Supplementary Appendix

Association of Longitudinal Trajectories of Insulin Resistance with Adverse Renal Outcomes

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Study population

KoGES is a prospective cohort study in which participants from the general population aged 40–69 years residing in a rural area of South Korea were enrolled from 2001 to 2002. The participants were followed every 2 years with the seventh check-up in 2014. The participants underwent anthropometric examination, laboratory tests, and completed questionnaires on lifestyle and medical history at every check-up. The aim of KoGES study is to track public health trends and to provide novel insights into preventive health care issues in South Korea by the Korean government.

Data collection

The anthropometric examinations were conducted by trained nurses following the standard protocols. All blood samples were obtained after 8h fasting and analyzed by Seoul Clinical Laboratories (Seoul, Republic of Korea) within 24h of sampling. Serum creatinine, blood urea nitrogen, glucose, insulin, alanine transaminase, aspartate transaminase, HbA1c, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and high sensitivity C-reactive protein were analyzed. Urine samples were obtained after the first void, and a urine test was conducted with a calibrated urine reagent strip (URiSCAN Pro II; YD Diagnostics Corp., Seoul, Korea). Throughout the study period, two types of chemistry analyzers were used (ADVIA 1650, Siemens, Tarrytown, NY from September 2002 to December 2010; ADVIA 1800, Siemens, Tarrytown, NY after January 2011). To minimize the measurement variability between the analyzers, adequate equations per the manufacturers were applied to convert the values measured by ADVIA 1800 to that from ADVIA 1650 for serum glucose, total cholesterol, high-density lipoprotein cholesterol, triglyceride, alanine transaminase, aspartate transaminase, blood urea nitrogen, and creatinine.

Latent class analysis for classification of the participants by time-serial insulin resistance trajectory

The fitness of the model was estimated using the following three prespecified criteria. First, the Bayesian information criterion (BIC) was used to estimate the model performance. Second, the average probability of the final group membership across the trajectory groups should be over 90%. Third, at least 5% of all participants should be included in each group (1). We constructed models ranging from two to five trajectories and assessed the fitness of each model. Although BIC tends to decrease with an increasing number of trajectories, the average probability of the final group membership across the trajectory groups declined to less than 90% (**Supplementary Table S1**). Therefore, two homeostatic model assessment for insulin resistance (HOMA-IR) trajectories were identified to meet all three prespecified criteria. Consequently, the time-serial trajectories of HOMA-IR were defined as either stable or increasing.

As a sensitivity analysis for the differential association of the identified HOMA-IR trajectories with renal outcomes, three and four trajectories were used, and their association with outcomes was analyzed; however, they did not meet all three prespecified criteria of model fitness.

Statistical analyses

Continuous variables are shown as mean±standard deviation, and categorical variables as numbers (percentages). For comparison between groups, the Student's t-test or analysis of variance was used for continuous variables, and the chi-square test was used for categorical variables. For the survival analysis, Kaplan-Meier censoring estimates were used to calculate the cumulative event rates, and the log-rank test was used to compare the survival curves

between groups. The Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI), and the model assumption was assessed using Schoenfeld residuals. In the sensitivity analysis of patients with estimated glomerular filtration rate (eGFR) ≥90 mL/min/1.73m^2 at baseline and fourth check-ups, covariates were individually adjusted to avoid overfitting due to the small number of adverse renal outcomes in this population. For the sensitivity analysis to minimize the confounding effect of diabetes mellitus at baseline, subgroup analysis in subjects with or without diabetes mellitus at baseline was performed. In each subpopulation, the association of the HOMA-IR trajectory with adverse renal outcomes was evaluated. To account for newly developed diabetes during the exposure period, the outcome analysis was performed in subjects with diabetes mellitus at the end of the exposure period (fourth check-up). The outcomes by HOMA-IR trajectory were also investigated in each subgroup according to the clinical characteristics such as age ≥60 years, sex, body mass index ≥25 kg/m^2, the presence of hypertension and dyslipidemia at baseline check-up, baseline HOMA-IR ≥2.01 (75th percentile), and baseline eGFR <90 mL/min/1.73m^2. To eliminate the potential bias by baseline HOMA-IR levels, 1:1 matching by baseline HOMA-IR between the HOMA-IR trajectory groups was performed using propensity score matching using a logistic regression model with the nearest-neighbor method without replacement and a caliper of 0.01 of the score.

