by calculating interaction term *P* values in the multivariable model. We selected BMI ≥25 kg/m^2, which is the definition for overweight in the international guidelines, because obesit is determined by the cutoff in the Korean guidelines on the basis of the nationwide BMI distribution.[16] Because this value was close to the mean level in the study population, selecting it was further supported by the fact it would divide participants into subgroups with similar numbers.

In addition, because the clinical significance of BMI variability may be different in those with increasing and decreasing trends in BMI, we determined the trends by calculating the linear regression slope of the individuals' collected BMI values. An increasing trend was defined as a slope ≥0 (positive), and a decreasing trend was defined as a slope <0 (negative). The Cox regression analysis described above was also performed in the subgroups stratified by the BMI changes and the quartiles of BMI variability.

Next, the variability in the collected metabolic parameters and their associations with the adverse outcomes were assessed by Cox regression analysis as above. Finally, the ordinal score for overall metabolic variability was constructed as described above, and its association with the risks of adverse outcomes were assessed by Cox regression analysis, as above.

All statistical analyses were performed with SAS (version 9.4, SAS institute), and two-sided *P* values <0.05 were considered statistically significant. When the ordinal outcome was included in the regression models as the exposure variable, the *P* for trend for the higher exposure grades was calculated. Interaction term *P* values <0.1 were considered indicative of the possible presence of an interaction.

RESULTS

Study Population

We identified 11,651,753 individuals who underwent ≥3 health screenings during the exposure assessment period (Figure 2). There were 5,402,903 individuals with two health screenings; however, although the information may determine CKD, this population was not considered because metabolic variabilities require ≥3 health screenings. Among them, 128,658 individuals had a persistent eGFR <60 ml/min per 1.73 m^2 or dipstick albuminuria ≥1. After excluding those with prevalent ESKD, myocardial infarction, and stroke, 84,636 patients with predialysis CKD with identifiable BMI or metabolic parameter variability were included in the study population.

Baseline Characteristics

The study population had a median age of 68 (IQR, 60–74) years old, and 51% were male. The median BMI value was 24.6 (IQR, 22.6–26.7) kg/m^2. When we stratified the characteristics according to BMI variability (Table 1), the number of health exams did not show a linear trend according to

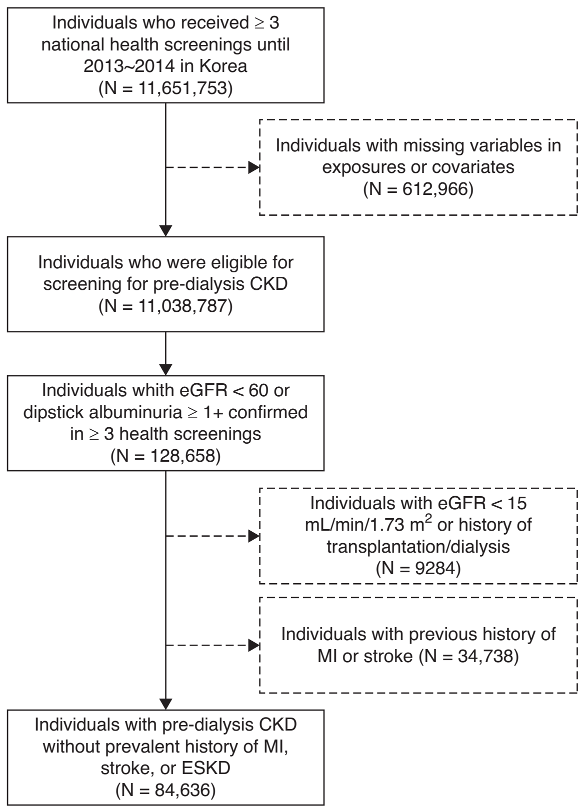


Figure 2. Study population. MI, myocardial infarction.

BMI variability. Those with lower BMI variability had a higher proportion of individuals who engaged in regular physical activity. The prevalence of diabetes was the highest in those with high BMI variability, which was also the stratum with the highest proportion of subjects who had a baseline eGFR ≥60 ml/min per 1.73 m^2 but had albuminuria. The distributions of the other metabolic parameters were relatively similar among the BMI variability quartiles.

Prognosis According to Baseline BMI and BMI Variability

During the median follow-up of 4.0 (IQR, 3.4–4.5) years, 4782 (6%) mortality, 3276 (4%) maintenance KRT, 1839 (2%) myocardial infarction, and 2666 (3%) stroke events were identified. In the regression analysis, baseline BMI was inversely associated with the risks of all studied adverse outcomes after multivariable adjustment (Supplemental Table 1). However, those with higher BMI variability had significantly higher risks of adverse outcomes (Table 2, Figure 3). Those with high (Q4 VIM) BMI variability had approximately 60% higher hazards for all-cause mortality and 20% higher hazards for myocardial infarction, stroke, and KRT, than those with low variability (Q1 VIM), even after adjusting for various characteristics, including baseline BMI, baseline eGFR, and eGFR variability during the exposure assessment period. The results were similar when other variability indexes were used as the exposure variable (Supplemental Table 2).

Subgroup Analysis Results for BMI Variability

After stratification by sex, there was a suspected interaction with all-cause mortality; otherwise, the interactions were nonsignificant (Supplemental Table 3). Nevertheless, the risk of all-cause mortality was significantly higher in those with higher BMI variability in both sex subgroups, and this was similar to the result for KRT risk in the fully adjusted model (Supplemental Table 4). Although the statistical significance remained in the model adjusted by age, sex, and number of health screenings, the significance was attenuated for stroke or myocardial infarction outcome.

Baseline BMI ≥25 kg/m^2 had possible interactions with all-cause mortality and KRT outcomes (Supplemental Table 3). However, the results were significant for both all-cause mortality and the need for KRT regardless of whether baseline BMI was ≥25 kg/m^2 (Supplemental Table 5). Statistical significance was attenuated for myocardial infarction and stroke in those with baseline BMI ≥25 kg/m^2.

Diabetes had a significant interaction with the need for KRT (Supplemental Table 3). However, the association between high BMI variability and KRT risk remained significant regardless of the presence of diabetes (Supplemental Table 6). Some attenuation was identified for myocardial infarction or stroke risk, yet there were nonsignificant interactions with diabetes for outcomes according to the presence of diabetes.

Baseline eGFR <60 ml/min per 1.73 m^2 showed significant interactions with the risk of KRT but not other adverse outcomes (Supplemental Table 3). However, the risk for necessity of KRT was higher in those with higher BMI variability in both subgroups, including those with reduced eGFR and with preserved eGFR (Supplemental Table 7). There was some attenuation of the significance for myocardial infarction and stroke in those with baseline eGFR ≥60 ml/min per 1.73 m^2; however, the assessed number of subjects was small, with a low incidence rate of adverse outcomes in the subgroup.

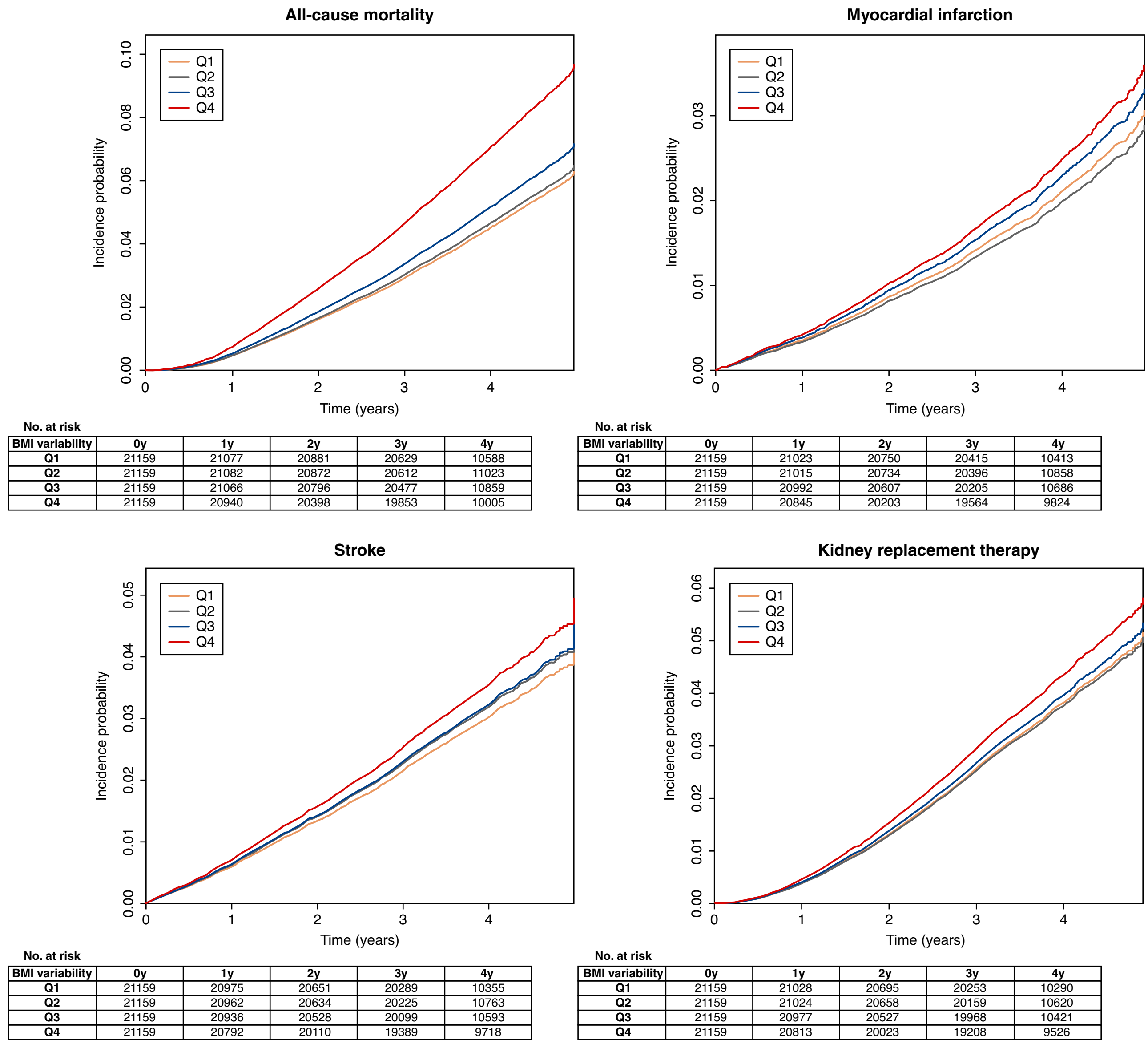
Analysis of Trends in BMI

When the slope of the change in BMI was calculated, there were 38,157 (45%) individuals with an increasing BMI trend (≥0 regression beta), whereas 46,479 (55%) individuals had a decreasing trend in BMI. The analysis of the trends in BMI yielded significant results, indicating a possible interaction for all-cause mortality (Supplemental Table 3). When we assessed the prognostic significance in the subgroups stratified by trend in BMI, higher BMI variability was significantly associated with higher risks of all-cause mortality and KRT in the multivariable model (Table 3). Although statistical significance was not achieved for stroke in those with an increasing BMI trend or for myocardial infarction and stroke in those with a decreasing BMI trend, the interaction term analysis indicated there was an absence of a significant interaction for the outcomes according to the trend in BMI (Supplemental Table 3).

Table 1. Baseline characteristics of the study population according to BMI variability

Characteristics	Total (n=84,636)	Q1 (n=21,159)	Q2 (n=21,159)	Q3 (n=21,159)	Q4 (n=21,159)
Age, yrs	68 (60, 74)	68 (60, 74)	68 (58, 74)	68 (60, 74)	70 (62, 76)
Male sex	41,665 (49)	11,397 (54)	11,096 (52)	10,421 (49)	8751 (41)
BMI, kg/m^2	24.61 (22.59, 26.73)	25 (23.18, 26.95)	24.75 (22.86, 26.78)	24.56 (22.59, 26.67)	24 (21.72, 26.44)
BMI variability					
Variation independent mean, unit	0.64 (0.40, 0.98)	0.27 (0.19, 0.34)	0.52 (0.46, 0.58)	0.78 (0.71, 0.87)	1.3 (1.11, 1.65)
Standard deviation, kg/m^2	0.66 (0.41, 1.02)	0.27 (0.2, 0.36)	0.54 (0.47, 0.61)	0.81 (0.72, 0.92)	1.35 (1.14, 1.71)
Coefficient of variation, %	2.69 (1.68, 4.11)	1.13 (0.8, 1.45)	2.17 (1.93, 2.42)	3.29 (2.98, 3.67)	5.47 (4.68, 6.95)
Actual real variability, kg/m^2 per measure	0.77 (0.48, 1.19)	0.33 (0.21, 0.44)	0.63 (0.5, 0.8)	0.92 (0.75, 1.17)	1.54 (1.2, 2.05)
Number of health screenings					
3	74,407 (88)	18,990 (90)	17,926 (85)	18,242 (86)	19,249 (91)
4	5680 (7)	1248 (6)	1621 (8)	1632 (8)	1179 (6)
5	4549 (5)	921 (4)	1612 (8)	1285 (6)	731 (3)
Social factors					
Urban residence	38,315 (45)	9956 (47)	9861 (47)	9627 (46)	8871 (42)
Low income (<25th percentile)	15,790 (19)	3629 (17)	3918 (19)	3985 (19)	4258 (20)
Lifestyle factors					
Current smoker	10,374 (12)	2549 (12)	2724 (13)	2699 (13)	2402 (11)
Alcohol intake (> 0 g/day)	22,862 (27)	6319 (30)	6298 (30)	5840 (28)	4405 (21)
Regular physical activity	19,242 (23)	5285 (25)	5131 (24)	4848 (23)	3978 (19)
Comorbidities					
Diabetes mellitus	25,019 (30)	5809 (27)	5919 (28)	6196 (29)	7095 (34)
Hypertension	58,703 (69)	14,587 (69)	14,483 (68)	14,736 (70)	14,897 (70)
Cancer	3608 (4)	797 (4)	830 (4)	894 (4)	1087 (5)
Chronic lung disease	9689 (11)	2181 (10)	2256 (11)	2443 (12)	2809 (13)
Dyslipidemia	36,697 (43)	9136 (43)	9202 (43)	9272 (44)	9087 (43)
Chronic heart failure	4232 (5)	862 (4)	913 (4)	1057 (5)	1400 (7)
Atrial fibrillation	2327 (3)	498 (2)	551 (3)	600 (3)	678 (3)
Medication history					
ACE I or ARB	33,419 (39)	8429 (40)	8531 (40)	8278 (39)	8181 (39)
Insulin	7425 (9)	1510 (7)	1656 (8)	1838 (9)	2421 (11)
Statin	34,313 (41)	8514 (40)	8559 (40)	8663 (41)	8577 (41)
Laboratory/anthropometric findings					
Waist circumference, cm	86 (80, 91)	86 (80, 91)	85 (79, 90)	84 (79, 90)	83 (77, 90)
Systolic BP, mmHg	130 (120, 139)	130 (120, 139)	130 (120, 139)	130 (120, 139)	130 (120, 140)
Diastolic BP, mmHg	79 (70, 83)	79 (70, 83)	79 (70, 83)	79 (70, 83)	79 (70, 83)
Fasting glucose, mg/dl	101 (92, 117)	101 (92, 117)	100 (91, 117)	100 (91, 117)	101 (91, 118)
Total cholesterol, mg/dl	188 (163, 216)	188 (163, 216)	189 (163, 218)	188 (162, 217)	185 (159, 215)
HDL, mg/dl	48 (40, 57)	48 (40, 57)	48 (41, 57)	48 (41, 58)	49 (41, 59)
LDL, mg/dl	109 (85, 134)	109 (85, 134)	109 (85, 135)	108 (84, 134)	106 (83, 133)
Triglycerides, mg/dl	134 (96, 188)	134 (96, 188)	134 (95, 188)	131 (94, 184)	126 (91, 178)
Hemoglobin, g/dl	13.4 (12.2, 14.7)	13.4 (12.2, 14.7)	13.3 (12.1, 14.6)	13.1 (12, 14.4)	12.7 (11.5, 13.9)
Urine albuminuria, ≥ 1+	27220 (32)	6823 (32)	6976 (33)	6913 (33)	6508 (31)
Serum Cr,mg/dl	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)	1.3 (1.1, 1.5)
eGFR, ml/min per 1.73 m^2		52.9 (45.85, 58.52)	52.74 (45.46, 58.56)	52.28 (44.5, 58.35)	51.41 (42.39, 57.71)
≥60	4905 (6)	960 (5)	1085 (5)	1241 (6)	1619 (8)
≤30 to <60	65844 (78)	16634 (79)	16400 (78)	16345 (77)	16465 (78)
≤15 to <30	13887 (16)	3565 (17)	3674 (17)	3573 (17)	3075 (15)

