Comparative performance of risk prediction models for renal disease: an external validation using 0.5 million UK Biobank participants

Appendix

Contents

Table S1. Definitions for outcomes in UK Biobank

Outcome	ICD-10 Code
Not specified by author	
Chronic Kidney Disease	R80, N181, N182, N183, N184, N189, N289, E112, E142, N083, N180, N185, N19, Z940, Z992, Y841
Kidney failure	N180, N185, N19, Z940, Z992, Y841
Author specified	
Chronic Kidney Disease (Jardine)	R80, N181, N182, N183, N184, N189, N289, E112, E142, N083, N180, N185, N19, Z940, Z992, Y841, E853, N165, T824, T861, Y602, Y612, Y622, Z490, Z491, Z492
Chronic Kidney Disease(UKPDS OM2)	E102, E112, E132, E142, N18, N19; Death due to: N00-N29, N392, Z905
Chronic Kidney Disease* (ZODIAC-36)	R80, N181, E112, E142, N083
Kidney failure (Jardine)	N180, N185, Z940, Z992, Y841, E853, N165, T824, T861, Y602, Y612, Y622, Z490, Z491, Z492; Death due to: N00-N29, E112, I12, I13
Kidney failure (Wan)	E116, N180, N185, N19, E112
Kidney failure (Elley)	N180, N185, Z940, Z992, Y841, E853, N165, T824, T861, Y602, Y612, Y622, Z490, Z491, Z492, E112, E132, E142, I120, I130, I131, I132, N188, N189, N19, T857

* Only include early-stage renal complication

Table S2. Missing values of biomarkers

Variables	Missing data, n (%)	
	Cohort without diabetes (n=474,598)	Cohort with type 2 diabetes (n=23,298)
BMI (kg/m^2)	2755 (0.6)	252 (1.1)
Urate (umol/L)	31419 (6.6)	1,652 (7.1)
Diastolic blood pressure (mmHg)	32544 (6.9)	1,571 (6.7)
Systolic blood pressure (mmHg)	32556 (6.9)	1,572 (6.7)
Hba1c (mmol/mol)	33765 (7.1)	1,795 (7.7)
Cholesterol (mmol/L)	30889 (6.5)	1,623 (7.0)
LDL (mmol/L)	31696 (6.7)	1,694 (7.3)
HDL (mmol/L)	68408 (14.4)	3,465 (14.9)
Triglycerides (mmol/L)	31220 (6.6)	1,663 (7.1)
White blood cell (10^9 cells/L)	22803 (4.8)	1,226 (5.3)
Creatinine (mmol/L)	31104 (6.6)	1,641 (7.0)
Urinary Creatinine (mmol /L)	16809 (3.5)	1,065 (4.6)
Albumin (g/L)	68231 (14.4)	3,443 (14.8)
Albumin in urine (mg/L)	336028 (70.8)	11,302 (48.5)
eGFR (ml/min/1.73 m^2)	31104 (6.6)	1641 (7.0)

Table S3. Baseline Characteristics of the Validation Dataset: comparison of cases with and without missing urine albumin data

Variables	n (%) or mean (± SD)			
	Cohort without diabetes (n=474,598)		Cohort with type 2 diabetes (n=23,298)	
	Without missing urine albumin (n=138,570)	With missing urine albumin (n=336,028)	Without missing urine albumin (n=11,996)	With missing urine albumin (n=11,302)
Demographics				
Age (years)	57.5 (± 8.2)	56.6 (± 8.1)	60.6 (± 7.0)	60.4 (± 6.9)
40-49	28,963 (20.9)	78,673 (23.4)	1,045 (8.7)	1,042 (9.2)
50-59	42,698 (30.8)	113,416 (33.7)	3,303 (27.5)	3,176 (28.1)
60-69	63,455 (45.8)	137,996 (41.1)	7,203 (60.0)	6,717 (59.4)
70 and above	3,454 (2.5)	5,939 (1.8)	445 (3.7)	367 (3.2)
Ethnicity				
White	129,618 (93.5)	318,769 (94.9)	10,435 (87.0)	9,926 (87.8)
Other	8,952 (6.5)	17,259 (5.1)	1,561 (13.0)	1,376 (12.2)
Sex				
Male	69,328 (50.0)	142,873 (42.5)	8,195 (68.3)	6,549 (57.9)
Female	69,242 (50.0)	193,155 (57.5)	3,801 (31.7)	4,753 (42.1)
Clinical features				
Smoking status				
Never	73,094 (52.7)	187,645 (55.8)	5,059 (42.2)	5,309 (47.0)
Former smoker	47,721 (34.4)	113,517 (33.8)	5,406 (45.1)	4,803 (42.5)
Current smoker	16,924 (12.2)	32,944 (9.8)	1,452 (12.1)	1,118 (9.9)
Diabetes				
Age at diagnosis of diabetes (year)	-	-	52.6 (± 9.5)	52.6 (± 9.9)
Duration of diabetes (years)	-	-	8.0 (± 7.4)	7.8 (± 7.7)
BMI (kg/m^2)	28.1 (± 5.1)	26.8 (± 4.4)	32.2 (± 5.8)	30.7 (± 5.8)
Diastolic blood pressure (mmHg)	84.4 (± 11.4)	81.4 (± 10.3)	82.5 (± 10.6)	80.5 (± 9.9)
Systolic blood pressure (mmHg)	143.5 (± 21.0)	137.9 (± 18.9)	145.6 (± 19.1)	141.5 (± 17.6)
Biomarkers				
Urate (umol/L)	321.4 (± 83.5)	302.1 (± 77.3)	341.2 (± 86.4)	325.3 (± 83.3)
Hba1c (mmol/mol)*	35.4 (5.0)	34.9 (4.7)	51.7 (16.7)	48.9 (14.3)
Cholesterol (mmol/L)	5.7 (± 1.1)	5.8 (± 1.1)	4.5 (± 1.0)	4.5 (± 1.0)
LDL (mmol/L)	3.6 (± 0.9)	3.6 (± 0.8)	2.7 (± 0.8)	2.7 (± 0.7)
HDL (mmol/L)*	1.4 (0.5)	1.4 (0.5)	1.1 (0.4)	1.2 (0.4)
Triglycerides (mmol/L)*	1.6 (1.2)	1.4 (1.0)	2 (1.4)	1.7 (1.2)
White blood cell (10^9 cells/L)*	6.9 (2.3)	6.5 (2.1)	7.7 (2.5)	7.2 (2.4)
Creatinine (mmol /L)*	70.7 (17.7)	70.7 (17.7)	70.7 (26.5)	70.7 (17.7)
Urinary Creatinine (mmol /L)*	12287 (8684.0)	5936 (5754.0)	11281 (7887.5)	6519 (5468.0)
Albumin (g/L)	45.2 (± 2.7)	45.2 (± 2.6)	45 (± 2.9)	44.9 (± 2.8)
eGFR (ml/min/1.73 m^2)*	85.4 (21.3)	85.9 (19.9)	87.8 (28.1)	87.9 (24.7)