Supplementary Table

Supplementary Table S1. Estimation process for the most optimal number of HOMA-IR trajectories.

Number of groups	BIC	Average probability of group membership	Proportion of groups (%)				
			Group 1	Group 2	Group 3	Group 4	Group 5
2	45802	95.1%	89.2	10.8			
3	45327	85.6%	79.1	14.1	6.8		
4	45310	70.1%	59.8	24.0	8.5	7.7	
5	45286	56.4%	41.5	29.2	15.6	7.1	6.7

BIC, Bayesian information criterion; HOMA-IR, homeostatic model assessment of insulin resistance.

Supplementary Table S2. Multivariate analyses for the association between increasing HOMA-IR trajectory and adverse renal outcomes using various definitions of dyslipidemia.

Model 2 with other definitions of dyslipidemia	HR (95%CI)	P-value
Age + sex + baseline eGFR + BMI ≥25kg/m^2 + diabetes mellitus + hypertension + various definitions of dyslipidemia as below:		
Total cholesterol ≥200 mg/dL or treatment with any lipid-lowering medications (n=2010)	1.58 (1.22 – 2.05)	<0.001
Total cholesterol ≥240 mg/dL or treatment with any lipid-lowering medications (n=555)	1.58 (1.22 – 2.05)	<0.001
Triglyceride ≥150 mg/dL or treatment with any lipid-lowering medications (n=2220)	1.53 (1.18 – 1.99)	0.001
Triglyceride ≥200 mg/dL or treatment with any lipid-lowering medications (n=1245)	1.56 (1.20 – 2.03)	<0.001
LDL-C ≥100 mg/dL or treatment with any lipid-lowering medications (n=3567)	1.57 (1.21 – 2.04)	<0.001
LDL-C ≥130 mg/dL or treatment with any lipid-lowering medications (n=1622)	1.58 (1.22 – 2.05)	<0.001
LDL-C ≥160 mg/dL or treatment with any lipid-lowering medications (n=538)	1.58 (1.22 – 2.05)	<0.001
HDL-C <40 mg/dL or treatment with any lipid-lowering medications (n=1816)	1.58 (1.22 – 2.05)	<0.001
Triglyceride ≥150 mg/dL or HDL-C <40 mg/dL or treatment with any lipid-lowering medications (n=2859)	1.56 (1.20 – 2.02)	<0.001
Triglyceride ≥200 mg/dL or HDL-C <40 mg/dL or treatment with any lipid-lowering medications (n=2277)	1.56 (1.20 – 2.03)	<0.001
Triglyceride ≥150 mg/dL or LDL-C ≥100 mg/dL or treatment with any lipid-lowering medications (n=4363)	1.58 (1.22 – 2.05)	<0.001
Triglyceride ≥200 mg/dL or LDL-C ≥160 mg/dL or treatment with any lipid-lowering medications (n=1569)	1.57 (1.21 – 2.04)	<0.001
Triglyceride ≥150 mg/dL or HDL-C <40 mg/dL or LDL-C ≥100 mg/dL or treatment with any lipid-lowering medications (n=4603)	1.58 (1.21 – 2.05)	<0.001
Triglyceride ≥200 mg/dL or HDL-C <40 mg/dL or LDL-C ≥160 mg/dL or treatment with any lipid-lowering medications (n=2560)	1.57 (1.21 – 2.04)	<0.001

HR (95% CI) for adverse renal outcomes of increasing HOMA-IR trajectory compared to stable HOMA-IR trajectory is presented.

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

Supplementary Table S3. Risk of adverse renal outcomes in patients without adverse renal outcomes during the exposure period (n=5,126).