Continuous variables are presented as medians (interquartile ranges), and categorical variables are presented as frequencies (percentages). There were no missing data in the table.



All-cause mortality — No. at risk

BMI variability	0y	1y	2y	3y	4y
Q1	21159	21077	20881	20629	10588
Q2	21159	21082	20872	20612	11023
Q3	21159	21066	20796	20477	10859
Q4	21159	20940	20398	19853	10005

Myocardial infarction — No. at risk

BMI variability	0y	1y	2y	3y	4y
Q1	21159	21023	20750	20415	10413
Q2	21159	21015	20734	20396	10858
Q3	21159	20992	20607	20205	10686
Q4	21159	20845	20203	19564	9824

Stroke — No. at risk

BMI variability	0y	1y	2y	3y	4y
Q1	21159	20975	20651	20289	10355
Q2	21159	20962	20634	20225	10763
Q3	21159	20936	20528	20099	10593
Q4	21159	20792	20110	19389	9718

Kidney replacement therapy — No. at risk

BMI variability	0y	1y	2y	3y	4y
Q1	21159	21028	20695	20253	10290
Q2	21159	21024	20658	20159	10620
Q3	21159	20977	20527	19968	10421
Q4	21159	20813	20023	19208	9526

Figure 3. Adjusted survival curves showing the cumulative risks of the study outcome. The *y* axes indicate cumulative adjusted incidence probability, and the *x* axes indicate the time (years). The survival curves are stratified by BMI variability quartiles (black: Q1, low variability; red: Q2; green: Q3; and blue: Q4, high variability). The survival tables are presented below the adjusted survival curves. A multivariable model was adjusted for age, sex, number of exams, current smoking, alcohol consumption, regular physical activity, low-income status, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline BMI, waist circumference, fasting glucose, systolic BP, diastolic BP, HDL, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Prognosis According to Metabolic Parameter Variability

When variabilities of other metabolic parameters were considered (Table 4), the metabolic parameters with higher variability that were significantly associated with a higher risk of all-cause mortality in the fully adjusted model were waist circumference, fasting blood glucose, systolic BP, diastolic BP, total cholesterol, LDL cholesterol, and HDL cholesterol. For the risk of myocardial infarction, fasting blood glucose, and high-density lipoprotein cholesterol variabilities, with both categorical and continuous exposures, were significant. For the risk of stroke, variabilities in fasting blood glucose, diastolic BP, and high-density lipoprotein were prominently associated with the outcomes in the multivariable model. Fasting blood glucose and total cholesterol variabilities were significantly associated with the risk of the need for KRT in the fully adjusted model.

Table 2. Risk of adverse outcomes according to BMI variability (VIM) in patients with predialysis CKD

Outcome	BMI Variability Independent of Mean Exposure		*N*	Event	Follow-up Person-years	Incidence Rate (/1000 Person-years)	Univariable Model		Age, Sex, and Number of Exams Adjusted Model		Multivariable Model[a]	
							HR (95% CI)	*P* for trend	Adjusted HR (95% CI)	*P* for trend	Adjusted HR (95% CI)	*P* for trend
All-cause mortality	Continuous				NA		1.37 (1.33 to 1.40)	<0.001	1.30 (1.26 to 1.33)	<0.001	1.20 (1.17, 1.23)	<0.001
	Categorical	Q1 (low)	21,159	847	82,939	10.21	Reference	<0.001	Reference	<0.001	Reference	<0.001
		Q2	21,159	878	83,500	10.52	1.03 (0.93 to 1.13)		1.07 (0.97 to 1.17)		1.03 (0.94 to 1.14)	
		Q3	21,159	1105	83,184	13.28	1.297 (1.186 to 1.419)		1.298 (1.187 to 1.420)		1.172 (1.071 to 1.282)	
		Q4 (high)	21,159	1952	81,560	23.93	2.349 (2.167 to 2.547)		2.068 (1.906 to 2.244)		1.662 (1.530 to 1.806)	
Myocardial infarction	Continuous				NA		1.140 (1.094 to 1.188)	<0.001	1.113 (1.068 to 1.160)	<0.001	1.072 (1.028 to 1.117)	0.001
	Categorical	Q1 (low)	21,159	410	82,361	4.98	Reference	<0.001	Reference	<0.001	Reference	0.003
		Q2	21,159	388	82,892	4.68	0.937 (0.815 to 1.076)		0.959 (0.834 to 1.102)		0.942 (0.820 to 1.083)	
		Q3	21,159	470	82,461	5.70	1.141 (1.000 to 1.303)		1.145 (1.002 to 1.307)		1.092 (0.956, 1.247)	
		Q4 (high)	21,159	571	80,783	7.07	1.421 (1.252 to 1.613)		1.332 (1.172 to 1.514)		1.191 (1.046 to 1.356)	
Stroke	Continuous				NA		1.128 (1.090 to 1.168)	<0.001	1.090 (1.053 to 1.128)	<0.001	1.058 (1.020 to 1.093)	0.002
	Categorical	Q1 (low)	21,159	584	82,008	7.12	Reference	<0.001	Reference	<0.001	Reference	0.01
		Q2	21,159	610	82,459	7.40	1.038 (0.926 to 1.162)		1.07 (0.955 to 1.199)		1.059 (0.945 to 1.187)	
		Q3	21,159	652	82,106	7.94	1.114 (0.997 to 1.246)		1.115 (0.997 to 1.247)		1.074 (0.96 to 1.202)	
		Q4 (high)	21,159	820	80,306	10.21	1.436 (1.291 to 1.597)		1.304 (1.172 to 1.451)		1.189 (1.067 to 1.325)	
KRT	Continuous				NA		1.183 (1.147 to 1.220)	<0.001	1.241 (1.203 to 1.281)	<0.001	1.069 (1.035 to 1.103)	<0.001
	Categorical	Q1 (low)	21,159	646	82,054	7.87	Reference	<0.001	Reference	<0.001	Reference	<0.001
		Q2	21,159	754	82,395	9.15	1.16 (1.045 to 1.289)		1.135 (1.021 to 1.261)		0.991 (0.892 to 1.101)	
		Q3	21,159	832	81,896	10.16	1.29 (1.164 to 1.430)		1.319 (1.190 to 1.462)		1.066 (0.962 to 1.182)	
		Q4 (high)	21,159	1044	79,957	13.06	1.67 (1.514 to 1.842)		1.906 (1.728 to 2.104)		1.201 (1.087 to 1.327)	

[a]Multivariable model was adjusted for age, sex, number of exams, current smoking, drinking alcohol consumption, regular physical activity, low-income status, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline BMI, waist circumference, fasting glucose, systolic BP, diastolic BP, HDL, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Table 3. Risk of adverse outcomes according to BMI variability in patients with predialysis CKD stratified by trends in BMI

Subgroup	Outcome	BMI Variability Independent of Mean Exposure		*N*	Event	Follow-up Person-years	Incidence rate (/1000 Person-years)	Univariable Model		Age, Sex, and Number of Exams Adjusted Model		Multivariable Model[a]	
								HR (95% CI)	*P* for trend	Adjusted HR (95% CI)	*P* for trend	Adjusted HR (95% CI)	*P* for trend
Increasing trend (regression $\beta \geq 0$)	All-cause mortality	Continuous				NA		1.241 (1.189 to 1.295)	<0.001	1.217 (1.167 to 1.269)	<0.001	1.165 (1.118 to 1.215)	<0.001
		Categorical	Q1 (low)	9861	387	38,706	10.00	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	9974	364	39,515	9.21	0.917 (0.794 to 1.058)		0.917 (0.794 to 1.058)		0.992 (0.86 to 1.146)	
			Q3	9719	467	38,386	12.17	1.211 (1.058 to 1.385)		1.211 (1.058 to 1.385)		1.213 (1.06 to 1.389)	
			Q4 (high)	8603	597	33,405	17.87	1.79 (1.575 to 2.034)		1.79 (1.575 to 2.034)		1.531 (1.345 to 1.742)	
	Myocardial infarction	Continuous				NA		1.142 (1.071 to 1.217)	<0.001	1.132 (1.063 to 1.206)	<0.001	1.093 (1.025 to 1.164)	0.006
		Categorical	Q1 (low)	9861	179	38,449	4.66	Reference	<0.001	Reference	0.001	Reference	0.04
			Q2	9974	178	39,232	4.54	0.971 (0.789 to 1.195)		1.01 (0.82 to 1.243)		0.997 (0.81 to 1.228)	
			Q3	9719	213	38,045	5.60	1.198 (0.982 to 1.461)		1.229 (1.008 to 1.5)		1.186 (0.972 to 1.448)	
			Q4 (high)	8603	221	33,096	6.68	1.436 (1.179 to 1.748)		1.409 (1.156 to 1.718)		1.265 (1.036 to 1.544)	
	Stroke	Continuous				NA		1.114 (1.057 to 1.174)	<0.001	1.101 (1.045 to 1.161)	<0.001	1.066 (1.012 to 1.023)	0.02
		Categorical	Q1 (low)	9861	273	38,290	7.13	Reference	<0.001	Reference	0.002	Reference	0.10
			Q2	9974	265	39,045	6.79	0.951 (0.803 to 1.126)		1.008 (0.851 to 1.194)		1.005 (0.848 to 1.19)	
			Q3	9719	297	37,908	7.83	1.098 (0.932 to 1.294)		1.139 (0.966 to 1.343)		1.101 (0.934 to 1.298)	
			Q4 (high)	8603	317	32,914	9.63	1.355 (1.152 to 1.593)		1.32 (1.122 to 1.553)		1.198 (1.017 to 1.411)	
	KRT	Continuous				NA		1.142 (1.087 to 1.199)	<0.001	1.181 (1.124 to 1.240)	<0.001	1.049 (0.998 to 1.104)	0.06
		Categorical	Q1 (low)	9861	290	38,324	7.57	Reference	<0.001	Reference	<0.001	Reference	0.01
			Q2	9974	343	39,008	8.79	1.159 (0.992 to 1.356)		1.132 (0.968 to 1.325)		0.943 (0.806 to 1.105)	
			Q3	9719	327	37,857	8.64	1.14 (0.973 to 1.335)		1.161 (0.991 to 1.36)		0.931 (0.794 to 1.092)	
			Q4 (high)	8603	383	32,803	11.68	1.551 (1.332 to 1.807)		1.702 (1.461 to 1.984)		1.160 (0.993 to 1.355)	
Decreasing trend (regression $\beta < 0$)	All-cause mortality	Continuous				NA		1.438 (1.390 to 1.488)	<0.001	1.341 (1.296 to 1.387)	<0.001	1.213 (1.171 to 1.256)	<0.001
		Categorical	Q1 (low)	11,298	460	44,233	10.40	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	11,185	514	43,985	11.69	1.12 (0.988 to 1.271)		1.12 (0.988 to 1.271)		1.069 (0.942 to 1.212)	
			Q3	11,440	638	44,798	14.24	1.367 (1.213 to 1.541)		1.367 (1.213 to 1.541)		1.147 (1.016 to 1.294)	
			Q4 (high)	12,556	1355	48,155	28.14	2.713 (2.441 to 3.016)		2.713 (2.441 to 3.016)		1.719 (1.538 to 1.92)	
	Myocardial infarction	Continuous				NA		1.135 (1.075 to 1.198)	<0.001	1.099 (1.040 to 1.160)	<0.001	1.062 (1.003 to 1.123)	0.04
		Categorical	Q1 (low)	11,298	231	43,912	5.26	Reference	<0.001	Reference	0.001	Reference	0.05
			Q2	11,185	210	43,660	4.81	0.911 (0.756 to 1.098)		0.918 (0.761 to 1.107)		0.902 (0.748 to 1.088)	
			Q3	11,440	257	44,416	5.79	1.097 (0.918 to 1.31)		1.078 (0.902 to 1.288)		1.032 (0.863 to 1.234)	
			Q4 (high)	12,556	350	47,687	7.34	1.395 (1.182 to 1.647)		1.275 (1.078 to 1.508)		1.153 (0.969 to 1.372)	
	Stroke	Continuous				NA		1.136 (1.086 to 1.189)	<0.001	1.081 (1.033 to 1.131)	<0.001	1.047 (0.999 to 1.097)	0.06
		Categorical	Q1 (low)	11,298	311	43,718	7.11	Reference	<0.001	Reference	0.003	Reference	0.15
			Q2	11,185	345	43,414	7.95	1.116 (0.958 to 1.301)		1.123 (0.963 to 1.309)		1.102 (0.945 to 1.285)	
			Q3	11,440	355	44,199	8.03	1.129 (0.969 to 1.314)		1.096 (0.941 to 1.276)		1.052 (0.902 to 1.227)	
			Q4 (high)	12,556	503	47,392	10.61	1.493 (1.296 to 1.719)		1.295 (1.122 to 1.494)		1.178 (1.015 to 1.365)	
	KRT	Continuous				NA		1.206 (1.158 to 1.255)	<0.001	1.280 (1.228 to 1.334)	<0.001	1.071 (1.027 to 1.117)	0.001
		Categorical	Q1 (low)	11,298	356	43,730	8.14	Reference	<0.001	Reference	<0.001	Reference	0.009
			Q2	11,185	411	43,387	9.47	1.162 (1.008 to 1.339)		1.14 (0.989 to 1.314)		1.006 (0.872 to 1.16)	
			Q3	11,440	505	44,039	11.47	1.41 (1.231 to 1.615)		1.448 (1.265 to 1.659)		1.157 (1.009 to 1.326)	
			Q4 (high)	12,556	661	47,154	14.02	1.735 (1.526 to 1.974)		2.042 (1.794 to 2.325)		1.196 (1.046 to 1.367)	