* median (IQR)

Table S4. Risk factors included for validation

Author	Age	Sex	Smoking status	BMI	SBP/ DBP	Hba1c	UACR/ Urine albumin	eGFR	Other predictors included in the model
General population									
Chien (Clinical model)	√			√	√				History of stroke, diabetes
Kshirsagar (Simplified categorical model)	√	√							Anemia, hypertension, diabetes, history of cardiovascular disease, history of heart failure, peripheral vascular disease
Kshirsagar (Best-fitting categorical model)	√	√							Ethnicity, anemia, hypertension, diabetes, history of cardiovascular disease, history of heart failure, low high-density lipoprotein cholesterol level, peripheral vascular disease
Nelson	√	√	√	√		√*	√	√	Ethnicity, history of cardiovascular disease, hypertension, insulin use*, diabetes medication use*
O'Seaghdha	√						√	√	Hypertension, diabetes
Saranburut	√	√			√			√	Diabetes
Umesawa	√	√	√	√	√			√	History of proteinuria, haematuria, medicated for hypertension, fasting serum glucose, nonfasting serum glucose, medicated for diabetes mellitus, drinking status
People with type 2 diabetes									
Dunkler (Laboratory model)	√	√					√	√	Albuminuria stage
Jardine		√			√	√	√	√	History of diabetic retinopathy, age completed full time education, blood pressure lowering treatment, waist circumference
Low	√				√	√	√	√	LDL cholesterol
ZODIAC-36	√	√	√	√	√	√	√		History of macrovascular complication
UKPDS OM2		√		√	√			√	Ethnicity, age diagnosed diabetes, haemoglobin, microalbuminuria, macroalbuminuria, white blood cell, amputation history, blind history
RECODe	√	√	√		√	√	√		Ethnicity, history of cardiovascular disease, blood pressure-lowering drugs, oral diabetes drugs, anticoagulants, total cholesterol, HDL cholesterol, serum creatinine
Wan	√		√	√	√	√	√	√	Anti-hypertensive drug, STDR (Sight Threatening Diabetic Retinopathy), diastolic blood pressure, anti-glucose oral drug, insulin, diabetes duration
Elley		√	√		√	√			Ethnicity, age diagnosed diabetes, diabetes duration, serum creatinine, microalbuminuria, macroalbuminuria, advanced albuminuria, history of cardiovascular disease

BMI: Body mass index; SBP: Systolic blood pressure; Hba1c: Hemoglobin A1C; UACR: Urine albumin-creatinine ratio; eGFR: Estimated glomerular filtration rate

* The risk factor was used exclusively for individuals with type 2 diabetes.

Table S5. Number of events in UK biobank validation dataset

Event	n	Prevalence (%)
Whole population		
Chronic kidney disease	19268	3.9
People without diabetes		
Chronic kidney disease	15670	3.3
People with type 2 diabetes		
Chronic kidney disease	3598	15.4
Chronic kidney disease (UKPDS OM2)	3067	13.2
Chronic kidney disease (ZODIAC-36)*	539	2.3
Chronic kidney disease (Jardine)	3420	14.7
Kidney failure	561	2.4
Kidney failure (Wan)	920	3.9
Kidney failure (Jardine)	573	2.5
Kidney failure (Elley)	301	1.3

* Only include early-stage renal complication

Table S6. Results of brier scores

Mode	Brier score [95% CI]
People without diabetes	
Chronic Kidney Disease	
Chien	0.18 [0.12, 0.23]
Kshirsagar (Simplified categorical model)	0.06 [0.05, 0.07]
Kshirsagar (Best-fitting categorical model)	0.06 [0.05, 0.07]
Nelson	0.17 [0.08, 0.26]
O'Seaghdha	0.03 [0.02, 0.04]
Saranburut	0.07 [0.03, 0.11]
Umesawa	0.11 [0.06, 0.15]
People with type 2 diabetes	
Chronic Kidney Disease	
Chien	0.23 [0.16, 0.29]
Kshirsagar (Simplified categorical model)	0.04 [0.03, 0.04]
Kshirsagar (Best-fitting categorical model)	0.02 [0.02, 0.03]
Nelson	0.20 [0.15, 0.25]
O'Seaghdha	0.02 [0.01, 0.03]
Saranburut	0.14 [0.05, 0.22]
Umesawa	0.05 [0.03, 0.07]
Dunkler(Laboratory model)	0.03 [0.02, 0.04]
Jardine	0.39 [0.33, 0.45]
Low	0.21 [0.17, 0.26]

UKPDS OM2	0.09 [0.06, 0.12]
ZODIAC-36 (Cox regression model)	0.02 [0.01, 0.03]
ZODIAC-36 (Competing risk model)	0.02 [0.01, 0.03]
Kidney failure	
Elley	0.01 [0.0, 0.02]
Jardine	0.02 [0.0, 0.03]
RECODe	0.01 [0.01, 0.02]
Wan	0.10 [0.05, 0.16]
ZODIAC-36 (Cox regression model)	0.02 [0.01, 0.03]
ZODIAC-36 (Competing risk model)	0.02 [0.01, 0.03]

Table S7. Discrimination and calibration performance using complete case analysis

