Online-Only Supplemental Material

Association between glycemic status and kidney cancer risk in men and women: A nationwide cohort study

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Supplemental Table S1. Baseline characteristics of the study population according to kidney cancer status

	Men			Women		
	Kidney cancer		*P* value	Kidney cancer		*P* value
	No	Yes		No	Yes	
	(n=5,195,920)	(n=8,834)		(n=4,284,030)	(n=3,547)	
Age (years), mean±SD	45.5 ±13.5	54.8 ±12.8	<0.001	48.9 ±14.5	57.7 ±11.9	<0.001
Anthropometrics, mean±SD						
BMI (kg/m^2)	24.2 ±3.3	24.8 ±3.0	<0.001	23.2 ±3.5	24.6 ±3.4	<0.001
Waist circumference (cm)	83.6 ±8.2	86.4 ±7.7	<0.001	76.3 ±9.3	80.5 ±8.8	<0.001
Systolic BP (mmHg)	124.7 ±14.1	128.3 ±15.1	<0.001	119.9 ±15.7	126.1 ±16.7	<0.001
Diastolic BP (mmHg)	78.1 ±9.7	79.8 ±10.1	<0.001	74.3 ±10.1	77.2 ±10.7	<0.001
Laboratory findings, mean±SD						
Fasting glucose (mg/dL)	99.0 ±25.7	103.5 ±28.7	<0.001	95.2 ±21.2	99.7 ±23.6	<0.001
Total cholesterol (mg/dL)	194.8 ±41.0	195.1 ±37.5	0.441	196.4 ±42.1	202.6 ±37.6	<0.001
HDL-cholesterol (mg/dL)	53.8 ±32.1	52.0 ±28.0	<0.001	60.1 ±34.7	58.0 ±36.4	<0.001
LDL-cholesterol (mg/dL)	111.9 ±39.2	112.1 ±39.1	0.537	115.6 ±38.5	120.8 ±38.0	<0.001
eGFR (mL/min/1.73 m^2)	87.9 ±49.5	84.0 ±54.2	<0.001	87.1 ±34.9	82.3 ±28.1	<0.001
Alcohol consumption[a], n (%)			<0.001			<0.001
None	1,537,613 (29.6)	3,118 (35.3)		3,163,887 (73.9)	2,982 (84.1)	
Light-to-moderate	2,925,111 (56.3)	4,415 (50.0)		1,071,215 (25.0)	541 (15.3)	
Heavy	733,196 (14.1)	1,301 (14.7)		48,928 (1.1)	24 (0.7)	
Smoking status, n (%)			<0.001			<0.001
Never	1,601,541 (30.8)	2,790 (31.6)		4,072,303 (95.1)	3,402 (95.9)	
<20 pack-years	2,377,319 (45.8)	3,086 (34.9)		194,429 (4.5)	110 (3.1)	
≥20 pack-years	1,217,060 (23.4)	2,958 (33.5)		17,298 (0.4)	35 (1.0)	
Regular exercise, n (%)	1,045,134 (20.1)	2,157 (24.4)	<0.001	669,156 (15.6)	632 (17.8)	<0.001
Low-income status, n (%)	769,240 (14.8)	1,271 (14.4)	0.270	898,578 (21.0)	666 (18.8)	0.001
Comorbidities, n (%)						
Diabetes	502,966 (9.7)	1,488 (16.8)	<0.001	319,214 (7.5)	497 (14.0)	<0.001
Hypertension	1,382,525 (26.6)	4,263 (48.3)	<0.001	1,063,766 (24.8)	1,650 (46.5)	<0.001
Dyslipidemia	862,652 (16.6)	2,192 (24.8)	<0.001	864,109 (20.2)	1,105 (31.2)	<0.001
Chronic kidney disease	308,019 (5.9)	973 (11.0)	<0.001	338,227 (7.9)	460 (13.0)	<0.001

BP, blood pressure; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Supplemental Table S2. Sex-specific dose-response associations between glycemic status and kidney cancer risk after adjusting for all potential confounders and mediators (Model 3) in never-smokers

Glycemic status	HR (95% CI)
	Model 3
Men	
Normoglycemia	1 (reference)
Prediabetes	1.003 (0.92–1.09)
Diabetes	1.07 (0.97–1.19)
Women	
Normoglycemia	1 (reference)
Prediabetes	1.14 (1.05–1.23)
Diabetes	1.19 (1.07–1.32)

Model 3: adjusted for age, alcohol consumption, physical activity, income, BMI, hypertension, dyslipidemia, and chronic kidney disease.

CI, confidence interval; HR, hazard ratio.