[a]Multivariable model was adjusted for age, sex, number of exams, current smoking, alcohol consumption, regular physical activity, low-income status, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline BMI, waist circumference, fasting glucose, systolic BP, diastolic BP, HDL, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Table 4. Prognostic significance of variabilities in various metabolic parameters in patients with predialysis CKD

Metabolic parameter	Outcome	Variability Independent of Mean Exposure		N	Event	Follow-up Person-years	Incidence rate (/1000 Person-years)	Univariable Model		Age, Sex, and Number of Exams Adjusted Model		Multivariable Model[a]	
								HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Waist circumference	All-cause mortality	Continuous				NA		1.141 (1.112 to 1.171)	<0.001	1.125 (1.096 to 1.154)	<0.001	1.097 (1.069 to 1.126)	<0.0001
		Categorical	Q1 (low)	21,176	1026	82,940	12.37	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,121	1087	82,976	13.10	1.057 (0.971 to 1.151)		1.066 (0.979 to 1.161)		1.044 (0.958 to 1.137)	
			Q3	21,190	1158	83,178	13.92	1.123 (1.033 to 1.222)		1.142 (1.05 to 1.243)		1.103 (1.014 to 1.2)	
			Q4 (high)	21,149	1511	82,088	18.41	1.49 (1.377 to 1.613)		1.427 (1.317 to 1.546)		1.321 (1.219 to 1.431)	
	Myocardial infarction	Continuous				NA		1.035 (0.994 to 1.078)	0.10	1.024 (0.983 to 1.067)	0.26	1.016 (0.974 to 1.058)	0.46
		Categorical	Q1 (low)	21,176	455	82,316	5.53	Reference	0.003	Reference	0.02	Reference	0.04
			Q2	21,121	455	82,295	5.53	0.998 (0.877 to 1.137)		1.003 (0.881 to 1.142)		1.002 (0.88 to 1.142)	
			Q3	21,190	412	82,555	4.99	0.901 (0.788 to 1.029)		0.905 (0.792 to 1.034)		0.895 (0.783 to 1.023)	
			Q4 (high)	21,149	517	81,330	6.36	1.15 (1.014 to 1.305)		1.112 (0.979 to 1.263)		1.086 (0.956 to 1.234)	
	Stroke	Continuous				NA		1.054 (1.019 to 1.09)	0.003	1.034 (0.999 to 1.07)	0.05	1.027 (0.992 to 1.062)	0.13
		Categorical	Q1 (low)	21,176	650	81,948	7.93	Reference	0.002	Reference	0.08	Reference	0.19
			Q2	21,121	609	81,958	7.43	0.936 (0.838 to 1.046)		0.942 (0.843 to 1.052)		0.942 (0.843 to 1.052)	
			Q3	21,190	670	82,084	8.16	1.028 (0.923 to 1.146)		1.029 (0.924 to 1.147)		1.024 (0.919 to 1.141)	
			Q4 (high)	21,149	737	80,890	9.11	1.149 (1.034 to 1.277)		1.084 (0.974 to 1.206)		1.061 (0.953 to 1.18)	
	KRT	Continuous				NA		1.002 (0.972 to 1.033)	0.89	1.062 (1.029 to 1.096)	<0.001	1.007 (0.976 to 1.04)	0.64
		Categorical	Q1 (low)	21,176	818	81,730	10.01	Reference	0.999	Reference	<0.001	Reference	0.26
			Q2	21,121	820	81,739	10.03	1.001 (0.909 to 1.103)		0.996 (0.904 to 1.098)		0.919 (0.834 to 1.013)	
			Q3	21,190	826	81,966	10.08	1.006 (0.913 to 1.108)		1.058 (0.961 to 1.166)		0.981 (0.89 to 1.081)	
			Q4 (high)	21,149	812	80,866	10.04	1.006 (0.913 to 1.108)		1.198 (1.086 to 1.321)		1.003 (0.909 to 1.106)	
Fasting blood glucose	All-cause mortality	Continuous				NA		1.201 (1.17 to 1.232)	<0.001	1.2 (1.17 to 1.232)	<0.001	1.113 (1.084 to 1.143)	<0.001
		Categorical	Q1 (low)	21,160	974	82,496	11.81	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,153	1006	82,889	12.14	1.025 (0.939 to 1.12)		1.059 (0.97 to 1.157)		1.016 (0.93 to 1.11)	
			Q3	21,164	1144	83,084	13.77	1.161 (1.066 to 1.265)		1.197 (1.099 to 1.304)		1.079 (0.99 to 1.176)	
			Q4 (high)	21,159	1658	82,713	20.05	1.691 (1.562 to 1.83)		1.701 (1.572 to 1.842)		1.368 (1.26 to 1.485)	
	Myocardial infarction	Continuous				NA		1.208 (1.159 to 1.259)	<0.001	1.206 (1.157 to 1.257)	<0.001	1.109 (1.062 to 1.157)	<0.001
		Categorical	Q1 (low)	21,160	377	81,923	4.60	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,153	372	82,344	4.52	0.979 (0.849 to 1.13)		1.001 (0.867 to 1.155)		0.965 (0.836 to 1.113)	
			Q3	21,164	452	82,423	5.48	1.187 (1.036 to 1.361)		1.206 (1.052 to 1.383)		1.081 (0.942 to 1.24)	
			Q4 (high)	21,159	638	81,807	7.80	1.688 (1.487 to 1.918)		1.686 (1.484 to 1.916)		1.328 (1.163 to 1.516)	
	Stroke	Continuous				NA		1.193 (1.152 to 1.235)	<0.001	1.193 (1.153 to 1.235)	<0.001	1.106 (1.067 to 1.146)	<0.001
		Categorical	Q1 (low)	21,160	528	81,647	6.47	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,153	586	81,931	7.15	1.105 (0.983 to 1.243)		1.138 (1.012 to 1.28)		1.097 (0.975 to 1.234)	
			Q3	21,164	666	82,043	8.12	1.254 (1.119 to 1.406)		1.286 (1.147 to 1.442)		1.162 (1.036 to 1.303)	
			Q4 (high)	21,159	886	81,258	10.90	1.686 (1.514 to 1.878)		1.699 (1.525 to 1.893)		1.362 (1.218 to 1.523)	
	KRT	Continuous				NA		1.351 (1.309 to 1.395)	<0.001	1.333 (1.291 to 1.376)	<0.001	1.059 (1.024 to 1.095)	0.001
		Categorical	Q1 (low)	21,160	543	81,719	6.64	Reference	<0.001	Reference	<0.001	Reference	0.008
			Q2	21,153	639	81,950	7.80	1.172 (1.045 to 1.314)		1.122 (1 to 1.258)		1.034 (0.921 to 1.159)	
			Q3	21,164	825	81,801	10.09	1.516 (1.36 to 1.689)		1.442 (1.293 to 1.607)		1.098 (0.984 to 1.226)	
			Q4 (high)	21,159	1269	80,832	15.70	2.366 (2.14 to 2.616)		2.247 (2.032 to 2.485)		1.179 (1.06 to 1.311)	
Systolic BP	All-cause mortality	Continuous				NA		1.155 (1.126 to 1.185)	<0.001	1.12 (1.092 to 1.149)	<0.001	1.075 (1.048 to 1.102)	<0.001
		Categorical	Q1 (low)	21,247	1029	82,886	12.41	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,070	1021	82,880	12.32	0.988 (0.906 to 1.078)		1.019 (0.934 to 1.111)		1.004 (0.921 to 1.095)	
			Q3	21,160	1193	82,917	14.39	1.156 (1.063 to 1.256)		1.14 (1.048 to 1.239)		1.082 (0.995 to 1.176)	
			Q4 (high)	21,159	1539	82,500	18.65	1.499 (1.385 to 1.622)		1.384 (1.279 to 1.498)		1.228 (1.134 to 1.329)	
	Myocardial infarction	Continuous				NA		1.079 (1.036 to 1.125)	<0.001	1.062 (1.019 to 1.106)	0.004	1.035 (0.993 to 1.078)	0.10
		Categorical	Q1 (low)	21,247	426	82,262	5.18	Reference	0.001	Reference	0.03	Reference	0.38
			Q2	21,070	421	82,283	5.12	0.985 (0.86 to 1.126)		1.005 (0.878 to 1.15)		0.995 (0.87 to 1.139)	
			Q3	21,160	466	82,233	5.67	1.091 (0.957 to 1.244)		1.085 (0.951 to 1.238)		1.05 (0.921 to 1.198)	
			Q4 (high)	21,159	526	81,718	6.44	1.239 (1.091 to 1.408)		1.185 (1.043 to 1.347)		1.099 (0.966 to 1.25)	

(continued)

Table 4. Prognostic significance of variabilities in various metabolic parameters in patients with predialysis CKD (cont.)

Metabolic parameter	Outcome	Variability Independent of Mean Exposure		N	Event	Follow-up Person-years	Incidence rate (/1000 Person-years)	Univariable Model		Age, Sex, and Number of Exams Adjusted Model		Multivariable Model[a]	
								HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
	Stroke	Continuous				NA		1.084 (1.048 to 1.122)	<0.001	1.061 (1.026 to 1.098)	<0.001	1.038 (1.003 to 1.074)	0.03
		Categorical	Q1 (low)	21,247	616	81,928	7.52	Reference	<0.001	Reference	<0.001	Reference	0.13
			Q2	21,070	618	81,876	7.55	1.003 (0.897 to 1.121)		1.033 (0.923 to 1.155)		1.027 (0.918 to 1.148)	
			Q3	21,160	655	81,853	8.00	1.063 (0.953 to 1.187)		1.06 (0.95 to 1.184)		1.034 (0.926 to 1.154)	
			Q4 (high)	21,159	777	81,223	9.57	1.272 (1.144 to 1.414)		1.203 (1.082 to 1.337)		1.126 (1.012 to 1.252)	
	KRT	Continuous				NA		1.128 (1.094 to 1.164)	<0.001	1.156 (1.12 to 1.192)	<0.001	1.028 (0.997 to 1.061)	0.08
		Categorical	Q1 (low)	21,247	676	81,868	8.26	Reference	<0.001	Reference	<0.001	Reference	0.34
			Q2	21,070	778	81,729	9.52	1.15 (1.037 to 1.275)		1.11 (1.001 to 1.23)		0.999 (0.9 to 1.108)	
			Q3	21,160	853	81,641	10.45	1.264 (1.143 to 1.398)		1.256 (1.135 to 1.389)		1.048 (0.947 to 1.161)	
			Q4 (high)	21,159	969	81,064	11.95	1.449 (1.313 to 1.598)		1.542 (1.397 to 1.701)		1.077 (0.975 to 1.188)	
Diastolic BP	All-cause mortality	Continuous				NA		1.139 (1.111 to 1.169)	<0.001	1.096 (1.068 to 1.124)	<0.001	1.059 (1.032 to 1.086)	<0.001
		Categorical	Q1 (low)	21,161	1008	82,778	12.18	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,157	1145	82,989	13.80	1.13 (1.038 to 1.23)		1.068 (0.982 to 1.163)		1.035 (0.951 to 1.126)	
			Q3	21,025	1085	82,602	13.14	1.076 (0.987 to 1.172)		1.068 (0.98 to 1.163)		1.043 (0.957 to 1.136)	
			Q4 (high)	21,293	1544	82,813	18.64	1.531 (1.414 to 1.658)		1.332 (1.23 to 1.442)		1.193 (1.101 to 1.292)	
	Myocardial infarction	Continuous				NA		1.056 (1.013 to 1.1)	0.01	1.036 (0.995 to 1.079)	0.09	1.012 (0.971 to 1.054)	0.58
		Categorical	Q1 (low)	21,161	439	82,144	5.34	Reference	<0.001	Reference	0.03	Reference	0.23
			Q2	21,157	452	82,347	5.49	1.024 (0.898 to 1.168)		0.992 (0.87 to 1.131)		0.969 (0.849 to 1.105)	
			Q3	21,025	415	82,040	5.06	0.944 (0.825 to 1.079)		0.941 (0.823 to 1.077)		0.918 (0.803 to 1.05)	
			Q4 (high)	21,293	533	81,965	6.50	1.216 (1.071 to 1.379)		1.133 (0.998 to 1.286)		1.049 (0.923 to 1.191)	
	Stroke	Continuous				NA		1.115 (1.077 to 1.154)	<0.001	1.088 (1.052 to 1.126)	<0.001	1.066 (1.031 to 1.103)	<0.001
		Categorical	Q1 (low)	21,161	554	81,875	6.77	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,157	685	81,891	8.36	1.236 (1.105 to 1.382)		1.191 (1.065 to 1.332)		1.161 (1.038 to 1.299)	
			Q3	21,025	612	81,595	7.50	1.108 (0.987 to 1.243)		1.11 (0.99 to 1.246)		1.089 (0.971 to 1.222)	
			Q4 (high)	21,293	815	81,519	10.00	1.479 (1.327 to 1.647)		1.353 (1.215 to 1.508)		1.265 (1.135 to 1.41)	
	KRT	Continuous				NA		1.126 (1.092 to 1.161)	<0.001	1.138 (1.103 to 1.173)	<0.001	1.012 (0.981 to 1.043)	0.47
		Categorical	Q1 (low)	21,161	710	81,749	8.69	Reference	<0.001	Reference	<0.001	Reference	0.28
			Q2	21,157	723	81,939	8.82	1.015 (0.915 to 1.125)		1.027 (0.926 to 1.139)		0.934 (0.842 to 1.037)	
			Q3	21,025	867	81,243	10.67	1.228 (1.112 to 1.356)		1.187 (1.075 to 1.311)		1.028 (0.93 to 1.136)	
			Q4 (high)	21,293	976	81,371	11.99	1.385 (1.257 to 1.525)		1.448 (1.314 to 1.595)		1.005 (0.912 to 1.108)	
Total cholesterol	All-cause mortality	Continuous				NA		1.08 (1.053 to 1.108)	<0.001	1.092 (1.064 to 1.12)	<0.001	1.037 (1.01 to 1.065)	0.007
		Categorical	Q1 (low)	21,159	1053	82,816	12.71	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,158	1188	83,021	14.31	1.123 (1.034 to 1.221)		1.154 (1.062 to 1.253)		1.105 (1.017 to 1.201)	
			Q3	21,160	1193	83,096	14.36	1.126 (1.037 to 1.224)		1.15 (1.059 to 1.25)		1.046 (0.962 to 1.137)	
			Q4 (high)	21,159	1348	82,249	16.39	1.291 (1.191 to 1.4)		1.34 (1.236 to 1.453)		1.151 (1.058 to 1.252)	
	Myocardial infarction	Continuous				NA		1.102 (1.057 to 1.148)	<0.001	1.101 (1.057 to 1.147)	<0.001	1.034 (0.99 to 1.079)	0.13
		Categorical	Q1 (low)	21,159	387	82,255	4.70	Reference	<0.001	Reference	<0.001	Reference	0.18
			Q2	21,158	445	82,379	5.40	1.146 (1 to 1.313)		1.162 (1.014 to 1.332)		1.119 (0.977 to 1.283)	
			Q3	21,160	493	82,373	5.98	1.269 (1.111 to 1.45)		1.28 (1.12 to 1.462)		1.159 (1.014 to 1.325)	
			Q4 (high)	21,159	514	81,489	6.31	1.343 (1.177 to 1.532)		1.342 (1.176 to 1.531)		1.111 (0.968 to 1.274)	
	Stroke	Continuous				NA		1.049 (1.014 to 1.086)	0.006	1.049 (1.014 to 1.086)	0.005	0.999 (0.965 to 1.035)	0.97
		Categorical	Q1 (low)	21,159	615	81,797	7.52	Reference	0.05	Reference	0.04	Reference	0.67
			Q2	21,158	660	81,906	8.06	1.071 (0.96 to 1.196)		1.096 (0.982 to 1.223)		1.065 (0.954 to 1.189)	
			Q3	21,160	682	82,037	8.31	1.105 (0.991 to 1.232)		1.12 (1.004 to 1.249)		1.034 (0.926 to 1.153)	
			Q4 (high)	21,159	709	81,140	8.74	1.163 (1.044 to 1.296)		1.167 (1.048 to 1.301)		1.009 (0.901 to 1.129)	
	KRT	Continuous				NA		1.371 (1.328 to 1.416)	<0.001	1.403 (1.359 to 1.449)	<0.001	1.068 (1.033 to 1.104)	<0.001
		Categorical	Q1 (low)	21,159	491	82,120	5.98	Reference	<0.001	Reference	<0.001	Reference	0.001
			Q2	21,158	646	82,085	7.87	1.315 (1.17 to 1.479)		1.266 (1.125 to 1.423)		1.083 (0.963 to 1.219)	
			Q3	21,160	929	81,684	11.37	1.904 (1.707 to 2.124)		1.889 (1.694 to 2.108)		1.194 (1.069 to 1.334)	
			Q4 (high)	21,159	1210	80,413	15.05	2.532 (2.28 to 2.812)		2.654 (2.39 to 2.948)		1.218 (1.092 to 1.359)	