Mode	C-index [95% CI]	Calibration slope (intercept)
People without diabetes		
Chronic Kidney Disease		
Chien	0.71 [0.71-0.72]	0.132 (-0.004)
Kshirsagar (Simplified categorical model)	0.69 [0.69-0.70]	0.561 (-0.020)
Kshirsagar (Best-fitting categorical model)	0.71 [0.71-0.72]	0.531 (-0.018)
Nelson	0.80 [0.79-0.80]	0.226 (-0.008)
O'Seaghdha	0.80 [0.79-0.80]	0.831 (-0.012)
Saranburut	0.77 [0.77-0.77]	0.299 (0.002)
Umesawa	0.80 [0.79-0.80]	0.231 (-0.018)
People with type 2 diabetes		
Chronic Kidney Disease		
Chien	0.60 [0.59-0.61]	0.215 (0.041)
Kshirsagar (Simplified categorical model)	0.65 [0.64-0.66]	1.127 (-0.034)
Kshirsagar (Best-fitting categorical model)	0.66 [0.65-0.67]	1.132 (-0.058)
Nelson	0.75 [0.74-0.76]	0.511 (-0.008)
O'Seaghdha	0.74 [0.73-0.75]	1.175 (0.008)
Saranburut	0.71 [0.70-0.72]	0.563 (0.049)
Umesawa	0.75 [0.74-0.75]	0.589 (0.000)
Dunkler (Laboratory model)	0.59 [0.57-0.60]	0.672 (0.060)
Jardine	0.69 [0.68-0.70]	0.556 (-0.093)
Low	0.67 [0.66-0.68]	0.613 (-0.019)
UKPDS OM2	0.59 [0.57-0.61]	0.130 (0.127)
ZODIAC-36 (Cox regression model)	0.77 [0.74-0.80]	10.873 (-0.008)
ZODIAC-36 (Competing risk model)	0.77 [0.74-0.79]	10.817 (-0.011)
Kidney failure		

Elley	0.89 [0.86-0.92]	4.918 (-0.003)
Jardine	0.83 [0.79-0.85]	3.292 (0.006)
RECODe	0.75 [0.73-0.78]	3.976 (-0.081)
Wan	0.70 [0.67-0.73]	0.293 (0.009)
ZODIAC-36 (Cox regression model)	0.75 [0.73-0.76]	513.646 (-0.007)
ZODIAC-36 (Competing risk model)	0.73 [0.71-0.75]	33.393 (-0.013)

Table S8. Discrimination and calibration performance using multiple imputation for urinary albumin

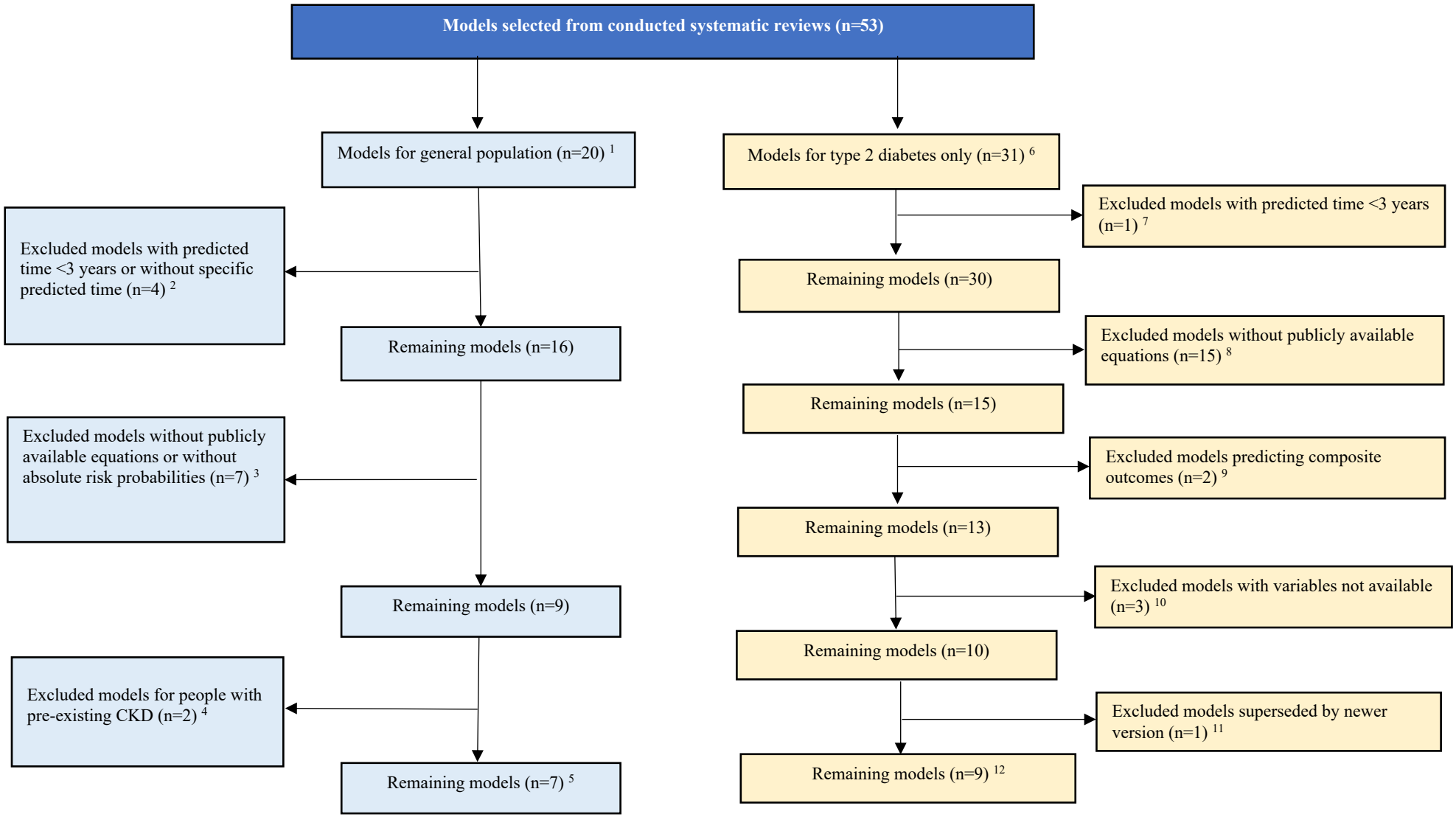
Mode	**C-index [95% CI]**	**Calibration slope (intercept)**
People without diabetes		
Chronic Kidney Disease		
Chien	0.72 [0.71-0.70]	0.132 (-0.004)
Kshirsagar (Simplified categorical model)	0.74 [0.74-0.74]	0.562 (-0.020)
Kshirsagar (Best-fitting categorical model)	0.74 [0.73-0.75]	0.527 (-0.018)
Nelson	0.83 [0.82-0.83]	0.171 (-0.007)
O'Seaghdha	0.83 [0.83-0.83]	0.689 (-0.011)
Saranburut	0.77 [0.76-0.78]	0.300 (0.002)
Umesawa	0.83 [0.82-0.83]	0.324 (-0.013)
People with type 2 diabetes		
Chronic Kidney Disease		
Chien	0.59 [0.59-0.59]	0.219 (0.041)
Kshirsagar (Simplified categorical model)	0.80 [0.80-0.83]	1.127 (-0.034)
Kshirsagar (Best-fitting categorical model)	0.75 [0.75-0.76]	1.120 (-0.055)
Nelson	0.77 [0.77-0.79]	0.470 (-0.025)
O'Seaghdha	0.75 [0.75-0.76]	0.934 (-0.003)
Saranburut	0.63 [0.62-0.64]	0.572 (0.047)
Umesawa	0.77 [0.74-0.80]	0.738 (0.020)
Dunkler (Laboratory model)	0.56 [0.55-0.60]	0.848 (0.032)
Jardine	0.66 [0.65-0.67]	0.374 (-0.065)
Low	0.69 [0.68-0.69]	0.420 (-0.011)
*UKPDS OM2	0.67 [0.67-0.69]	2.658 (0.044)
ZODIAC-36 (Cox regression model)	0.67 [0.66-0.68]	20.418 (0.070)
ZODIAC-36 (Competing risk model)	0.63 [0.62-0.64]	19.226 (0.069)
Kidney failure		
Elley	0.96 [0.94-0.98]	4.995 (0.002)
Jardine	0.93 [0.89-0.96]	3.006 (0.000)
RECODe	0.83 [0.79-0.83]	2.867 (-0.058)