HOMA-IR trajectory	Unadjusted HR (95%CI)	P-value	Model 1 HR (95% CI)	P-value	Model 2 HR (95% CI)	P-value	Model 3 HR (95% CI)	P-value
Stable	1 (ref)	NA	1 (ref)	NA	1 (ref)	NA	1 (ref)	NA
Increasing	1.83 (1.39 – 2.40)	<0.001	1.65 (1.26 – 2.17)	<0.001	1.40 (1.04 – 1.88)	0.027	1.55 (1.13 – 2.12)	0.007

HR (95% CI) for adverse renal outcomes of increasing HOMA-IR trajectory compared to stable HOMA-IR trajectory is presented. In this population, adverse renal outcomes occurred in 372 patients during the event accrual period.

Model 1, adjusted for age, sex, baseline eGFR.

Model 2, Model 1 + BMI $\geq$25kg/m^2, diabetes mellitus, hypertension, dyslipidemia

Model 3, Model 1 + baseline BMI, SBP, LDL-C, HOMA-IR, hs-CRP

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Supplementary Table S4. Risk of adverse renal outcomes in patients with eGFR ≥90 mL/min/1.73m^2 at baseline and fourth check-ups (n=704).

Adjusted variables	HR (95% CI)	P-value
Age	4.04 (1.42 – 11.51)	0.009
Sex	3.82 (1.34 – 10.89)	0.012
Baseline eGFR	3.97 (1.40 – 11.30)	0.010
BMI ≥25kg/m^2	3.84 (1.31 – 11.26)	0.014
Diabetes mellitus	3.73 (1.22 – 11.34)	0.021
Hypertension	3.03 (1.03 – 8.96)	0.045
Dyslipidemia	3.13 (1.09 – 9.02)	0.035
Baseline BMI	3.30 (1.11 – 9.82)	0.032
Baseline SBP	3.22 (1.12 – 9.24)	0.030
Baseline LDL-C	3.87 (1.23 – 12.21)	0.021
Baseline HOMA-IR	3.83 (1.26 – 11.68)	0.018
Baseline hs-CRP	3.92 (1.38 – 11.15)	0.010

HR (95% CI) for adverse renal outcomes of the increasing HOMA-IR trajectory compared to the stable HOMA-IR trajectory is presented. Due to the small number of adverse renal outcomes (n=17) in this population, covariates were individually adjusted to avoid overfitting.

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Supplementary Table S5. Baseline characteristics by three HOMA-IR trajectories.

	HOMA-IR trajectory			
	Stable with low baseline HOMA-IR (n=4,232)	Stable with high baseline HOMA-IR (n=752)	Increasing (n=363)	P-value
Age, years	51.0±8.2	51.2±8.0	51.8±8.4	0.071
Male	2004 (47.4)	357 (47.5)	196 (54.0)	0.051
BMI, kg/m^2	24.1±2.9	26.7±2.9	26.5±3.2	<0.001
Waist circumference, cm	81.1±8.2	88.5±7.6	87.6±8.1	<0.001
SBP, mmHg	119.0±17.0	126.5±18.3	123.9±18.0	<0.001
DBP, mmHg	79.1±10.9	83.8±11.2	82.8±11.5	<0.001
ALT, units/L	25.6±20.3	34.4±20.8	45.2±89.2	<0.001
AST, units/L	28.2±12.9	29.8±11.9	38.6±47.4	<0.001
BUN, mg/dl	14.2±3.6	14.2±3.4	14.6±3.6	0.041
Creatinine, mg/dl	0.83±0.16	0.83±0.17	0.84±0.17	0.099
Cholesterol, mg/dl	188.3±33.8	197.5±34.7	200.4±37.7	<0.001
HDL-C, mg/dl	45.4±10.0	41.0±8.0	41.8±9.2	<0.001
Fasting glucose, mg/dl	82.9±10.7	98.8±31.9	105.5±35.9	<0.001
HbA1c, %	5.6±0.5	6.2±1.2	6.7±1.6	<0.001
eGFR, ml/min/1.73m^2	93.1±12.3	92.3±12.8	92.4±12.7	0.071
HOMA-IR	1.4±0.6	3.1±1.9	2.0±1.2	<0.001
hs-CRP	0.2±0.6	0.2±0.3	0.3±0.6	0.003
Diabetes mellitus	316 (7.5)	231 (30.7)	181 (49.9)	<0.001
Hypertension	1097 (25.9)	329 (43.8)	154 (42.4)	<0.001
Dyslipidemia	1845 (43.6)	507 (67.4)	240 (66.1)	<0.001

All values are presented as number (percentage) or mean ± standard deviation.