(continued)

Table 4. Prognostic significance of variabilities in various metabolic parameters in patients with predialysis CKD (cont.)

Metabolic parameter	Outcome	Variability Independent of Mean Exposure		*N*	Event	Follow-up Person-years	Incidence rate (/1000 Person-years)	Univariable Model HR (95% CI)	Univariable Model *P*	Age, Sex, and Number of Exams Adjusted Model Adjusted HR (95% CI)	Age, Sex, and Number of Exams Adjusted Model *P*	Multivariable Model[a] Adjusted HR (95% CI)	Multivariable Model[a] *P*
LDL cholesterol	All-cause mortality	Continuous				NA		1.106 (1.078 to 1.134)	<0.001	1.091 (1.063 to 1.119)	<0.001	1.029 (1.002 to 1.058)	0.04
		Categorical	Q1 (low)	21,159	1055	83,059	12.70	Reference	<0.001	Reference	<0.001	Reference	0.03
			Q2	21,159	1111	83,101	13.37	1.051 (0.966 to 1.144)		1.037 (0.954 to 1.129)		0.964 (0.886 to 1.049)	
			Q3	21,159	1214	82,858	14.65	1.154 (1.062 to 1.253)		1.123 (1.034 to 1.22)		0.994 (0.913 to 1.081)	
			Q4 (high)	21,159	1402	82,164	17.06	1.348 (1.245 to 1.46)		1.292 (1.193 to 1.4)		1.083 (0.995 to 1.178)	
	Myocardial infarction	Continuous				NA		1.05 (1.008 to 1.094)	0.02	1.037 (0.995 to 1.08)	0.08	0.947 (0.907 to 0.99)	0.02
		Categorical	Q1 (low)	21,159	446	82,380	5.41	Reference	0.047	Reference	0.16	Reference	0.07
			Q2	21,159	431	82,491	5.22	0.964 (0.844 to 1.1)		0.956 (0.838 to 1.092)		0.89 (0.779 to 1.017)	
			Q3	21,159	458	82,164	5.57	1.029 (0.903 to 1.172)		1.009 (0.885 to 1.149)		0.866 (0.758 to 0.99)	
			Q4 (high)	21,159	504	81,462	6.19	1.146 (1.009 to 1.301)		1.104 (0.972 to 1.255)		0.842 (0.735 to 0.964)	
	Stroke	Continuous				NA		1.058 (1.023 to 1.095)	0.001	1.047 (1.011 to 1.083)	0.009	0.976 (0.941 to 1.012)	0.19
		Categorical	Q1 (low)	21,159	612	82,063	7.46	Reference	0.01	Reference	0.07	Reference	0.50
			Q2	21,159	651	82,006	7.94	1.064 (0.953 to 1.188)		1.06 (0.949 to 1.184)		0.999 (0.895 to 1.116)	
			Q3	21,159	687	81,738	8.40	1.127 (1.011 to 1.257)		1.108 (0.993 to 1.235)		0.985 (0.881 to 1.101)	
			Q4 (high)	21,159	716	81,072	8.83	1.186 (1.065 to 1.321)		1.148 (1.03 to 1.279)		0.928 (0.828 to 1.04)	
	KRT	Continuous				NA		1.325 (1.284 to 1.368)	<0.001	1.319 (1.278 to 1.362)	<0.001	1.001 (0.967 to 1.035)	0.98
		Categorical	Q1 (low)	21,159	469	82,361	5.69	Reference	<0.001	Reference	<0.001	Reference	0.06
			Q2	21,159	739	82,028	9.01	1.583 (1.41 to 1.777)		1.556 (1.386 to 1.747)		1.152 (1.026 to 1.294)	
			Q3	21,159	941	81,434	11.56	2.035 (1.822 to 2.274)		2.039 (1.825 to 2.278)		1.112 (0.993 to 1.245)	
			Q4 (high)	21,159	1127	80,479	14.00	2.476 (2.223 to 2.758)		2.426 (2.178 to 2.702)		1.053 (0.94 to 1.178)	
HDL cholesterol	All-cause mortality	Continuous				NA		1.242 (1.21 to 1.274)	<0.001	1.142 (1.113 to 1.172)	<0.001	1.085 (1.054 to 1.116)	<0.001
		Categorical	Q1 (low)	21,159	856	82,673	10.35	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,157	1062	83,126	12.78	1.229 (1.123 to 1.345)		1.169 (1.069 to 1.28)		1.137 (1.039 to 1.245)	
			Q3	21,164	1208	82,957	14.56	1.401 (1.284 to 1.53)		1.239 (1.135 to 1.353)		1.16 (1.06 to 1.269)	
			Q4 (high)	21,156	1656	82,426	20.09	1.934 (1.781 to 2.101)		1.516 (1.396 to 1.647)		1.303 (1.191 to 1.426)	
	Myocardial infarction	Continuous				NA		1.242 (1.191 to 1.295)	<0.001	1.185 (1.137 to 1.236)	<0.001	1.093 (1.044 to 1.145)	<0.001
		Categorical	Q1 (low)	21,159	337	82,168	4.10	Reference	<0.001	Reference	<0.001	Reference	<0.001
			Q2	21,157	410	82,526	4.97	1.207 (1.045 to 1.395)		1.171 (1.013 to 1.352)		1.102 (0.953 to 1.274)	
			Q3	21,164	441	82,293	5.36	1.302 (1.13 to 1.501)		1.212 (1.051 to 1.397)		1.067 (0.922 to 1.234)	
			Q4 (high)	21,156	651	81,510	7.99	1.942 (1.702 to 2.215)		1.693 (1.483 to 1.932)		1.336 (1.156 to 1.544)	
	Stroke	Continuous				NA		1.183 (1.143 to 1.225)	<0.001	1.123 (1.085 to 1.163)	0.04	1.044 (1.005 to 1.085)	0.03
		Categorical	Q1 (low)	21,159	517	81,874	6.31	Reference	<0.001	Reference	0.03	Reference	0.02
			Q2	21,157	627	82,114	7.64	1.208 (1.075 to 1.357)		1.172 (1.043 to 1.317)		1.107 (0.985 to 1.245)	
			Q3	21,164	650	81,871	7.94	1.256 (1.119 to 1.41)		1.164 (1.037 to 1.307)		1.034 (0.918 to 1.164)	
			Q4 (high)	21,156	872	81,021	10.76	1.704 (1.529 to 1.9)		1.461 (1.31 to 1.63)		1.178 (1.045 to 1.328)	
	KRT	Continuous				NA		1.272 (1.233 to 1.312)	<0.001	1.268 (1.228 to 1.309)	<0.001	1.03 (0.995 to 1.067)	0.10
		Categorical	Q1 (low)	21,159	580	81,821	7.09	Reference	<0.001	Reference	<0.001	Reference	0.41
			Q2	21,157	685	82,134	8.34	1.174 (1.051 to 1.311)		1.133 (1.014 to 1.265)		1.039 (0.929 to 1.162)	
			Q3	21,164	861	81,663	10.54	1.487 (1.339 to 1.652)		1.429 (1.286 to 1.589)		1.055 (0.946 to 1.177)	
			Q4 (high)	21,156	1150	80,683	14.25	2.017 (1.825 to 2.228)		1.979 (1.789 to 2.189)		1.098 (0.983 to 1.227)	
Triglycerides	All-cause mortality	Continuous				NA		0.985 (0.961 to 1.011)	0.25	1.038 (1.012 to 1.065)	0.004	1.018 (0.992 to 1.044)	0.17
		Categorical	Q1 (low)	21,159	1203	82,338	14.61	Reference	0.66	Reference	0.03	Reference	0.47
			Q2	21,159	1212	82,744	14.65	1 (0.923 to 1.083)		1.068 (0.986 to 1.157)		1.043 (0.963 to 1.13)	
			Q3	21,159	1201	83,012	14.47	0.986 (0.91 to 1.068)		1.089 (1.006 to 1.18)		1.061 (0.979 to 1.149)	
			Q4 (high)	21,159	1166	83,088	14.03	0.956 (0.882 to 1.036)		1.124 (1.037 to 1.219)		1.055 (0.973 to 1.144)	
	Myocardial infarction	Continuous				NA		1.004 (0.964 to 1.046)	0.84	1.03 (0.989 to 1.073)	0.16	1.021 (0.98 to 1.064)	0.33
		Categorical	Q1 (low)	21,159	469	81,639	5.74	Reference	0.42	Reference	0.24	Reference	0.37
			Q2	21,159	429	82,124	5.22	0.907 (0.795 to 1.033)		0.94 (0.824 to 1.071)		0.933 (0.819 to 1.064)	
			Q3	21,159	473	82,345	5.74	0.995 (0.876 to 1.131)		1.048 (0.922 to 1.191)		1.034 (0.91 to 1.176)	
			Q4 (high)	21,159	468	82,388	5.68	0.984 (0.866 to 1.118)		1.065 (0.937 to 1.211)		1.036 (0.911 to 1.178)	

(continued)

Table 4. Prognostic significance of variabilities in various metabolic parameters in patients with predialysis CKD (cont.)