Wan	0.52 [0.51-0.55]	0.168 (0.001)
ZODIAC-36 (Cox regression model)	0.85 [0.85-0.85]	327.430 (-0.005)
ZODIAC-36 (Competing risk model)	0.83 [0.83-0.83]	21.196 (-0.008)

Table S9. Calibration performance after intercept-only recalibration among people with type 2 diabetes

Mode	Calibration slope (intercept)	
	Slope	Intercept
Chronic Kidney Disease		
Chien	0.350	0.076
Kshirsagar (Simplified categorical model)	1.209	-0.032
Kshirsagar (Best-fitting categorical model)	1.311	-0.048
Nelson	0.619	0.048
O'Seaghdha	1.003	0.000
Saranburut	0.619	0.058
Umesawa	0.817	0.028
Dunkler (Laboratory model)	0.722	0.028
Jardine	0.787	0.026
Low	0.832	0.023
ZODIAC-36 (Cox regression model)	1.402	-0.009
ZODIAC-36 (Competing risk model)	1.435	-0.010
Kidney failure		
Elley	1.682	-0.008
Jardine	1.139	-0.003
RECODe	3.446	-0.058
Wan	0.582	0.014
ZODIAC-36 (Cox regression model)	1.257	-0.006
ZODIAC-36 (Competing risk model)	1.378	-0.008

Figure S1. Selection of models for validation



[1] The models for general population from systematic reviews: Chien et al, Chang et al, Hanratty et al, Hemmelgarn et al, QKidney Scores, Johnson et al, Nelson et al, Kshirsagar et al (best-fitting categorical model), Kshirsagar et al (best-fitting categorical model), O'Seaghdha et al, Saranburut et al, Schroeder et al, Umesawa et al, Al-Shamsi et al, Hao et al, Halbesma et al, Kwon et al, Thakkinstian et al, Wen et al, Yu et al

[2] Excluded models: Chang et al, Hemmelgarn et al, Hao et al, Thakkinstian et al

[3] Excluded models: Hanratty et al, QKidney Scores, Al-Shamsi et al, Halbesma et al, Kwon et al, Wen et al, Yu et al

[4] Excluded models: Johnson et al, Schroeder et al

[5] Remaining models: Chien et al, Nelson et al, Kshirsagar et al (best-fitting categorical model), Kshirsagar et al (best-fitting categorical model), O'Seaghdha et al, Saranburut et al, Umesawa et al

[6] The models for people with type 2 diabetes only from systematic reviews: Afghahi et al, Altemtam et al, RECODe, Cheng et al, UKPDS OM1, Dagliati et al, Dunkler et al (clinical model), Dunkler et al (laboratory model), Elley et al, GoldfarbRumyantzev et al, Hu et al, Imbroll et al, Jardine et al, Keane et al, Li et al, Lin et al, Low et al, Miao et al, Parrinello et al, ZODIAC-36 (Cox regression model), ZODIAC-36 (Competing risk model), Rodriguez et al, Sun et al, Tanaka et al, Wada et al, Wan et al, Woodward et al, Wysham et al, Yang et al, Blech et al, Wu et al, UKPDS OM2

[7] Excluded models: Wysham et al

[8] Excluded models: Afghahi et al, Cheng et al, Dagliati et al, GoldfarbRumyantzev et al, Hu et al, Imbroll et al, Keane et al, Li et al, Miao et al, Parrinello et al, Sun et al, Tanaka et al, Wada et al, Yang et al, Wu et al