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure.

Supplementary Table S6. Baseline characteristics by four HOMA-IR trajectories.

	HOMA-IR trajectory				
	Stable with low baseline HOMA-IR (n=3,200)	Stable with high baseline HOMA-IR (n=410)	Slightly increasing (n=1,283)	Rapidly increasing (n=454)	P-value
Age, years	51.1±8.3	50.8±7.9	50.8±8.1	51.9±8.4	0.470
Male	1525 (47.7)	189 (46.1)	600 (46.8)	243 (53.5)	0.071
BMI, kg/m^2	23.7±2.8	26.9±3.0	25.6±2.7	26.5±3.1	<0.001
Waist circumference, cm	79.9±8.0	89.2±7.9	85.2±7.8	87.7±8.0	<0.001
SBP, mmHg	118.0±16.8	126.1±18.1	122.8±17.7	124.8±17.8	<0.001
DBP, mmHg	78.4±10.7	83.7±11.1	81.6±11.4	83.1±11.1	<0.001
ALT, units/L	24.6±20.4	34.1±20.4	29.6±20.4	43.1±80.4	<0.001
AST, units/L	28.1±13.4	29.6±12.3	28.7±11.0	37.0±42.8	<0.001
BUN, mg/dl	14.2±3.6	14.2±3.5	14.2±3.5	14.6±3.6	0.063
Creatinine, mg/dl	0.82±0.16	0.83±0.18	0.84±0.17	0.84±0.17	0.001
Cholesterol, mg/dl	187.0±33.6	195.2±35.2	193.8±34.0	201.4±37.6	<0.001
HDL-C, mg/dl	46.2±10.2	41.2±8.7	42.6±8.9	41.6±8.7	<0.001
Fasting glucose, mg/dl	81.9±9.9	104.0±36.8	86.6±12.3	104.9±36.2	<0.001
HbA1c, %	5.5±0.5	6.3±1.3	5.7±0.6	6.7±1.6	<0.001
eGFR, ml/min/1.73m^2	93.4±12.2	93.3±12.7	91.9±12.6	92.4±12.6	0.001
HOMA-IR	1.2±0.5	3.7±2.2	1.8±0.6	2.1±1.2	<0.001
hs-CRP	0.2±0.4	0.2±0.3	0.3±0.9	0.3±0.5	<0.001
Diabetes mellitus	205 (6.4)	133 (32.4)	172 (13.4)	218 (48.0)	<0.001
Hypertension	745 (23.3)	175 (42.7)	462 (36.0)	198 (43.6)	<0.001
Dyslipidemia	1269 (39.7)	268 (65.4)	751 (58.5)	304 (67.0)	<0.001

All values are presented as number (percentage) or mean ± standard deviation.

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure.

Supplementary Table S7. Annual rate of eGFR decline during the event accrual period according to the HOMA-IR trajectories.

HOMA-IR trajectory	Slopes of eGFR decline, ml/min/1.73m^2 per year	P-value
Increasing	-1.64 ± 1.82	
Stable	-1.43 ± 1.61	0.008

eGFR, glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance.

Supplementary Table S8. Baseline characteristics according to the HOMA-IR trajectories in subjects with and without prevalent diabetes mellitus at baseline.