Metabolic parameter	Outcome	Variability Independent of Mean Exposure		*N*	Event	Follow-up Person-years	Incidence rate (/1000 Person-years)	Univariable Model		Age, Sex, and Number of Exams Adjusted Model		Multivariable Model[a]	
								HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
	Stroke	Continuous				NA		0.984 (0.951 to 1.017)	0.34	1.016 (0.982 to 1.051)	0.37	1.006 (0.973 to 1.041)	0.73
		Categorical	Q1 (low)	21,159	691	81,225	8.51	Reference	0.32	Reference	0.32	Reference	0.49
			Q2	21,159	669	81,676	8.19	0.962 (0.865 to 1.07)		1.009 (0.907 to 1.122)		0.999 (0.898 to 1.111)	
			Q3	21,159	631	81,994	7.70	0.903 (0.811 to 1.006)		0.966 (0.867 to 1.076)		0.952 (0.854 to 1.061)	
			Q4 (high)	21,159	675	81,984	8.23	0.966 (0.869 to 1.074)		1.069 (0.961 to 1.189)		1.038 (0.933 to 1.155)	
	KRT	Continuous				NA		1.059 (1.027 to 1.092)	<0.001	1.041 (1.009 to 1.074)	0.01	0.996 (0.965 to 1.027)	0.79
		Categorical	Q1 (low)	21,159	731	81,280	8.99	Reference	0.001	Reference	0.04	Reference	0.22
			Q2	21,159	798	81,562	9.78	1.086 (0.982 to 1.201)		1.035 (0.936 to 1.144)		1.051 (0.95 to 1.163)	
			Q3	21,159	880	81,710	10.77	1.194 (1.083 to 1.318)		1.13 (1.024 to 1.247)		1.076 (0.975 to 1.188)	
			Q4 (high)	21,159	867	81,750	10.61	1.176 (1.066 to 1.298)		1.112 (1.008 to 1.227)		0.983 (0.89 to 1.086)	

[a]Multivariable model was adjusted for age, sex, number of exams, current smoking, drinking alcohol, regular physical activity, low-income state, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline BMI, waist circumference, fasting glucose, systolic BP, diastolic BP, HDL, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Table 5. Risk of adverse outcomes according to the number of metabolic parameters with high variability (Q4) from each domain

Outcome	Number of High Variability (Q4) Components[a]	*N*	Event	Follow-up Person-years	Incidence Rate (/1000 Person-years)	Univariable Model		Age, Sex, and Number of Exams Adjusted Model		Multivariable Model[b]	
						HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
All-cause mortality	0	29,405	1023	115,685	8.84	Reference	<0.001	Reference	<0.001	Reference	<0.001
	1	32,282	1765	126,694	13.93	1.574 (1.457 to 1.700)		1.475 (1.366 to 1.594)		1.320 (1.221 to 1.427)	
	2	17,190	1332	66,765	19.95	2.26 (2.083 to 2.452)		2.002 (1.845 to 2.173)		1.590 (1.462 to 1.729)	
	3	5062	580	19,357	29.96	3.406 (3.076 to 3.771)		2.959 (2.671 to 3.277)		2.141 (1.926 to 2.379)	
	4	697	82	2682	30.58	3.465 (2.767 to 4.339)		3.243 (2.589 to 4.062)		2.108 (1.678 to 2.649)	
Myocardial infarction	0	29,405	481	114,961	4.18	Reference	<0.001	Reference	<0.001	Reference	<0.001
	1	32,282	679	125,690	5.40	1.29 (1.148 to 1.45)		1.237 (1.101 to 1.391)		1.114 (0.990 to 1.253)	
	2	17,190	492	66,073	7.45	1.782 (1.571 to 2.02)		1.654 (1.458 to 1.876)		1.338 (1.176 to 1.524)	
	3	5062	162	19,129	8.47	2.029 (1.698 to 2.424)		1.861 (1.556 to 2.224)		1.373 (1.143 to 1.650)	
	4	697	25	2644	9.46	2.263 (1.514 to 3.383)		2.138 (1.430 to 3.196)		1.423 (0.948 to 2.137)	
Stroke	0	29,405	731	114,485	6.39	Reference	<0.001	Reference	<0.001	Reference	<0.001
	1	32,282	1001	125,047	8.01	1.254 (1.140 to 1.379)		1.187 (1.079 to 1.306)		1.086 (0.986 to 1.196)	
	2	17,190	649	65,773	9.87	1.547 (1.392 to 1.72)		1.403 (1.262 to 1.56)		1.171 (1.050 to 1.306)	
	3	5062	247	18,965	13.02	2.046 (1.771 to 2.363)		1.82 (1.574 to 2.103)		1.403 (1.209 to 1.628)	
	4	697	38	2610	14.56	2.287 (1.65 to 3.168)		2.12 (1.530 to 2.938)		1.491 (1.072 to 2.074)	
KRT	0	29,405	704	114,674	6.14	Reference	<0.001	Reference	<0.001	Reference	<0.001
	1	32,282	1201	124,905	9.62	1.569 (1.430 to 1.722)		1.699 (1.548 to 1.865)		1.129 (1.028 to 1.241)	
	2	17,190	900	65,375	13.77	2.258 (2.046 to 2.492)		2.550 (2.309 to 2.815)		1.218 (1.100 to 1.349)	
	3	5062	393	18,778	20.93	3.454 (3.053 to 3.908)		4.065 (3.591 to 4.601)		1.410 (1.240 to 1.603)	
	4	697	78	2569	30.36	5.027 (3.979 to 6.351)		5.957 (4.713 to 7.529)		1.248 (0.980 to 1.589)	

[a]Number of high variability components were calculated by summing the presence of high variability (Q4) in a metabolic parameter from each metabolic syndrome domain (BMI, fasting blood glucose, systolic BP, and total cholesterol).

[b]Multivariable model was adjusted for age, sex, number of exams, current smoking, alcohol consumption, regular physical activity, low-income status, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline BMI, waist circumference, fasting glucose, systolic BP, diastolic BP, HDL, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Prognosis According to Cumulative Metabolic Variability Score

We constructed the cumulative metabolic variability score by summing the number of parameters from among BMI, fasting blood glucose, systolic BP, and total cholesterol that had high variability (Q4). There were 29,405, 32,282, 17,190, 5062, and 697 individuals with 0–4 highly variable metabolic syndrome components in the study population, respectively (Table 5). In the regression analysis, a higher cumulative metabolic variability score was significantly associated with higher risks of all assessed adverse outcomes.

DISCUSSION

In this observational study, we demonstrated that higher BMI variability was significantly associated with higher risks of all-cause mortality, myocardial infarction, stroke, and progression to the state requiring KRT in patients with predialysis CKD. Higher BMI variability was a significant risk factor for adverse outcomes regardless of obesity, sex, diabetes, reduced baseline eGFR, or even positive or negative trends in BMI. In addition, certain metabolic parameter variabilities showed significant associations with prognosis in patients with predialysis CKD. Furthermore, the cumulative metabolic variability score analysis showed that those with a higher burden of metabolic variability suffered from a worse prognosis. Thus, our study suggests the prognostic significance of BMI and metabolic parameter variabilities in patients with predialysis CKD.

Unlike the traditional concept of a higher BMI causing metabolic disorders, thus leading to higher risks of cardiovascular diseases or all-cause mortality in the general population, an inverse association between BMI and prognosis has been reported in patients with CKD.[6] Even among those with obesity or morbid obesity, a higher BMI was associated with better survival in patients with ESKD.[17,18] In individuals with predialysis CKD, a previous study investigating >0.4 million US veterans reported a U-shaped association between baseline BMI and the risk of mortality.[19] In individuals with a BMI <40 kg/m^2, a higher BMI was associated with a lower risk of mortality, and those with a BMI <20 kg/m^2 had the highest risk of mortality, further supporting the so-called "obesity paradox" in patients with CKD. There were similar findings for other adverse outcomes, including the progression of kidney function impairment.[4] Previous studies investigated whether these findings were associated with residual confounding effects by implementing marginal structural model analysis to account for time-varying confounders and reported that the inverse association between BMI and the risk of mortality was observed with all utilized statistical methods.[20] Thus, the consensus is that higher baseline BMI is associated with a better prognosis in patients with CKD, although the biologic plausibility needs further investigation. The unexplained "obesity paradox," which is different from the findings in the general population, confused the interpretation of the importance of BMI in patients with CKD, although BMI is one of the most well-recognized modifiable risk factors for various metabolic disorders and cardiovascular diseases.

In this study, we primarily aimed to investigate the clinical significance of BMI variability, rather than baseline BMI levels, in patients with predialysis CKD. In this large-scale cohort, we again identified inverse associations between baseline BMI and mortality and other major adverse outcomes in this predialysis CKD population. Furthermore, we identified that higher BMI variability was significantly associated with higher risks of all-cause mortality, KRT, myocardial infarction, and stroke. The significance remained even after the regression models were adjusted for various demographics, lifestyle factors, metabolic parameters, and baseline BMI, eGFR, or eGFR variability. The inclusion of a large number of patients with predialysis CKD with sequential measurements of BMI enabled subgroup analyses, and we identified the risks of adverse outcomes were significantly higher in those with higher BMI variability regardless of sex, obesity, diabetes, reduced eGFR, and trends in BMI. Although some statistical significance was attenuated in the multivariable models for some outcomes other than mortality, the interaction term analysis indicated the possibility of significant interactions with the variables used to determine the subgroups was minimal for the outcomes with attenuated associations, suggesting the findings may be generally applied to the studied population of patients with predialysis CKD. These findings encourage health care providers in the field of nephrology to carefully assess not only baseline BMI values, but also variability in BMI, because high BMI variability was an independent risk factor for major adverse outcomes in patients with CKD.

In addition, there were certain metabolic parameters, the variabilities of which showed significant associations with the risks of adverse outcome in patients with predialysis CKD. The most prominent association was identified for fasting blood glucose variability, the prognostic significance of which has been previously suggested in the general population and in those with diabetes.[3,21] Variabilities in waist circumference, systolic BP, and some cholesterol levels also showed certain notable associations, further supporting the clinical importance of metabolic variability in patients with predialysis CKD. In the results, the null findings in the fully adjusted model should be interpreted with caution, because we stringently adjusted for many clinicodemographic characteristics to ensure the robustness of the analysis; however, some adjusted variables might have certain mediating effects on the influence of previous variabilities in metabolic parameters on adverse outcomes. For instance, the fact that components with significant associations with the risk of requirement for KRT were relatively rare might be because the adjustment for baseline eGFR or eGFR variability might have already reflected the effect of metabolic variability on kidney function. Thus, although our results may prioritize the metabolic parameters with particularly important variabilities in patients with predialysis CKD, additional investigation is warranted to ascertain the individual effects of variabilities in metabolic parameters. In addition, that metabolic parameters are certainly correlated with each other (*e.g.*, high waist circumference, indicating central obesity, being a risk factor for impaired glucose tolerance or high blood pressure) should be minded when interpreting the findings.

Previous studies reported the importance of metabolic variability in the general population and in those with diabetes, and a higher degree of variability in metabolic parameters was significantly associated with a worse prognosis.[3,22,23] A previous study showed large fluctuations in weight lead to a decrease in muscle mass, but an increase in abdominal fat mass, which may lead to higher risks of metabolic and cardiovascular diseases.[5,9] In addition, those with high BMI variability have unstable metabolic parameters, such as blood pressure, which has also been reported to be associated with adverse outcomes.[24] In an animal experiment, weight cycling induced increased inflammation in adipose tissue, resulting in insulin resistance.[25] In addition, high BMI variability may indicate repetitive overshoot in metabolic stress, which may lead to the accumulation of pathologic changes in the cardiovascular system during the period of worsening metabolic health.[26] The above suggested mechanisms may also support the presence of the effects of high BMI variability on adverse outcomes in patients with CKD, because metabolic health is an important prognostic determinant in people with impaired kidney function. The results of the analysis of the metabolic variability score further emphasize the importance of the cumulative burden of variability in metabolic status in patients with predialysis CKD, supporting this mechanistic explanation. A future clinical trial should investigate the effect of minimizing BMI fluctuations or compare the effect of such interventions with that of rapid weight reduction, because rapid weight loss may cause weight regain or cycling, to further confirm the causality of the identified association between BMI variability and prognosis in patients with CKD.[27]

The study has several limitations. First, whether high BMI variability or metabolic parameter variability was associated with intentional or unintentional weight changes or lifestyle modifications could not be investigated due to the retrospective nature of the study. It should be noted that the effects of intentional weight changes may be different from those of BMI changes related to external factors. Because of this limitation, it is impossible to disregard the possibility that intentionally reducing weight at a modest rate may still be helpful for metabolic health in patients with CKD, despite the fact that doing so would increase BMI variability.[7] Second, there was the possibility of selection bias, because those with severe illness would be less likely to undergo general health screenings (healthy volunteer bias), which was reflected in the relatively low prevalence of CKD in the utilized database when compared with the prevalence of CKD of 8.2% in the general population in Korea.[28] In addition, the distinct age ranges and Asian ethnicities in this study suggest the need for more studies in other populations to improve the generalizability of the results. Third, survivorship bias should also be considered, because the study population had to undergo successive health screenings within a certain period to be included in this study. Fourth, measurement bias should be considered as follows: although the health screening centers were quality controlled, the weight scales were not directly standardized, and some patients might have visited different centers for their multiple health screenings. In addition, the dipstick albuminuria test has limitations and might have missed modest degrees of albuminuria. Last, the follow-up duration was relatively short; thus, the long-term association between metabolic variability and adverse outcomes in patients with predialysis CKD could not be investigated in this study.

In conclusion, high BMI variability is associated with a worse prognosis in patients with predialysis CKD. In addition to the assessment of metabolic status at a single time point, health care providers in the field of nephrology should pay attention to recent trends in metabolic parameters in CKD patients, because a higher degree of fluctuation may be associated with future risks of mortality or major adverse outcomes.

DISCLOSURES

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020121694/-/DCSupplemental.

Supplemental Table 1. Risk of adverse outcomes according to baseline BMI in patients with predialysis CKD.

Supplemental Table 2. Risk of adverse outcomes according to BMI variability by other indexes in patients with predialysis CKD.

Supplemental Table 3. Interaction term analysis results for the subgroup analysis.

Supplemental Table 4. Risk of adverse outcomes according to BMI variability in patients with predialysis CKD stratified by sex.

Supplemental Table 5. Risk of adverse outcomes according to BMI variability in patients with predialysis CKD stratified by baseline BMI $\geq$25 kg/m^2.

Supplemental Table 6. Risk of adverse outcomes according to BMI variability in patients with predialysis CKD stratified by the presence of diabetes mellitus.

Supplemental Table 7. Risk of adverse outcomes according to BMI variability in patients with predialysis CKD stratified by baseline eGFR <60 ml/min per 1.73 m^2.

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Online Supplemental Material

The prognostic significance of body mass index and metabolic parameter variabilities in predialysis chronic kidney disease: a nationwide observational cohort study

Authors

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Supplemental Material Table of Contents

Supplemental Table 1. Risk of adverse outcomes according to baseline body mass index in predialysis CKD patients.