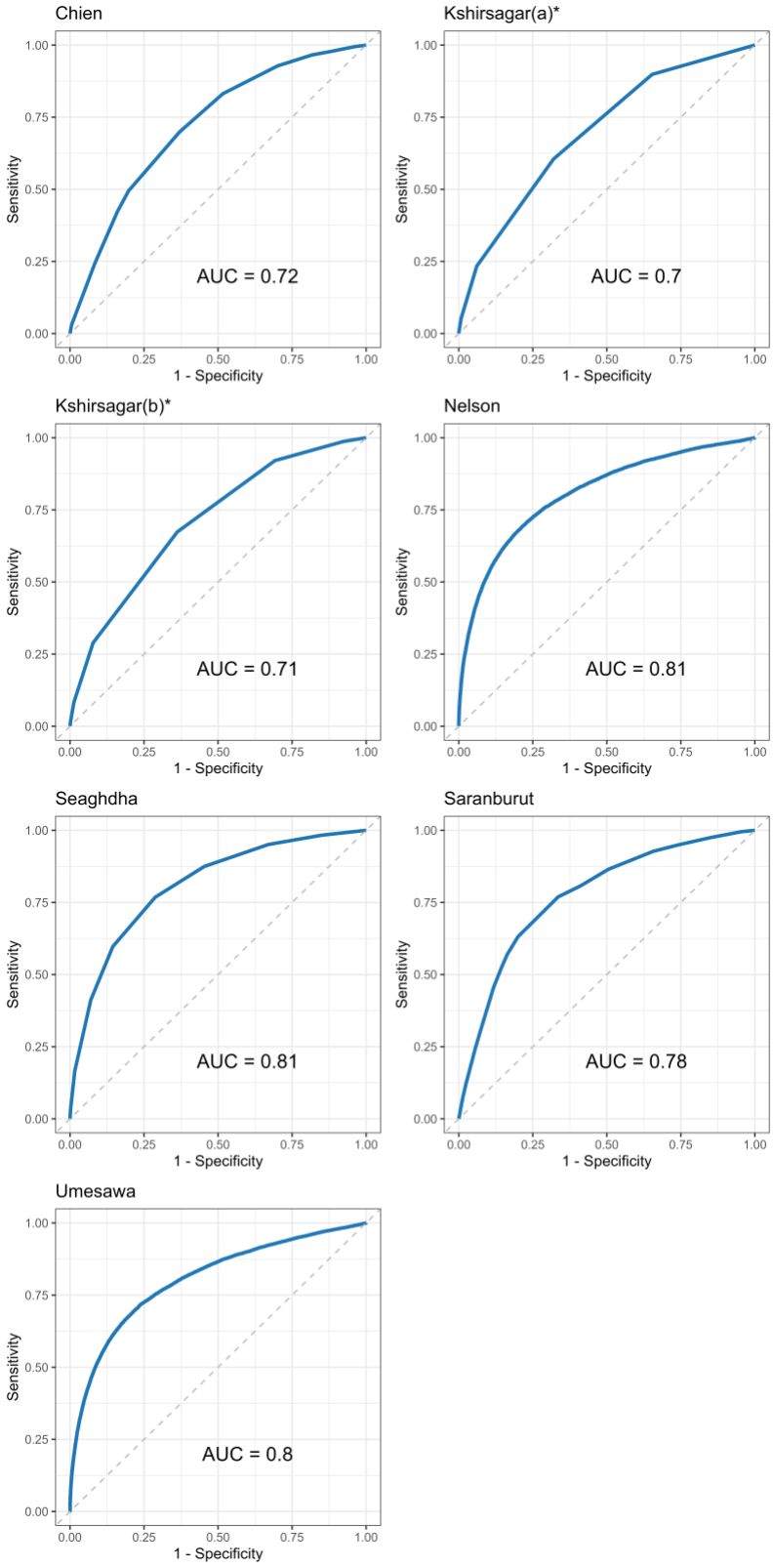
[9] Excluded models: Rodriguez et al, Woodward et al

[10] Excluded models: Altemtam et al, Lin et al, Blech et al

[11] Excluded models: UKPDS OM1

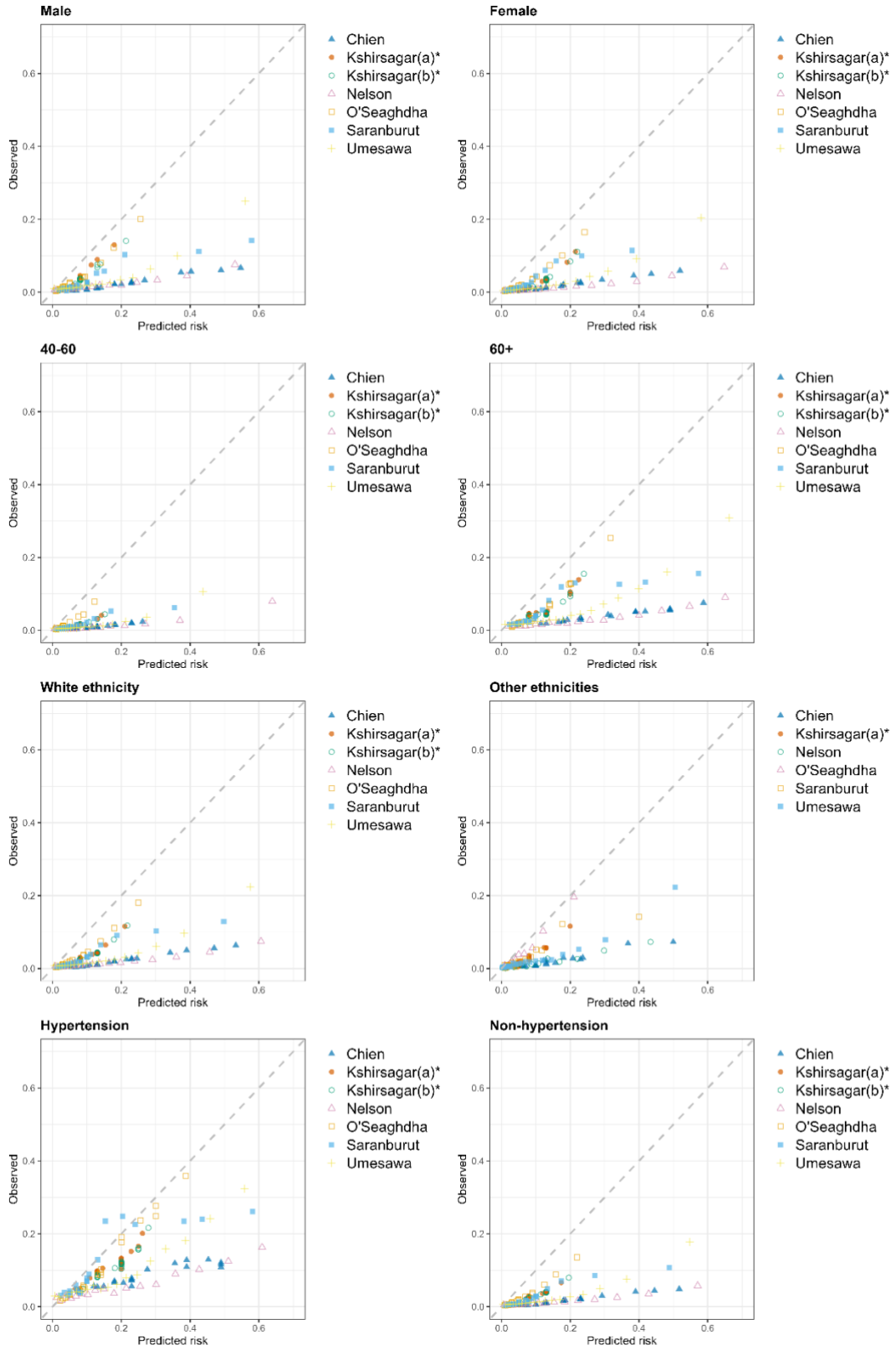
[12] Remaining models: RECODe, Dunkler et al (laboratory model), Elley et al, Jardine et al, Low et al, ZODIAC-36 (Cox regression model), ZODIAC-36 (Competing risk model), Wan et al, UKPDS OM2