	Subjects without diabetes mellitus at baseline			Subjects with diabetes mellitus at baseline			Subjects with diabetes mellitus at the end of the exposure period (4th check-up)		
	Stable (n=4,318)	Increasing (n=301)	P-value	Stable (n=452)	Increasing (n=276)	P-value	Stable (n=735)	Increasing (n=386)	P-value
Age, years	50.6±8.1	50.8±8.2	0.709	54.4±8.4	52.6±8.1	0.004	52.9±8.3	52.0±8.0	0.085
Male	2019 (46.8)	154 (51.2)	0.155	240 (53.1)	144 (52.2)	0.868	400 (54.4)	203 (52.6)	0.602
BMI, kg/m^2	24.3±2.9	26.7±3.1	<0.001	25.1±3.1	26.6±3.2	<0.001	25.1±2.9	26.7±3.1	<0.001
Waist circumference, cm	81.5±8.4	88.1±8.4	<0.001	85.6±8.1	88.3±7.6	<0.001	84.7±8.1	88.4±7.8	<0.001
SBP, mmHg	119.0±17.1	124.7±17.0	<0.001	126.1±18.2	126.9±18.7	0.612	124.5±18.2	126.1±18.1	0.171
DBP, mmHg	79.3±11.0	84.0±10.7	<0.001	82.1±11.2	83.2±11.6	0.188	81.7±11.0	83.4±11.3	0.014
ALT, units/L	25.8±20.0	40.0±45.9	<0.001	32.4±23.1	44.7±92.8	0.032	31.0±17.4	44.0±83.3	0.003
AST, units/L	28.0±12.3	35.0±29.3	<0.001	30.9±15.6	37.3±46.7	0.029	29.7±11.2	36.7±41.9	0.001
BUN, mg/dl	14.1±3.5	14.5±3.5	0.083	14.5±3.7	14.7±3.5	0.459	14.3±3.6	14.7±3.5	0.082
Creatinine, mg/dl	0.83±0.16	0.83±0.17	0.398	0.83±0.17	0.85±0.17	0.187	0.84±0.17	0.84±0.17	0.842
Cholesterol, mg/dl	188.2±33.3	196.9±33.9	<0.001	198.3±37.9	205.8±40.3	0.012	196.1±34.0	204.0±38.1	0.001
HDL-C, mg/dl	45.1±9.9	40.9±8.6	<0.001	43.5±10.0	41.5±8.8	0.178	43.1±8.9	41.0±8.5	<0.001
Fasting glucose, mg/dl	82.3±8.2	86.9±9.5	<0.001	104.5±31.9	133.0±45.6	<0.001	96.9±26.1	118.9±42.8	<0.001
HbA1c, %	5.5±0.3	5.7±0.4	<0.001	6.6±1.3	7.7±1.7	<0.001	6.2±1.1	7.2±1.6	<0.001
eGFR, ml/min/1.73m^2	93.2±12.3	93.5±12.6	0.706	91.3±12.9	90.8±12.9	0.625	91.2±12.9	91.9±12.8	0.425
HOMA-IR	1.5±0.9	2.2±1.5	<0.001	1.9±1.2	3.2±2.1	<0.001	1.7±1.0	2.9±2.0	<0.001
hs-CRP	0.2±0.6	0.3±0.5	0.077	0.3±0.5	0.3±0.3	0.890	0.2±0.4	0.3±0.3	0.384
Hypertension	1117 (25.9)	126 (41.9)	<0.001	204 (45.1)	133 (48.2)	0.468	277 (37.7)	179 (46.4)	0.006
Dyslipidemia	1916 (44.4)	200 (66.4)	<0.001	282 (62.4)	194 (70.3)	0.036	435 (59.2)	274 (71.0)	<0.001

All values are presented as number (percentage) or mean ± standard deviation.

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure.

Supplementary Figure Legends

Supplementary Figure S1. Time-serial trend in the change of HOMA-IR during the exposure period according to each HOMA-IR trajectory group.

Distinct HOMA-IR trajectory groups were defined with latent variable mixture modeling using the HOMA-IR information at each follow-up during the exposure period. (*A*) Mean HOMA-IR at each biennial check-up in the entire cohort and in each HOMA-IR trajectory group. (*B*) Changes in HOMA-IR from baseline at each biennial check-up in the entire cohort and in each HOMA-IR trajectory group.

HOMA-IR, homeostatic model assessment of insulin resistance.

Supplementary Figure S2. Cumulative incidence of adverse renal outcomes in patients without adverse renal outcomes during the exposure period (n=5,126) or with normal renal function (n=704).