Outcome	Baseline BMI exposure [a]		N	Event	Follow-up person-years	Incidence rate (/1000PY)	Univariable model		Age, sex, and number of exams adjusted model		Multivariable model [b]	
							HR (95% CI)	P	adjusted HR (95% CI)	P	adjusted HR (95% CI)	P
All-cause mortality	Continuous		NA				0.772 (0.752, 0.792)	< 0.001	0.844 (0.822, 0.867)	< 0.001	0.822 (0.791, 0.854)	< 0.001
	Categorical	Q1 (12.33–22.59)	21198	1781	82119	21.69	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
		Q2 (22.60–24.61)	21138	1182	82694	14.29	0.657 (0.611, 0.707)		0.703 (0.653, 0.757)		0.702 (0.648, 0.761)	
		Q3 (24.61–26.72)	21130	950	83102	11.43	0.525 (0.485, 0.568)		0.598 (0.552, 0.647)		0.584 (0.532, 0.642)	
		Q4 (26.73–46.43)	21170	869	83267	10.44	0.479 (0.442, 0.52)		0.642 (0.591, 0.697)		0.583 (0.519, 0.656)	
Myocardial infarction	Continuous		NA				0.963 (0.924, 1.003)	0.07	0.999 (0.959, 1.042)	0.97	0.901 (0.848, 0.956)	< 0.001
	Categorical	Q1 (12.33–22.59)	21198	475	81498	5.83	Reference	0.10	Reference	0.74	Reference	0.003
		Q2 (22.60–24.61)	21138	463	82012	5.65	0.967 (0.851, 1.099)		0.973 (0.856, 1.106)		0.880 (0.768, 1.01)	
		Q3 (24.61–26.72)	21130	483	82369	5.86	1.003 (0.884, 1.139)		1.037 (0.913, 1.177)		0.863 (0.742, 1.004)	
		Q4 (26.73–46.43)	21170	418	82618	5.06	0.866 (0.76, 0.988)		0.974 (0.853, 1.112)		0.699 (0.579, 0.845)	
Stroke	Continuous		NA				0.958 (0.926, 0.991)	0.01	1.007 (0.973, 1.042)	0.70	0.914 (0.870, 0.961)	< 0.001
	Categorical	Q1 (12.33–22.59)	21198	706	80982	8.72	Reference	0.04	Reference	0.61	Reference	0.002
		Q2 (22.60–24.61)	21138	660	81645	8.08	0.926 (0.833, 1.03)		0.947 (0.852, 1.054)		0.866 (0.772, 0.97)	
		Q3 (24.61–26.72)	21130	684	81963	8.35	0.956 (0.86, 1.062)		1.014 (0.912, 1.127)		0.858 (0.757, 0.972)	
		Q4 (26.73–46.43)	21170	616	82290	7.49	0.857 (0.77, 0.955)		1.001 (0.897, 1.116)		0.737 (0.631, 0.862)	
Kidney replacement therapy	Continuous		NA				0.837 (0.812, 0.864)	< 0.001	0.806 (0.782, 0.832)	< 0.001	0.852 (0.813, 0.894)	< 0.001
	Categorical	Q1 (12.33–22.59)	21198	1092	80429	13.58	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
		Q2 (22.60–24.61)	21138	789	81571	9.67	0.709 (0.647, 0.777)		0.672 (0.613, 0.736)		0.752 (0.68, 0.831)	
		Q3 (24.61–26.72)	21130	741	82024	9.03	0.661 (0.602, 0.726)		0.605 (0.551, 0.664)		0.695 (0.619, 0.78)	
		Q4 (26.73–46.43)	21170	654	82277	7.95	0.582 (0.528, 0.641)		0.521 (0.473, 0.575)		0.612 (0.528, 0.709)	

HR = hazard ratio, CI = confidence interval

[a] The ranges of the BMI values in the quartile grades are presented within the parentheses.

[b] Multivariable model was adjusted for age, sex, number of exams, current-smoking, drinking alcohol, regular physical activity, low income state, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, waist circumference, fasting glucose, systolic BP, diastolic BP, high-density lipoprotein, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Supplemental Table 2. Risk of adverse outcomes according to body mass index variability by other indexes in predialysis CKD patients.

Metabolic parameter	Outcome	Variability independent of mean exposure		N	Event	Follow-up person-years	Incidence rate (/1000PY)	Univariable model HR (95% CI)	P	Age, sex, and number of exams adjusted adjusted HR (95% CI)	P	Multivariable model [a] adjusted HR (95% CI)	P
Standard deviation	All-cause mortality	Continuous		NA				1.309 (1.275, 1.344)	< 0.001	1.262 (1.229, 1.295)	< 0.001	1.193 (1.162, 1.225)	<0.001
		Categorical	Q1 (low)	21159	882	82887	10.64	Reference	<0.001	Reference	<0.001	Reference	< 0.001
			Q2	21159	936	83387	11.22	1.051 (0.959, 1.152)		1.092 (0.996, 1.197)		1.064 (0.971, 1.167)	
			Q3	21159	1115	83214	13.40	1.255 (1.149, 1.371)		1.256 (1.15, 1.372)		1.163 (1.064, 1.271)	
			Q4 (high)	21159	1849	81694	22.63	2.131 (1.966, 2.309)		1.953 (1.801, 2.117)		1.666 (1.535, 1.807)	
	Myocardial infarction	Continuous		NA				1.133 (1.087, 1.181)	< 0.001	1.112 (1.067, 1.159)	< 0.001	1.067 (1.024, 1.112)	0.002
		Categorical	Q1 (low)	21159	401	82326	4.87	Reference	<0.001	Reference	<0.001	Reference	0.016
			Q2	21159	408	82762	4.93	1.009 (0.879, 1.158)		1.026 (0.894, 1.178)		1.004 (0.874, 1.153)	
			Q3	21159	468	82490	5.67	1.161 (1.016, 1.326)		1.157 (1.012, 1.322)		1.097 (0.96, 1.254)	
			Q4 (high)	21159	562	80918	6.95	1.426 (1.255, 1.621)		1.356 (1.192, 1.543)		1.199 (1.053, 1.365)	
	Stroke	Continuous		NA				1.127 (1.089, 1.166)	< 0.001	1.096 (1.059, 1.134)	< 0.001	1.056 (1.021, 1.093)	0.002
		Categorical	Q1 (low)	21159	582	81965	7.10	Reference	<0.001	Reference	<0.001	Reference	0.015
			Q2	21159	608	82368	7.38	1.039 (0.927, 1.164)		1.063 (0.949, 1.191)		1.047 (0.935, 1.174)	
			Q3	21159	663	82124	8.07	1.136 (1.016, 1.27)		1.13 (1.011, 1.263)		1.079 (0.965, 1.207)	
			Q4 (high)	21159	813	80422	10.11	1.425 (1.282, 1.586)		1.32 (1.186, 1.47)		1.184 (1.063, 1.319)	
	Kidney replacement therapy	Continuous		NA				1.142 (1.107, 1.178)	< 0.001	1.19 (1.153, 1.228)	< 0.001	1.060 (1.027, 1.094)	<0.001
		Categorical	Q1 (low)	21159	696	81911	8.50	Reference	<0.001	Reference	<0.001	Reference	< 0.001
			Q2	21159	742	82293	9.02	1.059 (0.955, 1.175)		1.055 (0.951, 1.171)		0.961 (0.866, 1.067)	
			Q3	21159	840	81924	10.25	1.206 (1.091, 1.333)		1.232 (1.114, 1.362)		1.004 (0.908, 1.111)	
			Q4 (high)	21159	998	80174	12.45	1.473 (1.337, 1.623)		1.663 (1.509, 1.833)		1.178 (1.068, 1.3)	
Coefficient of variation	All-cause mortality	Continuous		NA				1.366 (1.331, 1.403)	< 0.001	1.296 (1.262, 1.33)	< 0.001	1.199 (1.167, 1.231)	<0.001
		Categorical	Q1 (low)	21159	847	82941	10.21	Reference	<0.001	Reference	<0.001	Reference	< 0.001
			Q2	21158	879	83492	10.53	1.027 (0.935, 1.129)		1.068 (0.971, 1.173)		1.035 (0.941, 1.137)	
			Q3	21160	1104	83188	13.27	1.296 (1.185, 1.417)		1.297 (1.186, 1.419)		1.171 (1.07, 1.281)	
			Q4 (high)	21159	1952	81561	23.93	2.349 (2.167, 2.547)		2.068 (1.907, 2.244)		1.662 (1.53, 1.806)	
	Myocardial infarction	Continuous		NA				1.14 (1.094, 1.188)	< 0.001	1.113 (1.068, 1.16)	< 0.001	1.072 (1.028, 1.117)	0.001
		Categorical	Q1 (low)	21159	410	82362	4.98	Reference	<0.001	Reference	<0.001	Reference	0.003
			Q2	21158	388	82885	4.68	0.937 (0.816, 1.077)		0.959 (0.834, 1.102)		0.943 (0.82, 1.083)	
			Q3	21160	470	82465	5.70	1.141 (1, 1.303)		1.145 (1.002, 1.307)		1.093 (0.956, 1.248)	
			Q4 (high)	21159	571	80784	7.07	1.421 (1.252, 1.613)		1.332 (1.172, 1.514)		1.191 (1.046, 1.356)	
	Stroke	Continuous		NA				1.128 (1.09, 1.168)	< 0.001	1.09 (1.053, 1.128)	< 0.001	1.056 (1.020, 1.093)	0.002
		Categorical	Q1 (low)	21159	584	82010	7.12	Reference	<0.001	Reference	<0.001	Reference	0.015
			Q2	21158	610	82452	7.40	1.038 (0.927, 1.163)		1.07 (0.955, 1.199)		1.06 (0.946, 1.187)	
			Q3	21160	652	82111	7.94	1.114 (0.997, 1.246)		1.115 (0.997, 1.247)		1.075 (0.961, 1.202)	
			Q4 (high)	21159	820	80308	10.21	1.436 (1.291, 1.597)		1.304 (1.172, 1.452)		1.189 (1.067, 1.325)	
	Kidney replacement therapy	Continuous		NA				1.183 (1.147, 1.221)	< 0.001	1.242 (1.203, 1.282)	< 0.001	1.068 (1.035, 1.103)	<0.001
		Categorical	Q1 (low)	21159	647	82054	7.89	Reference	<0.001	Reference	<0.001	Reference	< 0.001
			Q2	21158	751	82392	9.12	1.154 (1.039, 1.282)		1.128 (1.016, 1.254)		0.989 (0.89, 1.099)	
			Q3	21160	834	81897	10.18	1.291 (1.165, 1.431)		1.32 (1.191, 1.463)		1.067 (0.963, 1.183)	
			Q4 (high)	21159	1044	79959	13.06	1.667 (1.511, 1.839)		1.903 (1.725, 2.1)		1.199 (1.085, 1.325)	
Actual real variability	All-cause mortality	Continuous		NA				1.291 (1.258, 1.325)	< 0.001	1.236 (1.204, 1.269)	< 0.001	1.179 (1.148, 1.210)	<0.001
		Categorical	Q1 (low)	21158	877	83157	10.55	Reference	<0.001	Reference	<0.001	Reference	< 0.001
			Q2	21160	953	83298	11.44	1.083 (0.988, 1.187)		1.072 (0.978, 1.175)		1.057 (0.964, 1.159)	
			Q3	21159	1179	82982	14.21	1.347 (1.234, 1.47)		1.308 (1.198, 1.428)		1.207 (1.105, 1.317)	
			Q4 (high)	21159	1773	81745	21.69	2.064 (1.903, 2.238)		1.824 (1.681, 1.979)		1.6 (1.474, 1.737)	
	Myocardial infarction	Continuous		NA				1.128 (1.082, 1.175)	< 0.001	1.101 (1.057, 1.148)	< 0.001	1.060 (1.017, 1.105)	0.006
		Categorical	Q1 (low)	21158	399	82571	4.83	Reference	<0.001	Reference	<0.001	Reference	0.03
			Q2	21160	411	82699	4.97	1.027 (0.895, 1.178)		1.022 (0.89, 1.173)		0.997 (0.869, 1.145)	
			Q3	21159	481	82259	5.85	1.209 (1.059, 1.381)		1.19 (1.042, 1.359)		1.13 (0.989, 1.291)	
			Q4 (high)	21159	548	80968	6.77	1.403 (1.234, 1.597)		1.306 (1.147, 1.487)		1.163 (1.02, 1.326)	
	Stroke	Continuous		NA				1.118 (1.08, 1.157)	< 0.001	1.078 (1.042, 1.116)	< 0.001	1.042 (1.007, 1.079)	0.02
		Categorical	Q1 (low)	21158	590	82220	7.18	Reference	<0.001	Reference	<0.001	Reference	0.09
			Q2	21160	614	82273	7.46	1.04 (0.929, 1.164)		1.038 (0.927, 1.162)		1.018 (0.909, 1.14)	
			Q3	21159	657	81891	8.02	1.118 (1.001, 1.25)		1.092 (0.977, 1.22)		1.043 (0.933, 1.166)	
			Q4 (high)	21159	805	80495	10.00	1.396 (1.255, 1.552)		1.256 (1.129, 1.398)		1.134 (1.018, 1.263)	
	Kidney replacement therapy	Continuous		NA				1.099 (1.066, 1.134)	< 0.001	1.158 (1.123, 1.195)	< 0.001	1.052 (1.019, 1.086)	0.002
		Categorical	Q1 (low)	21158	712	82136	8.67	Reference	<0.001	Reference	<0.001	Reference	0.002
			Q2	21160	791	82104	9.63	1.111 (1.004, 1.23)		1.078 (0.974, 1.193)		1.02 (0.922, 1.129)	
			Q3	21159	846	81697	10.36	1.196 (1.083, 1.322)		1.235 (1.118, 1.364)		1.011 (0.915, 1.118)	
			Q4 (high)	21159	927	80365	11.53	1.339 (1.214, 1.476)		1.548 (1.403, 1.708)		1.18 (1.068, 1.303)	

HR = hazard ratio, CI = confidence interval

[a] Multivariable model was adjusted for age, sex, number of exams, current-smoking, drinking alcohol, regular physical activity, low income state, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline body mass index, waist circumference, fasting glucose, systolic BP, diastolic BP, high-density lipoprotein, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

The P values for the correlation (by Pearson's correlation) between other body mass index variability indices with variation independent mean were P = 0.974 (standard deviation), P < 0.001 (coefficient of variation), and P < 0.001 (average real variability), respectively.

Supplemental Table 3. Interaction term analysis results for the subgroup analysis.