Figure S2. ROC curves and the area under the ROC curve for models predicting chronic kidney disease among people without diabetes



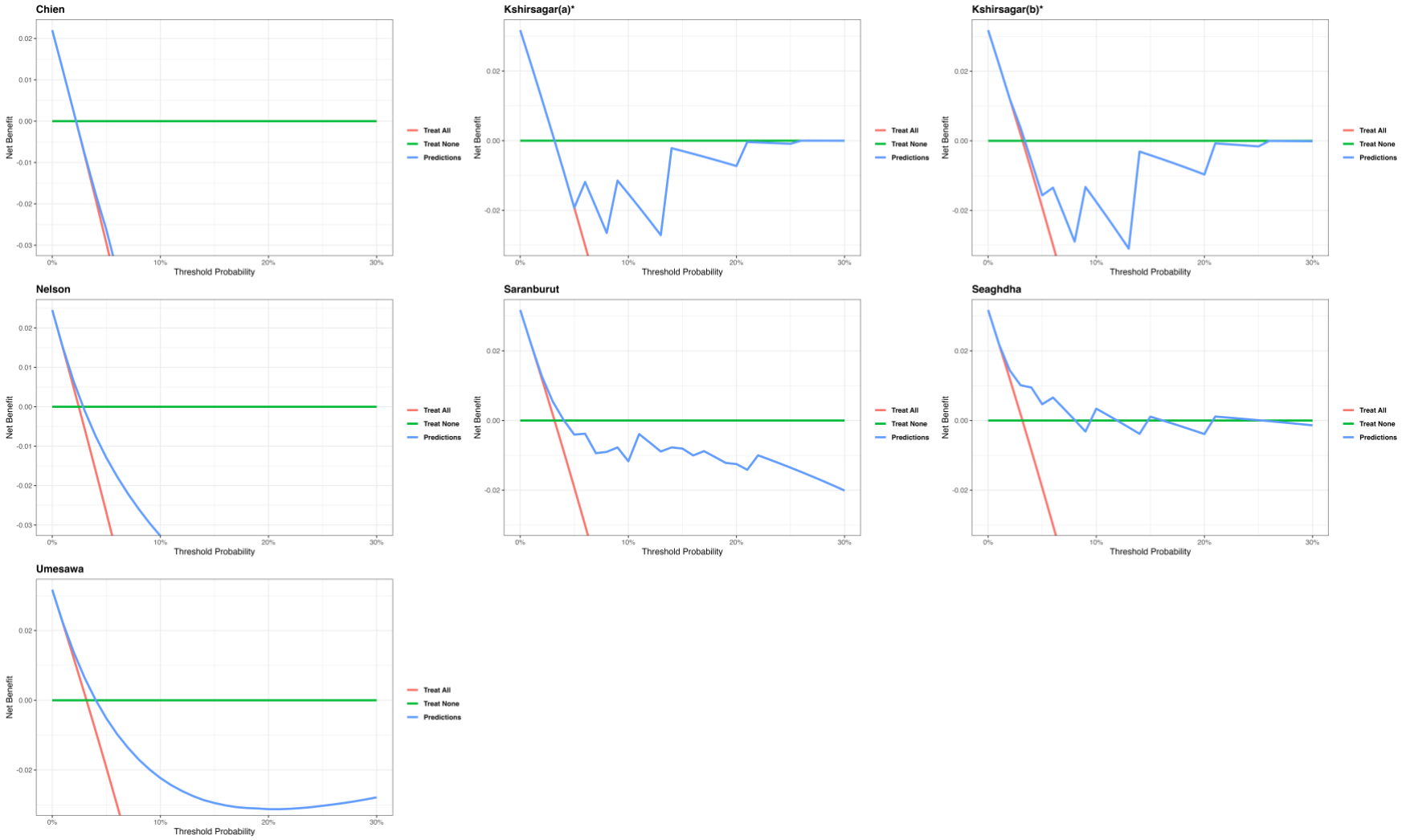
* Kshirsagar (a): Kshirsagar (simplified categorical model), Kshirsagar (b): Kshirsagar (best-fitting categorical model

Figure S3. Calibration plots for models predicting chronic kidney disease among people without diabetes by subgroup