Supplemental Table S3. Sensitivity analysis of sex-specific dose-response associations between glycemic status and kidney cancer risk considering individuals who developed incident diabetes during study follow-up in never-smokers

Glycemic status	n	Event, n	Person-years	IR	HR (95% CI)		
					Model 1	Model 2	Model 3
Men							
Normoglycemia	1,042,352	1,511	8,566,529	17.6	1 (reference)	1 (reference)	1 (reference)
Prediabetes	404,211	743	3,269,639	22.7	1.29 (1.18–1.41)	1.04 (0.95–1.13)	0.98 (0.90–1.07)
Diabetes	157,359	474	1,241,761	38.2	2.17 (1.96–2.41)	1.26 (1.13–1.39)	1.08 (0.98–1.20)
Women							
Normoglycemia	2,985,053	2,074	24,709,853	8.4	1 (reference)	1 (reference)	1 (reference)
Prediabetes	784,235	774	6,386,791	12.1	1.45 (1.33–1.57)	1.16 (1.07–1.26)	1.11 (1.02–1.21)
Diabetes	305,400	471	2,472,833	19.0	2.27 (2.06–2.51)	1.36 (1.23–1.51)	1.21 (1.09–1.34)

* Incidence rate of kidney cancer per 100,000 person-years.

Model 1: non-adjusted.

Model 2: adjusted for age, alcohol consumption, physical activity, income, and BMI.

Model 3: adjusted for age, alcohol consumption, physical activity, income, BMI, hypertension, dyslipidemia, and chronic kidney disease.

CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Supplemental Table S4. Sex-specific dose-response associations between glycemic status and kidney cancer risk after adjusting for all potential confounders and mediators (Model 3) in smokers

	Glycemic status	HR (95% CI)
		Model 3
Men		
Never-smokers	Normoglycemia	1 (reference)
Smokers	Normoglycemia	1.13 (1.06–1.20)
	Prediabetes	1.16 (1.08–1.25)
	Diabetes	1.29 (1.19–1.40)
Women		
Never-smokers	Normoglycemia	1 (reference)
Smokers	Normoglycemia	0.92 (0.73–1.15)
	Prediabetes	1.52 (1.11–2.06)
	Diabetes	1.67 (1.13–2.46)

Model 3: adjusted for age, alcohol consumption, physical activity, income, BMI, hypertension, dyslipidemia, and chronic kidney disease.

CI, confidence interval; HR, hazard ratio.

Supplemental Table S5. Sensitivity analysis of sex-specific dose-response associations between glycemic status and kidney cancer risk considering individuals who developed incident diabetes during study follow-up in smokers

	Glycemic status	n	Event, n	Person-years	IR	HR (95% CI)		
						Model 1	Model 2	Model 3
Men								
Never-smokers	Normoglycemia	1,042,352	1,511	8,566,529	17.6	1 (reference)	1 (reference)	1 (reference)
Smokers	Normoglycemia	2,318,063	3,256	19,040,265	17.1	0.97 (0.91–1.03)	1.12 (1.05–1.19)	1.13 (1.06–1.20)
	Prediabetes	934,508	1,668	7,566,653	22.0	1.25 (1.17–1.34)	1.21 (1.13–1.30)	1.16 (1.08–1.24)
	Diabetes	347,095	1,014	2,762,062	36.7	2.09 (1.93–2.26)	1.50 (1.39–1.63)	1.31 (1.20–1.42)
Women								
Never-smokers	Normoglycemia	2,985,053	2,074	24,709,853	8.4	1 (reference)	1 (reference)	1 (reference)
Smokers	Normoglycemia	159,298	74	1,308,428	5.7	0.68 (0.54–0.85)	0.89 (0.71–1.13)	0.90 (0.71–1.13)
	Prediabetes	38,207	41	306,426	13.4	1.60 (1.17–2.18)	1.60 (1.17–2.18)	1.55 (1.14–2.12)
	Diabetes	14,311	26	113,408	22.9	2.75 (1.87–4.05)	1.88 (1.27–2.76)	1.69 (1.15–2.50)

* Incidence rate of kidney cancer per 100,000 person-years.

Model 1: non-adjusted.

Model 2: adjusted for age, alcohol consumption, physical activity, income, and BMI.

Model 3: adjusted for age, alcohol consumption, physical activity, income, BMI, hypertension, dyslipidemia, and chronic kidney disease.

CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Supplemental Table S6. Associations between glycemic status and kidney cancer risk according to the smoking pack-years in men

Smoking pack-years	Glycemic status	N	Event	Person-years	IR	HR (95% CI)		
						Model 1	Model 2	Model 3
Never-smokers	Normoglycemia	1,042,497	1,533	8,589,563	17.8	1 (reference)	1 (reference)	1 (reference)
<20 pack-years	Normoglycemia	1,639,148	1,831	13,570,135	13.5	0.76 (0.71–0.81)	1.09 (1.01–1.16)	1.09 (1.01–1.17)
	Prediabetes	581,611	841	4,784,557	17.6	0.99 (0.91–1.07)	1.15 (1.06–1.25)	1.10 (1.01–1.19)
	Diabetes	159,646	414	1,284,479	32.2	1.81 (1.63–2.02)	1.50 (1.34–1.67)	1.30 (1.17–1.45)
≥20 pack-years	Normoglycemia	679,186	1,475	5,521,273	26.7	1.50 (1.40–1.61)	1.17 (1.09–1.25)	1.18 (1.10–1.27)
	Prediabetes	353,383	883	2,862,279	30.9	1.73 (1.59–1.88)	1.29 (1.19–1.40)	1.24 (1.13–1.34)
	Diabetes	187,449	600	1,477,583	40.6	2.29 (2.08–2.51)	1.49 (1.35–1.64)	1.29 (1.17–1.42)

* Incidence rate of kidney cancer per 100,000 person-years.

Model 1: non-adjusted.

Model 2: adjusted for age, sex, alcohol consumption, physical activity, income, and body mass index.

Model 3: adjusted for age, alcohol consumption, physical activity, income, BMI, hypertension, dyslipidemia, and chronic kidney disease.

CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Supplemental Table S7. Associations between glycemic status and kidney cancer risk according to the daily smoking amount (cigarettes/day) in men

Number of cigarettes/day	Glycemic status	n	Event, n	Person-years	IR	HR (95% CI)		
						Model 1	Model 2	Model 3
Never-smokers	Normoglycemia	1,042,497	1,533	8,589,563	17.8	1 (reference)	1 (reference)	1 (reference)
<10/day	Normoglycemia	241,287	320	1,982,459	16.1	0.91 (0.80–1.02)	1.01 (0.90–1.14)	1.02 (0.91–1.15)
	Prediabetes	88,702	140	721,800	19.4	1.09 (0.92–1.30)	0.97 (0.82–1.16)	0.93 (0.78–1.11)
	Diabetes	28,472	103	222,098	46.4	2.62 (2.14–3.19)	1.60 (1.31–1.96)	1.40 (1.15–1.71)
10-19/day	Normoglycemia	1,021,518	1,291	8,437,073	15.3	0.86 (0.80–0.92)	1.10 (1.02–1.19)	1.11 (1.03–1.19)
	Prediabetes	371,946	637	3,050,314	20.9	1.17 (1.07–1.29)	1.21 (1.11–1.33)	1.16 (1.06–1.27)
	Diabetes	113,235	322	903,392	35.6	2.01 (1.78–2.26)	1.47 (1.30–1.66)	1.28 (1.13–1.45)
≥20/day	Normoglycemia	1,055,529	1,695	8,671,876	19.5	1.10 (1.02–1.18)	1.17 (1.09–1.25)	1.17 (1.09–1.26)
	Prediabetes	474,346	947	3,874,722	24.4	1.37 (1.27–1.49)	1.27 (1.17–1.38)	1.21 (1.11–1.31)
	Diabetes	205,388	589	1,636,572	36.0	2.02 (1.84–2.23)	1.48 (1.35–1.63)	1.28 (1.17–1.41)

* Incidence rate of kidney cancer per 100,000 person-years.

Model 1: non-adjusted.

Model 2: adjusted for age, alcohol consumption, physical activity, income, and BMI.

Model 3: adjusted for age, alcohol consumption, physical activity, income, BMI, hypertension, dyslipidemia, and chronic kidney disease.

CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Supplemental Table S8. Associations between glycemic status and kidney cancer risk according to smoking duration (years) in men

Smoking duration	Glycemic status	n	Event, n	Person-years	IR	HR (95% CI)		
						Model 1	Model 2	Model 3
Never-smokers	Normoglycemia	1,042,497	1,533	8,589,563	17.8	1 (reference)	1 (reference)	1 (reference)
<10 years	Normoglycemia	430,651	342	3,579,869	9.6	0.54 (0.48–0.60)	0.97 (0.86–1.10)	0.97 (0.86–1.10)
	Prediabetes	122,083	139	1,008,071	13.8	0.77 (0.65–0.92)	1.07 (0.90–1.27)	1.02 (0.86–1.21)
	Diabetes	26,582	72	215,441	33.4	1.88 (1.48–2.38)	1.66 (1.31–2.10)	1.44 (1.13–1.82)
10-19 years	Normoglycemia	931,316	923	7,723,062	12.0	0.67 (0.62–0.73)	1.09 (1.00–1.18)	1.08 (0.99–1.18)
	Prediabetes	325,591	412	2,686,434	15.3	0.86 (0.77–0.96)	1.17 (1.05–1.31)	1.11 (1.00–1.24)
	Diabetes	78,888	168	641,723	26.2	1.47 (1.25–1.73)	1.46 (1.24–1.71)	1.26 (1.07–1.48)
≥20 years	Normoglycemia	956,367	2,041	7,788,477	26.2	1.47 (1.38–1.57)	1.16 (1.09–1.24)	1.18 (1.10–1.26)
	Prediabetes	487,320	1,173	3,952,331	29.7	1.67 (1.54–1.80)	1.26 (1.16–1.36)	1.20 (1.11–1.30)
	Diabetes	241,625	774	1,904,898	40.6	2.29 (2.10–2.49)	1.49 (1.37–1.63)	1.30 (1.19–1.42)