Variable to divide subgroups	Outcome	Interaction term P values in the multivariable model [a]
Sex	All-cause mortality	0.09
	Myocardial infarction	0.20
	Stroke	0.84
	Kidney replacement therapy	0.66
Baseline BMI ≥ 25 kg/m^2	All-cause mortality	0.03
	Myocardial infarction	0.88
	Stroke	0.41
	Kidney replacement therapy	0.04
Baseline diabetes mellitus	All-cause mortality	0.32
	Myocardial infarction	0.19
	Stroke	0.71
	Kidney replacement therapy	0.001
eGFR < 60 mL/min/1.73 m^2	All-cause mortality	0.79
	Myocardial infarction	0.47
	Stroke	0.75
	Kidney replacement therapy	0.01
BMI slope	All-cause mortality	0.08
	Myocardial infarction	0.70
	Stroke	0.64
	Kidney replacement therapy	0.16

BMI = body mass index, KRT = kidney replacement therapy

[a] Interaction term with the variable dividing the subgroup and the variability of BMI (VIM quartile) was included in the multivariable model adjusted for adjusted for age, sex, number of exams, current-smoking, drinking alcohol, regular physical activity, low income state, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline body mass index, waist circumference, fasting glucose, systolic BP, diastolic BP, high-density lipoprotein, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Supplemental Table 4. Risk of adverse outcomes according to body mass index variability in predialysis CKD patients stratified by sex.

Subgroup	Outcome	BMI variability independent of mean exposure		N	Event	Follow-up person-years	Incidence rate (/1000PY)	Univariable model		Age, sex, and number of exams adjusted model		Multivariable model [a]	
								HR (95% CI)	P	adjusted HR (95% CI)	P	adjusted HR (95% CI)	P
Male	All-cause mortality	Continuous		NA				1.402 (1.355, 1.45)	< 0.001	1.305 (1.262, 1.349)	< 0.001	1.198 (1.158, 1.24)	< 0.001
		Categorical	Q1 (low)	11397	547	44438	12.31	Reference	< 0.001	Reference	<0.001	Reference	<0.001
			Q2	11096	603	43672	13.81	1.116 (0.994, 1.253)		1.159 (1.032, 1.301)		1.119 (0.997, 1.257)	
			Q3	10421	690	40656	16.97	1.376 (1.23, 1.54)		1.359 (1.214, 1.52)		1.209 (1.08, 1.353)	
			Q4 (high)	8751	1072	33196	32.29	2.638 (2.38, 2.924)		2.187 (1.972, 2.425)		1.719 (1.546, 1.911)	
	Myocardial infarction	Continuous		NA				1.169 (1.103, 1.238)	< 0.001	1.138 (1.074, 1.205)	< 0.001	1.088 (1.027, 1.153)	0.004
		Categorical	Q1 (low)	11397	227	44116	5.15	Reference	< 0.001	Reference	<0.001	Reference	0.02
			Q2	11096	231	43310	5.33	1.032 (0.859, 1.239)		1.058 (0.881, 1.271)		1.033 (0.86, 1.242)	
			Q3	10421	239	40305	5.93	1.15 (0.959, 1.379)		1.153 (0.961, 1.382)		1.087 (0.906, 1.304)	
			Q4 (high)	8751	270	32839	8.22	1.604 (1.345, 1.914)		1.484 (1.243, 1.771)		1.298 (1.084, 1.554)	
	Stroke	Continuous		NA				1.13 (1.077, 1.185)	< 0.001	1.09 (1.039, 1.143)	< 0.001	1.054 (1.004, 1.106)	0.03
		Categorical	Q1 (low)	11397	331	43911	7.54	Reference	< 0.001	Reference	<0.001	Reference	0.13
			Q2	11096	350	43071	8.13	1.077 (0.927, 1.251)		1.117 (0.961, 1.299)		1.102 (0.948, 1.281)	
			Q3	10421	339	40117	8.45	1.121 (0.963, 1.304)		1.127 (0.968, 1.311)		1.074 (0.923, 1.251)	
			Q4 (high)	8751	363	32673	11.11	1.478 (1.273, 1.715)		1.328 (1.144, 1.542)		1.200 (1.031, 1.397)	
	Kidney replacement therapy	Continuous		NA				1.234 (1.188, 1.282)	< 0.001	1.244 (1.197, 1.292)	< 0.001	1.066 (1.026, 1.108)	0.001
		Categorical	Q1 (low)	11397	474	43750	10.83	Reference	< 0.001	Reference	<0.001	Reference	<0.001
			Q2	11096	535	42866	12.48	1.149 (1.015, 1.3)		1.113 (0.983, 1.26)		0.967 (0.854, 1.095)	
			Q3	10421	575	39725	14.47	1.337 (1.184, 1.51)		1.314 (1.164, 1.484)		1.081 (0.957, 1.221)	
			Q4 (high)	8751	652	32184	20.26	1.889 (1.679, 2.127)		1.921 (1.707, 2.162)		1.182 (1.047, 1.335)	
Female	All-cause mortality	Continuous		NA				1.405 (1.345, 1.467)	< 0.001	1.277 (1.223, 1.333)	< 0.001	1.188 (1.138, 1.241)	< 0.001
		Categorical	Q1 (low)	9762	300	38502	7.79	Reference	< 0.001	Reference	<0.001	Reference	<0.001
			Q2	10063	275	39827	6.90	0.885 (0.751, 1.042)		0.906 (0.769, 1.067)		0.874 (0.742, 1.03)	
			Q3	10738	415	42527	9.76	1.248 (1.076, 1.448)		1.187 (1.023, 1.377)		1.091 (0.94, 1.266)	
			Q4 (high)	12408	880	48364	18.20	2.338 (2.051, 2.666)		1.849 (1.62, 2.11)		1.515 (1.325, 1.732)	
	Myocardial infarction	Continuous		NA				1.128 (1.063, 1.198)	< 0.001	1.083 (1.02, 1.15)	0.009	1.048 (0.987, 1.113)	0.124
		Categorical	Q1 (low)	9762	183	38245	4.78	Reference	< 0.001	Reference	0.005	Reference	0.049
			Q2	10063	157	39582	3.97	0.827 (0.669, 1.024)		0.84 (0.679, 1.04)		0.833 (0.673, 1.031)	
			Q3	10738	231	42156	5.48	1.141 (0.94, 1.385)		1.12 (0.922, 1.36)		1.084 (0.893, 1.317)	
			Q4 (high)	12408	301	47943	6.28	1.311 (1.091, 1.576)		1.175 (0.977, 1.413)		1.07 (0.887, 1.29)	
	Stroke	Continuous		NA				1.142 (1.087, 1.2)	< 0.001	1.086 (1.034, 1.141)	0.001	1.054 (1.003, 1.107)	0.04
		Categorical	Q1 (low)	9762	253	38097	6.64	Reference	< 0.001	Reference	0.006	Reference	0.18
			Q2	10063	260	39388	6.60	0.994 (0.836, 1.181)		1.012 (0.851, 1.204)		1.004 (0.844, 1.194)	
			Q3	10738	313	41990	7.45	1.121 (0.95, 1.323)		1.096 (0.929, 1.294)		1.062 (0.9, 1.254)	
			Q4 (high)	12408	457	47633	9.59	1.446 (1.24, 1.686)		1.263 (1.083, 1.474)		1.158 (0.99, 1.354)	
	Kidney replacement therapy	Continuous		NA				1.219 (1.153, 1.289)	< 0.001	1.237 (1.169, 1.308)	< 0.001	1.083 (1.023, 1.146)	0.006
		Categorical	Q1 (low)	9762	172	38303	4.49	Reference	< 0.001	Reference	<0.001	Reference	0.02
			Q2	10063	219	39530	5.54	1.233 (1.01, 1.506)		1.191 (0.975, 1.454)		1.056 (0.864, 1.29)	
			Q3	10738	257	42171	6.09	1.356 (1.118, 1.644)		1.324 (1.091, 1.606)		1.045 (0.861, 1.269)	
			Q4 (high)	12408	392	47773	8.21	1.837 (1.536, 2.198)		1.889 (1.579, 2.26)		1.274 (1.063, 1.527)	

HR = hazard ratio, CI = confidence interval

[a] Multivariable model was adjusted for age, sex, number of exams, current-smoking, drinking alcohol, regular physical activity, low income state, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline body mass index, waist circumference, fasting glucose, systolic BP, diastolic BP, high-density lipoprotein, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Supplemental Table 5. Risk of adverse outcomes according to body mass index variability in predialysis CKD patients stratified by baseline body mass index ≥ 25 kg/m^2.

Subgroup	Outcome	BMI variability independent of mean exposure		N	Event	Follow-up person-years	Incidence rate (/1000PY)	Univariable model		Age, sex, and number of exams adjusted model		Multivariable model [a]	
								HR (95% CI)	P	adjusted HR (95% CI)	P	adjusted HR (95% CI)	P
BMI ≥ 25 kg/m^2	All-cause mortality	Continuous		NA				1.268 (1.213, 1.326)	< 0.001	1.269 (1.214, 1.326)	< 0.001	1.21 (1.158, 1.266)	< 0.001
		Categorical	Q1 (low)	10578	352	41638	8.45	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
			Q2	9767	319	38633	8.26	0.974 (0.837, 1.133)		1.033 (0.888, 1.203)		1.011 (0.868, 1.176)	
			Q3	9303	423	36671	11.54	1.361 (1.182, 1.568)		1.442 (1.252, 1.662)		1.347 (1.169, 1.552)	
			Q4 (high)	8173	515	31807	16.19	1.921 (1.678, 2.2)		1.947 (1.698, 2.232)		1.697 (1.479, 1.947)	
	Myocardial infarction	Continuous		NA				1.097 (1.031, 1.168)	0.004	1.1 (1.033, 1.171)	0.003	1.061 (0.996, 1.13)	0.07
		Categorical	Q1 (low)	10578	212	41328	5.13	Reference	0.003	Reference	0.004	Reference	0.08
			Q2	9767	172	38369	4.48	0.871 (0.712, 1.065)		0.897 (0.734, 1.098)		0.883 (0.722, 1.08)	
			Q3	9303	204	36334	5.61	1.092 (0.901, 1.323)		1.121 (0.924, 1.359)		1.066 (0.879, 1.292)	
			Q4 (high)	8173	205	31496	6.51	1.27 (1.048, 1.539)		1.282 (1.057, 1.556)		1.149 (0.946, 1.396)	
	Stroke	Continuous		NA				1.086 (1.031, 1.143)	0.002	1.082 (1.027, 1.14)	0.003	1.046 (0.993, 1.102)	0.09
		Categorical	Q1 (low)	10578	300	41151	7.29	Reference	0.01	Reference	0.02	Reference	0.33
			Q2	9767	275	38170	7.20	0.988 (0.839, 1.163)		1.03 (0.874, 1.213)		1.016 (0.862, 1.197)	
			Q3	9303	300	36169	8.29	1.137 (0.969, 1.335)		1.173 (1, 1.377)		1.123 (0.957, 1.319)	
			Q4 (high)	8173	287	31371	9.15	1.256 (1.069, 1.477)		1.246 (1.059, 1.467)		1.123 (0.953, 1.324)	
	Kidney replacement therapy	Continuous		NA				1.185 (1.127, 1.246)	< 0.001	1.238 (1.176, 1.303)	< 0.001	1.088 (1.034, 1.146)	0.001
		Categorical	Q1 (low)	10578	289	41246	7.01	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
			Q2	9767	290	38219	7.59	1.081 (0.918, 1.272)		1.051 (0.893, 1.238)		0.84 (0.712, 0.991)	
			Q3	9303	318	36176	8.79	1.255 (1.07, 1.472)		1.283 (1.094, 1.505)		1.037 (0.883, 1.218)	
			Q4 (high)	8173	361	31248	11.55	1.66 (1.422, 1.937)		1.878 (1.607, 2.195)		1.21 (1.033, 1.418)	
BMI < 25 kg/m^2	All-cause mortality	Continuous		NA				1.391 (1.346, 1.438)	< 0.001	1.289 (1.247, 1.332)	< 0.001	1.164 (1.125, 1.203)	< 0.001
		Categorical	Q1 (low)	10581	495	41301	11.99	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
			Q2	11392	559	44867	12.46	1.035 (0.917, 1.168)		1.065 (0.944, 1.202)		1.035 (0.917, 1.168)	
			Q3	11856	682	46513	14.66	1.219 (1.086, 1.369)		1.184 (1.054, 1.329)		1.057 (0.941, 1.187)	
			Q4 (high)	12986	1437	49753	28.88	2.414 (2.179, 2.673)		2.008 (1.811, 2.226)		1.524 (1.372, 1.694)	
	Myocardial infarction	Continuous		NA				1.17 (1.107, 1.237)	< 0.001	1.124 (1.064, 1.188)	< 0.001	1.084 (1.024, 1.147)	0.005
		Categorical	Q1 (low)	10581	198	41033	4.83	Reference	< 0.001	Reference	< 0.001	Reference	0.03
			Q2	11392	216	44523	4.85	1.001 (0.826, 1.214)		1.02 (0.841, 1.237)		0.997 (0.822, 1.209)	
			Q3	11856	266	46127	5.77	1.191 (0.991, 1.431)		1.175 (0.977, 1.412)		1.123 (0.933, 1.35)	
			Q4 (high)	12986	366	49287	7.43	1.54 (1.296, 1.831)		1.385 (1.164, 1.649)		1.243 (1.04, 1.485)	
	Stroke	Continuous		NA				1.161 (1.108, 1.215)	< 0.001	1.101 (1.051, 1.153)	< 0.001	1.059 (1.011, 1.11)	0.02
		Categorical	Q1 (low)	10581	284	40857	6.95	Reference	< 0.001	Reference	< 0.001	Reference	0.03
			Q2	11392	335	44290	7.56	1.087 (0.928, 1.273)		1.113 (0.95, 1.304)		1.099 (0.938, 1.288)	
			Q3	11856	352	45937	7.66	1.101 (0.942, 1.288)		1.082 (0.925, 1.265)		1.038 (0.887, 1.214)	
			Q4 (high)	12986	533	48935	10.89	1.569 (1.359, 1.812)		1.363 (1.178, 1.576)		1.221 (1.053, 1.417)	
	Kidney replacement therapy	Continuous		NA				1.165 (1.12, 1.212)	< 0.001	1.229 (1.18, 1.28)	< 0.001	1.044 (1.002, 1.087)	0.04
		Categorical	Q1 (low)	10581	357	40807	8.75	Reference	< 0.001	Reference	< 0.001	Reference	0.17
			Q2	11392	464	44176	10.50	1.199 (1.044, 1.376)		1.178 (1.026, 1.352)		1.087 (0.946, 1.249)	
			Q3	11856	514	45720	11.24	1.284 (1.122, 1.47)		1.313 (1.147, 1.503)		1.075 (0.939, 1.231)	
			Q4 (high)	12986	683	48710	14.02	1.613 (1.419, 1.834)		1.868 (1.643, 2.124)		1.16 (1.017, 1.322)	

HR = hazard ratio, CI = confidence interval

[a] Multivariable model was adjusted for age, sex, number of exams, current-smoking, drinking alcohol, regular physical activity, low income state, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline body mass index, waist circumference, fasting glucose, systolic BP, diastolic BP, high-density lipoprotein, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Supplemental Table 6. Risk of adverse outcomes according to body mass index variability in predialysis CKD patients stratified by the presence of diabetes mellitus.