(*A*) The cumulative incidence of adverse renal outcomes in 5,126 patients who did not develop adverse renal outcomes during the exposure period. (*B*) The cumulative incidence of adverse renal outcomes in 704 patients with eGFR ≥90 mL/min/1.73m^2 at baseline and fourth check-ups.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio.

Supplementary Figure S3. Time-serial trend in the change of HOMA-IR during the exposure period and cumulative incidence of adverse renal outcomes according to three HOMA-IR trajectory groups.

Distinct HOMA-IR trajectory groups were defined with latent variable mixture modeling using the HOMA-IR information at each follow-up during the exposure period. However,

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three HOMA-IR trajectory groups were used for a sensitivity analysis. (*A*) Mean HOMA-IR at each biennial check-up in the entire cohort and in the three HOMA-IR trajectory groups. (*B*) Changes in HOMA-IR from baseline at each biennial check-up in the entire cohort and in the three HOMA-IR trajectory groups. (*C*) The cumulative incidence of adverse renal outcomes in the stable with low HOMA-IR, stable with high HOMA-IR, and increasing HOMA-IR trajectory group is presented.

CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio.

Supplementary Figure S4. Time-serial trend in the change of HOMA-IR during the exposure period and cumulative incidence of adverse renal outcomes according to four HOMA-IR trajectory groups.

Four HOMA-IR trajectory groups were used for a sensitivity analysis. (*A*) Mean HOMA-IR at each biennial check-up in the entire cohort and in the four HOMA-IR trajectory groups. (*B*) Changes in HOMA-IR from baseline at each biennial check-up in the entire cohort and in the four HOMA-IR trajectory groups. (*C*) The cumulative incidence of adverse renal outcomes in the stable with low HOMA-IR, stable with high HOMA-IR, slightly increasing, and rapidly increasing HOMA-IR trajectory group is presented.

CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio.

Supplementary Figure S5. Cumulative incidence of different definitions of renal outcomes according to HOMA-IR trajectory groups.

The cumulative incidence of (*A*) both decreased eGFR and proteinuria and (*B*) eGFR <45 mL/min/1.73m^2 in at least 2 consecutive check-ups or albumin≥3+ on urine strip in the stable and increasing HOMA-IR trajectory group is presented.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio.

Supplementary Figure S6. Longitudinal HOMA-IR patterns and renal outcomes according to each HOMA-IR trajectory group in subjects with and without diabetes mellitus at baseline.

(*A*) HOMA-IR pattern during the exposure period and (*B*) the cumulative incidence of adverse renal outcomes in the stable and increasing HOMA-IR trajectory groups are presented in subjects without diabetes mellitus at baseline. (*C*) HOMA-IR pattern during the exposure period and (*D*) the cumulative incidence of adverse renal outcomes in the stable and increasing HOMA-IR trajectory groups are presented in subjects with diabetes mellitus at baseline.

CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio.

Supplementary Figure S7. Longitudinal HOMA-IR patterns and renal outcomes according to each HOMA-IR trajectory group in subjects with diabetes mellitus at the end of the exposure period (4th check-up).

(*A*) HOMA-IR pattern during the exposure period and (*B*) the cumulative incidence of adverse renal outcomes in the stable and increasing HOMA-IR trajectory groups are presented in subjects with diabetes mellitus at the end of the exposure period (4th check-up).

CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio.

Supplementary Figure S8. Risk of adverse renal outcomes in relation to baseline covariates.

Comparison of the risk of adverse renal outcomes between the subgroups of the stable and increasing HOMA-IR trajectory groups by various covariates or comorbidities at baseline, and baseline HOMA-IR value or eGFR are presented. The 75th percentile value of HOMA-IR was used to divide the whole population into subgroups based on HOMA-IR.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio.

Supplementary Figure S9. Longitudinal HOMA-IR patterns and adverse renal outcomes in 1:1 matched stable and increasing HOMA-IR trajectory group participants by baseline HOMA-IR.

In 1:1 matched pairs by baseline HOMA-IR, (*A*) HOMA-IR pattern during the exposure period and (*B*) the cumulative incidence of adverse renal outcomes in the stable and increasing HOMA-IR trajectory groups are presented.

CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio.

Supplementary References

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