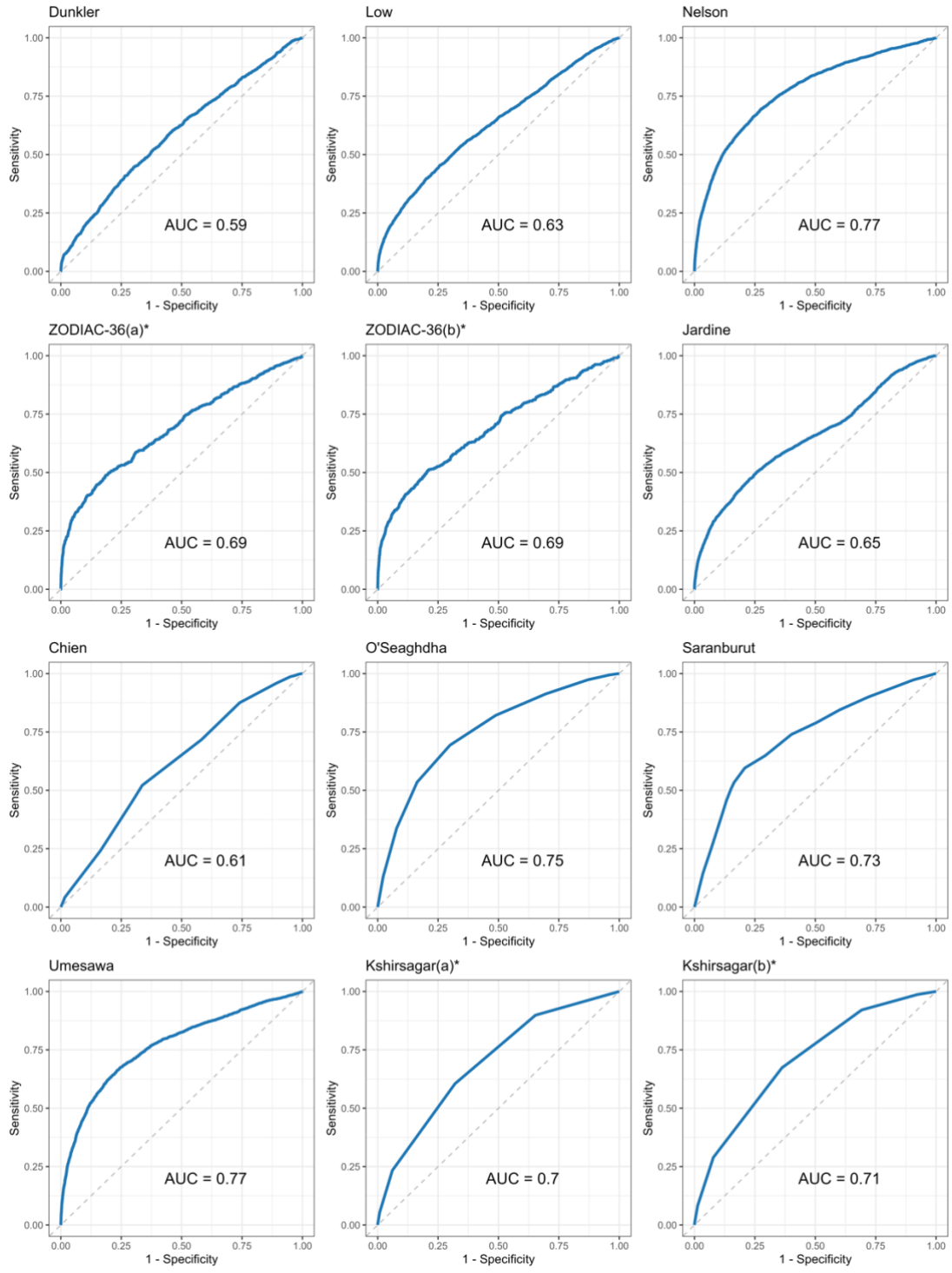
* Kshirsagar (a): Kshirsagar (simplified categorical model), Kshirsagar (b): Kshirsagar (best-fitting categorical model)

Figure S4. DCA curve for models predicting chronic kidney disease among people without diabetes



* Kshirsagar (a): Kshirsagar (simplified categorical model), Kshirsagar (b): Kshirsagar (best-fitting categorical model)

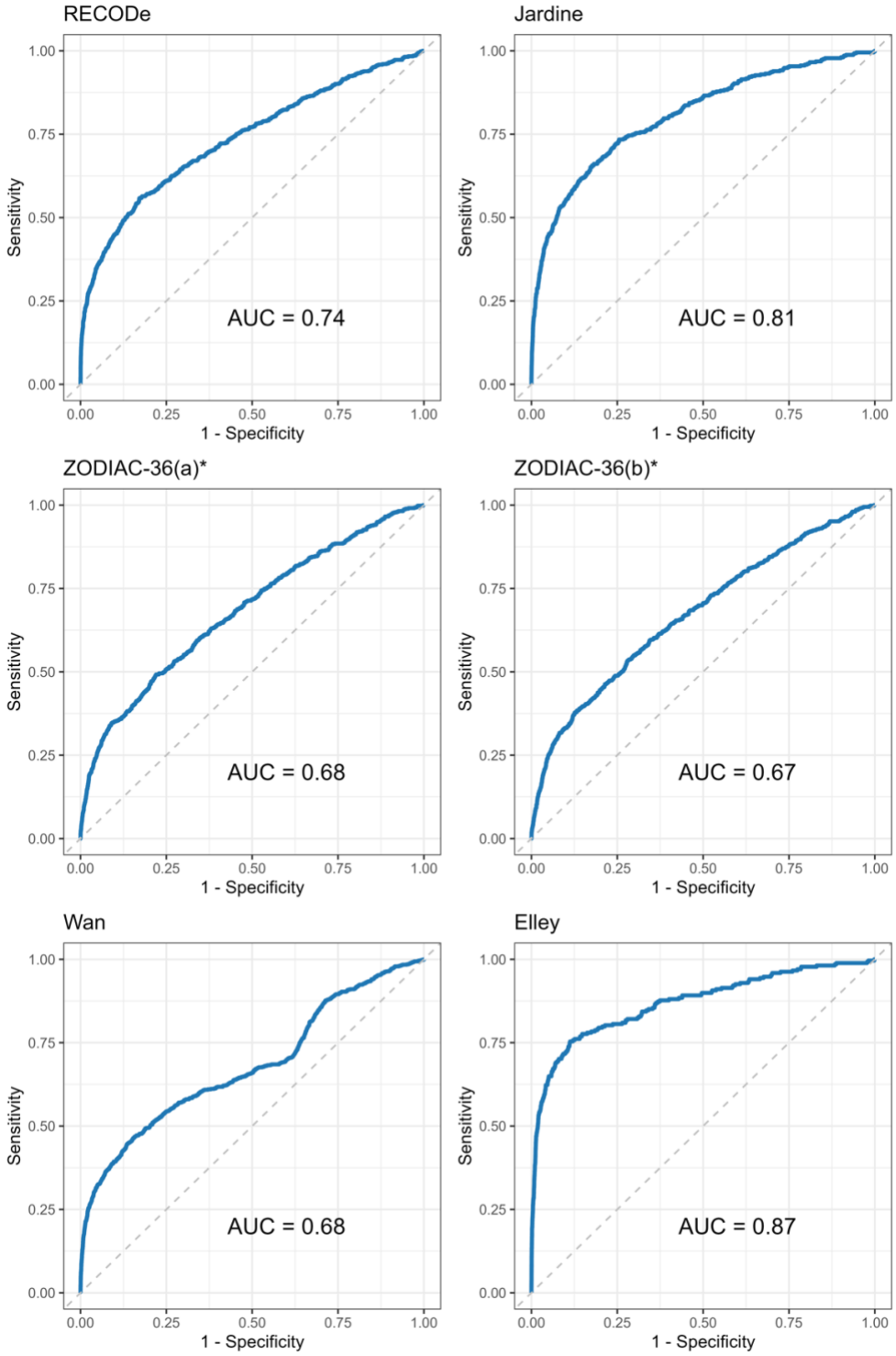
Figure S5. ROC curves and the area under the ROC curve for models predicting chronic kidney disease among people with diabetes