Subgroup	Outcome	BMI variability independent of mean exposure		N	Event	Follow-up person-years	Incidence rate (/1000PY)	Univariable model		Age, sex, and number of exams adjusted model		Multivariable model [a]	
								HR (95% CI)	P	adjusted HR (95% CI)	P	adjusted HR (95% CI)	P
DM (+)	All-cause mortality	Continuous		NA				1.309 (1.256, 1.365)	< 0.001	1.291 (1.239, 1.346)	< 0.001	1.221 (1.171, 1.274)	< 0.001
		Categorical	Q1 (low)	5809	323	22600	14.29	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
			Q2	5919	344	23242	14.80	1.03 (0.885, 1.199)		1.078 (0.926, 1.255)		1.044 (0.897, 1.215)	
			Q3	6196	471	24029	19.60	1.371 (1.19, 1.579)		1.397 (1.212, 1.609)		1.292 (1.121, 1.49)	
			Q4 (high)	7095	797	27017	29.50	2.075 (1.823, 2.361)		2.036 (1.787, 2.319)		1.737 (1.522, 1.982)	
	Myocardial infarction	Continuous		NA				1.053 (0.99, 1.12)	0.100	1.045 (0.982, 1.112)	0.16	1.015 (0.953, 1.08)	0.65
		Categorical	Q1 (low)	5809	186	22338	8.33	Reference	0.11	Reference	0.20	Reference	0.49
			Q2	5919	170	22982	7.40	0.885 (0.719, 1.09)		0.893 (0.725, 1.1)		0.876 (0.711, 1.079)	
			Q3	6196	196	23720	8.26	0.992 (0.812, 1.212)		0.99 (0.81, 1.211)		0.952 (0.778, 1.164)	
			Q4 (high)	7095	250	26663	9.38	1.129 (0.934, 1.365)		1.107 (0.914, 1.34)		1.014 (0.835, 1.23)	
	Stroke	Continuous		NA				1.108 (1.052, 1.167)	< 0.001	1.094 (1.039, 1.152)	< 0.001	1.071 (1.017, 1.129)	0.01
		Categorical	Q1 (low)	5809	242	22198	10.90	Reference	< 0.001	Reference	0.006	Reference	0.06
			Q2	5919	245	22819	10.74	0.984 (0.824, 1.176)		1.016 (0.85, 1.213)		1.006 (0.842, 1.202)	
			Q3	6196	288	23510	12.25	1.124 (0.948, 1.334)		1.135 (0.956, 1.347)		1.107 (0.932, 1.314)	
			Q4 (high)	7095	381	26430	14.42	1.324 (1.127, 1.556)		1.287 (1.095, 1.514)		1.211 (1.028, 1.427)	
	Kidney replacement therapy	Continuous		NA				1.158 (1.107, 1.212)	< 0.001	1.222 (1.167, 1.279)	< 0.001	1.099 (1.049, 1.151)	< 0.001
		Categorical	Q1 (low)	5809	302	22184	13.61	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
			Q2	5919	315	22765	13.84	1.014 (0.866, 1.187)		0.984 (0.84, 1.153)		0.827 (0.705, 0.969)	
			Q3	6196	390	23424	16.65	1.226 (1.055, 1.424)		1.256 (1.081, 1.46)		1.071 (0.92, 1.245)	
			Q4 (high)	7095	530	26189	20.24	1.499 (1.301, 1.726)		1.727 (1.499, 1.991)		1.21 (1.047, 1.399)	
DM (-)	All-cause mortality	Continuous		NA				1.383 (1.336, 1.431)	< 0.001	1.279 (1.236, 1.324)	< 0.001	1.181 (1.141, 1.223)	< 0.001
		Categorical	Q1 (low)	15350	524	60339	8.68	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
			Q2	15240	534	60257	8.86	1.017 (0.902, 1.148)		1.053 (0.933, 1.187)		1.028 (0.911, 1.16)	
			Q3	14963	634	59155	10.72	1.23 (1.095, 1.38)		1.217 (1.084, 1.366)		1.101 (0.98, 1.237)	
			Q4 (high)	14064	1155	54543	21.18	2.44 (2.201, 2.706)		2.003 (1.805, 2.224)		1.607 (1.444, 1.788)	
	Myocardial infarction	Continuous		NA				1.185 (1.121, 1.252)	< 0.001	1.144 (1.083, 1.209)	< 0.001	1.118 (1.057, 1.182)	< 0.001
		Categorical	Q1 (low)	15350	224	60022	3.73	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
			Q2	15240	218	59910	3.64	0.971 (0.806, 1.17)		0.999 (0.829, 1.204)		0.994 (0.825, 1.198)	
			Q3	14963	274	58741	4.66	1.244 (1.043, 1.484)		1.247 (1.045, 1.489)		1.212 (1.015, 1.446)	
			Q4 (high)	14064	321	54120	5.93	1.589 (1.339, 1.884)		1.442 (1.214, 1.713)		1.351 (1.135, 1.609)	
	Stroke	Continuous		NA				1.118 (1.068, 1.17)	< 0.001	1.064 (1.017, 1.114)	0.007	1.045 (0.998, 1.094)	0.06
		Categorical	Q1 (low)	15350	342	59810	5.72	Reference	< 0.001	Reference	0.03	Reference	0.17
			Q2	15240	365	59640	6.12	1.069 (0.922, 1.239)		1.099 (0.948, 1.273)		1.098 (0.947, 1.272)	
			Q3	14963	364	58596	6.21	1.085 (0.936, 1.257)		1.076 (0.928, 1.248)		1.053 (0.908, 1.221)	
			Q4 (high)	14064	439	53876	8.15	1.427 (1.238, 1.643)		1.236 (1.071, 1.425)		1.172 (1.013, 1.354)	
	Kidney replacement therapy	Continuous		NA				1.169 (1.12, 1.22)	< 0.001	1.222 (1.17, 1.276)	< 0.001	1.047 (1.003, 1.094)	0.04
		Categorical	Q1 (low)	15350	344	59870	5.75	Reference	< 0.001	Reference	< 0.001	Reference	0.03
			Q2	15240	439	59631	7.36	1.279 (1.111, 1.473)		1.236 (1.073, 1.424)		1.159 (1.006, 1.335)	
			Q3	14963	442	58472	7.56	1.313 (1.141, 1.512)		1.325 (1.15, 1.525)		1.056 (0.917, 1.217)	
			Q4 (high)	14064	514	53769	9.56	1.672 (1.459, 1.917)		1.887 (1.645, 2.164)		1.207 (1.05, 1.387)	

DM = diabetes mellitus, HR = hazard ratio, CI = confidence interval

[a] Multivariable model was adjusted for age, sex, number of exams, current-smoking, drinking alcohol, regular physical activity, low income state, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline body mass index, waist circumference, fasting glucose, systolic BP, diastolic BP, high-density lipoprotein, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.

Supplemental Table 7. Risk of adverse outcomes according to body mass index variability in predialysis CKD patients stratified by baseline eGFR < 60 mL/min/1.73 m^2.

Subgroup	Outcome	BMI variability independent of mean exposure		N	Event	Follow-up person-years	Incidence rate (/1000PY)	Univariable model		Age, sex, and number of exams adjusted model		Multivariable model [a]	
								HR (95% CI)	P	adjusted HR (95% CI)	P	adjusted HR (95% CI)	P
Baseline eGFR < 60	All-cause mortality	Continuous		NA				1.358 (1.321, 1.396)	< 0.001	1.291 (1.256, 1.327)	< 0.001	1.191 (1.158, 1.224)	< 0.001
		Categorical	Q1 (low)	17594	769	68941	11.15	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
			Q2	17485	786	68984	11.39	1.018 (0.921, 1.124)		1.051 (0.952, 1.161)		1.014 (0.918, 1.121)	
			Q3	17586	1000	69142	14.46	1.293 (1.177, 1.42)		1.283 (1.167, 1.409)		1.151 (1.047, 1.265)	
			Q4 (high)	18084	1784	69639	25.62	2.302 (2.116, 2.505)		2.035 (1.868, 2.216)		1.621 (1.486, 1.769)	
	Myocardial infarction	Continuous		NA				1.153 (1.104, 1.205)	< 0.001	1.126 (1.078, 1.177)	< 0.001	1.082 (1.035, 1.131)	< 0.001
		Categorical	Q1 (low)	17594	350	68439	5.11	Reference	< 0.001	Reference	< 0.001	Reference	0.002
			Q2	17485	341	68462	4.98	0.971 (0.836, 1.127)		0.988 (0.851, 1.147)		0.97 (0.836, 1.127)	
			Q3	17586	415	68503	6.06	1.181 (1.024, 1.361)		1.177 (1.021, 1.357)		1.122 (0.973, 1.294)	
			Q4 (high)	18084	520	68939	7.54	1.476 (1.289, 1.69)		1.386 (1.209, 1.588)		1.232 (1.072, 1.415)	
	Stroke	Continuous		NA				1.132 (1.092, 1.174)	< 0.001	1.092 (1.053, 1.133)	< 0.001	1.057 (1.019, 1.097)	0.003
		Categorical	Q1 (low)	17594	510	68138	7.48	Reference	< 0.001	Reference	< 0.001	Reference	0.02
			Q2	17485	530	68096	7.78	1.039 (0.92, 1.173)		1.065 (0.943, 1.203)		1.053 (0.932, 1.189)	
			Q3	17586	567	68222	8.31	1.109 (0.984, 1.25)		1.101 (0.977, 1.241)		1.059 (0.939, 1.194)	
			Q4 (high)	18084	742	68504	10.83	1.45 (1.295, 1.623)		1.314 (1.173, 1.472)		1.193 (1.063, 1.339)	
	Kidney replacement therapy	Continuous		NA				1.17 (1.134, 1.208)	< 0.001	1.246 (1.206, 1.287)	< 0.001	1.059 (1.025, 1.094)	< 0.001
		Categorical	Q1 (low)	17594	618	68087	9.08	Reference	< 0.001	Reference	< 0.001	Reference	0.002
			Q2	17485	726	67912	10.69	1.176 (1.057, 1.309)		1.149 (1.032, 1.28)		0.990 (0.888, 1.102)	
			Q3	17586	804	67885	11.84	1.305 (1.175, 1.449)		1.351 (1.217, 1.501)		1.059 (0.953, 1.177)	
			Q4 (high)	18084	995	68104	14.61	1.621 (1.466, 1.792)		1.927 (1.743, 2.132)		1.170 (1.056, 1.296)	
Baseline eGFR ≥ 60	All-cause mortality	Continuous		NA				1.383 (1.267, 1.51)	< 0.001	1.34 (1.229, 1.461)	< 0.001	1.242 (1.138, 1.355)	< 0.001
		Categorical	Q1 (low)	3565	78	13998	5.57	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
			Q2	3674	92	14516	6.34	1.132 (0.837, 1.531)		1.219 (0.901, 1.649)		1.192 (0.881, 1.613)	
			Q3	3573	105	14042	7.48	1.34 (1, 1.796)		1.44 (1.074, 1.931)		1.337 (0.996, 1.794)	
			Q4 (high)	3075	168	11921	14.09	2.538 (1.94, 3.319)		2.376 (1.813, 3.115)		1.921 (1.458, 2.532)	
	Myocardial infarction	Continuous		NA				1.016 (0.898, 1.148)	0.81	1.011 (0.894, 1.142)	0.87	0.983 (0.869, 1.111)	0.78
		Categorical	Q1 (low)	3565	60	13922	4.31	Reference	0.45	Reference	0.61	Reference	0.70
			Q2	3674	47	14430	3.26	0.753 (0.514, 1.103)		0.785 (0.536, 1.151)		0.791 (0.539, 1.161)	
			Q3	3573	55	13958	3.94	0.914 (0.634, 1.317)		0.951 (0.66, 1.372)		0.919 (0.636, 1.327)	
			Q4 (high)	3075	51	11844	4.31	1.002 (0.69, 1.455)		0.984 (0.676, 1.432)		0.909 (0.622, 1.328)	
	Stroke	Continuous		NA				1.077 (0.974, 1.191)	0.15	1.066 (0.965, 1.178)	0.21	1.036 (0.937, 1.146)	0.49
		Categorical	Q1 (low)	3565	74	13870	5.34	Reference	0.55	Reference	0.60	Reference	0.81
			Q2	3674	80	14363	5.57	1.047 (0.763, 1.436)		1.102 (0.803, 1.512)		1.094 (0.797, 1.501)	
			Q3	3573	85	13884	6.12	1.148 (0.841, 1.568)		1.214 (0.888, 1.658)		1.168 (0.854, 1.597)	
			Q4 (high)	3075	78	11802	6.61	1.239 (0.902, 1.703)		1.199 (0.871, 1.651)		1.102 (0.798, 1.522)	
	Kidney replacement therapy	Continuous		NA				1.291 (1.102, 1.512)	0.002	1.328 (1.132, 1.557)	< 0.001	1.199 (1.02, 1.409)	0.03
		Categorical	Q1 (low)	3565	28	13967	2.00	Reference	< 0.001	Reference	< 0.001	Reference	0.01
			Q2	3674	28	14483	1.93	0.958 (0.567, 1.617)		0.959 (0.568, 1.622)		0.915 (0.541, 1.549)	
			Q3	3573	28	14011	2.00	0.994 (0.589, 1.678)		1.018 (0.602, 1.72)		0.879 (0.518, 1.49)	
			Q4 (high)	3075	49	11854	4.13	2.078 (1.306, 3.307)		2.253 (1.414, 3.589)		1.698 (1.056, 2.729)	

HR = hazard ratio, CI = confidence interval

[a] Multivariable model was adjusted for age, sex, number of exams, current-smoking, drinking alcohol, regular physical activity, low income state, history of diabetes mellitus, hypertension, dyslipidemia, cancer, chronic lung disease, baseline body mass index, waist circumference, fasting glucose, systolic BP, diastolic BP, high-density lipoprotein, baseline eGFR, presence of dipstick albuminuria, and eGFR variability during the exposure assessment period.