* Incidence rate of kidney cancer per 100,000 person-years.

Model 1: non-adjusted.

Model 2: adjusted for age, alcohol consumption, physical activity, income, and BMI.

Model 3: adjusted for age, alcohol consumption, physical activity, income, BMI, hypertension, dyslipidemia, and chronic kidney disease.

CI, confidence interval; HR, hazard ratio; IR, incidence rate.

Supplemental Table S9. Kidney cancer risk according to antidiabetic medication use among never-smokers with diabetes

Never-smokers	Antidiabetic medications	Glycemic status	n	Event, n	Person-years	IR	HR (95% CI)		
							Model 1	Model 2	Model 3
Men									
	Insulin	No	144,405	428	1,147,928	37.3	1 (reference)	1 (reference)	1 (reference)
		Yes	12,954	46	93,833	49.0	2.35 (1.76–3.15)	1.33 (0.99–1.78)	1.14 (0.85–1.52)
	Sulfonylurea	No	78,659	215	628,038	34.2	1 (reference)	1 (reference)	1 (reference)
		Yes	78,700	259	613,722	42.2	2.10 (1.84–2.38)	1.15 (1.01–1.30)	1.03 (0.90–1.17)
	Metformin	No	83,129	245	659,136	37.2	1 (reference)	1 (reference)	1 (reference)
		Yes	74,230	229	582,625	39.3	1.93 (1.69–2.21)	1.10 (0.96–1.26)	0.98 (0.86–1.13)
	Thiazolidinedione	No	143,864	434	1,135,072	38.2	1 (reference)	1 (reference)	1 (reference)
		Yes	13,495	40	106,688	37.5	1.78 (1.30–2.43)	1.08 (0.79–1.47)	0.96 (0.70–1.32)
	DPP4 inhibitor	No	149,556	451	1,179,714	38.2	1 (reference)	1 (reference)	1 (reference)
		Yes	7,803	23	62,047	37.1	1.76 (1.16–2.65)	1.15 (0.76–1.73)	1.03 (0.68–1.55)
Women									
	Insulin	No	273,206	411	2,222,813	18.5	1 (reference)	1 (reference)	1 (reference)
		Yes	32,194	60	250,020	24.0	2.07 (1.52–2.77)	1.14 (0.80–1.57)	1.09 (0.80–1.46)
	Sulfonylurea	No	131,497	163	1,070,035	15.2	1 (reference)	1 (reference)	1 (reference)
		Yes	173,903	308	1,402,798	22.0	1.95 (1.70–2.24)	1.03 (0.87–1.20)	1.03 (0.89–1.19)
	Metformin	No	134,644	182	1,089,204	16.7	1 (reference)	1 (reference)	1 (reference)
		Yes	170,756	289	1,383,630	20.9	1.83 (1.58–2.11)	1.00 (0.84–1.17)	1.00 (0.86–1.16)
	Thiazolidinedione	No	277,136	430	2,243,243	19.2	1 (reference)	1 (reference)	1 (reference)
		Yes	28,264	41	229,590	17.9	1.43 (0.96–2.08)	0.81 (0.51–1.23)	0.84 (0.56–1.21)
	DPP4 inhibitor	No	286,601	453	2,319,551	19.5	1 (reference)	1 (reference)	1 (reference)
		Yes	18,799	18	153,282	11.7	0.82 (0.38–1.50)	0.45 (0.16–0.92)	0.51 (0.25–0.93)

* Incidence rate of kidney cancer per 100,000 person-years.

Model 1: non-adjusted.

Model 2: adjusted for age, alcohol consumption, physical activity, income, and BMI.

Model 3: adjusted for age, alcohol consumption, physical activity, income, BMI, hypertension, dyslipidemia, and chronic kidney disease.

CI, confidence interval; DPP4, dipeptidyl peptidase 4; HR, hazard ratio; IR, incidence rate.