* ZODIAC-36 (a): ZODIAC-36 (cox regression model), ZODIAC-36 (b): ZODIAC-36 (competing risk model)

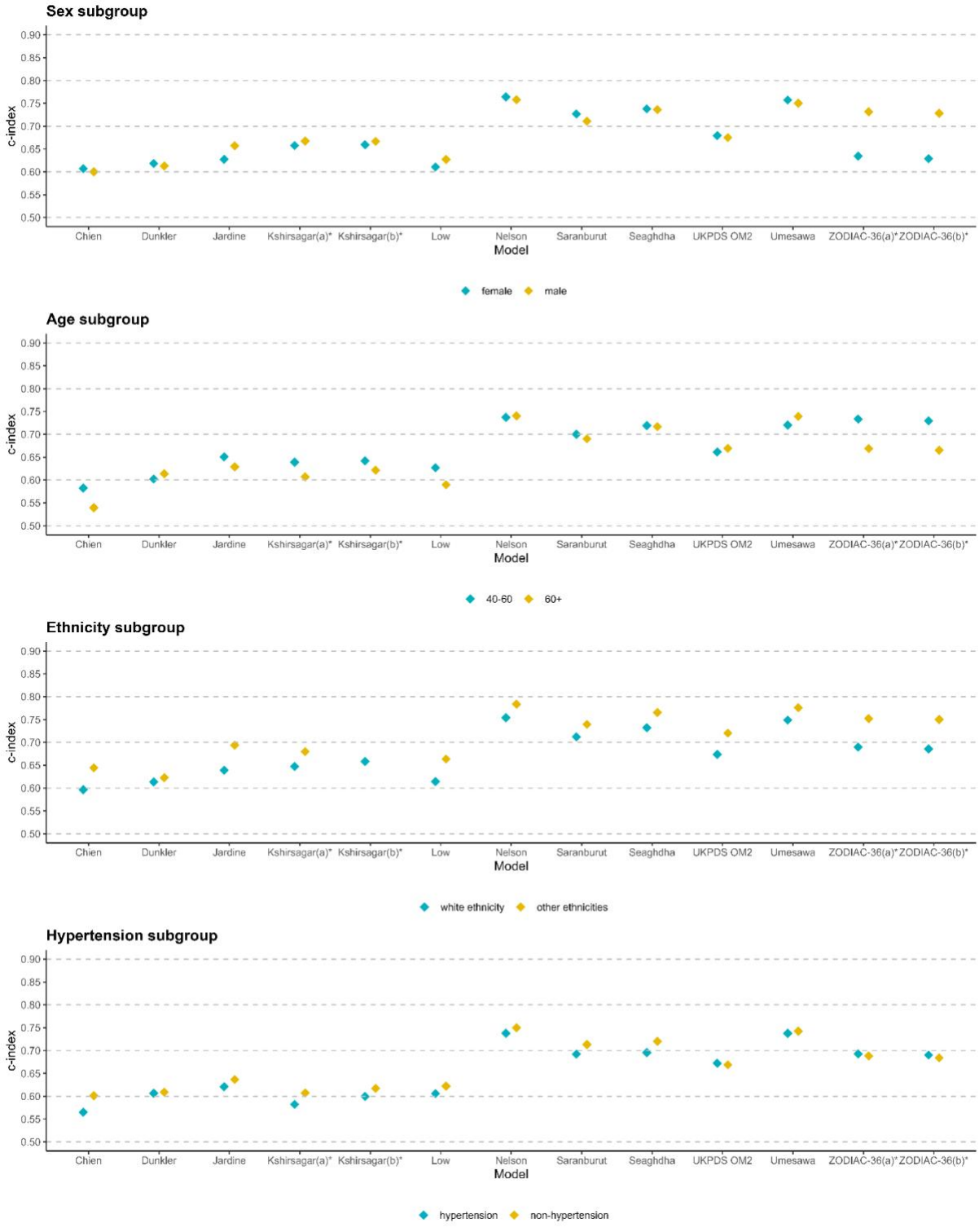
Kshirsagar (a): Kshirsagar (simplified categorical model), Kshirsagar (b): Kshirsagar (best-fitting categorical model)

Figure S6. ROC curves and the area under the ROC curve for models predicting kidney failure among people with diabetes



* ZODIAC-36 (a): ZODIAC-36 (cox regression model), ZODIAC-36 (b): ZODIAC-36 (competing risk model)

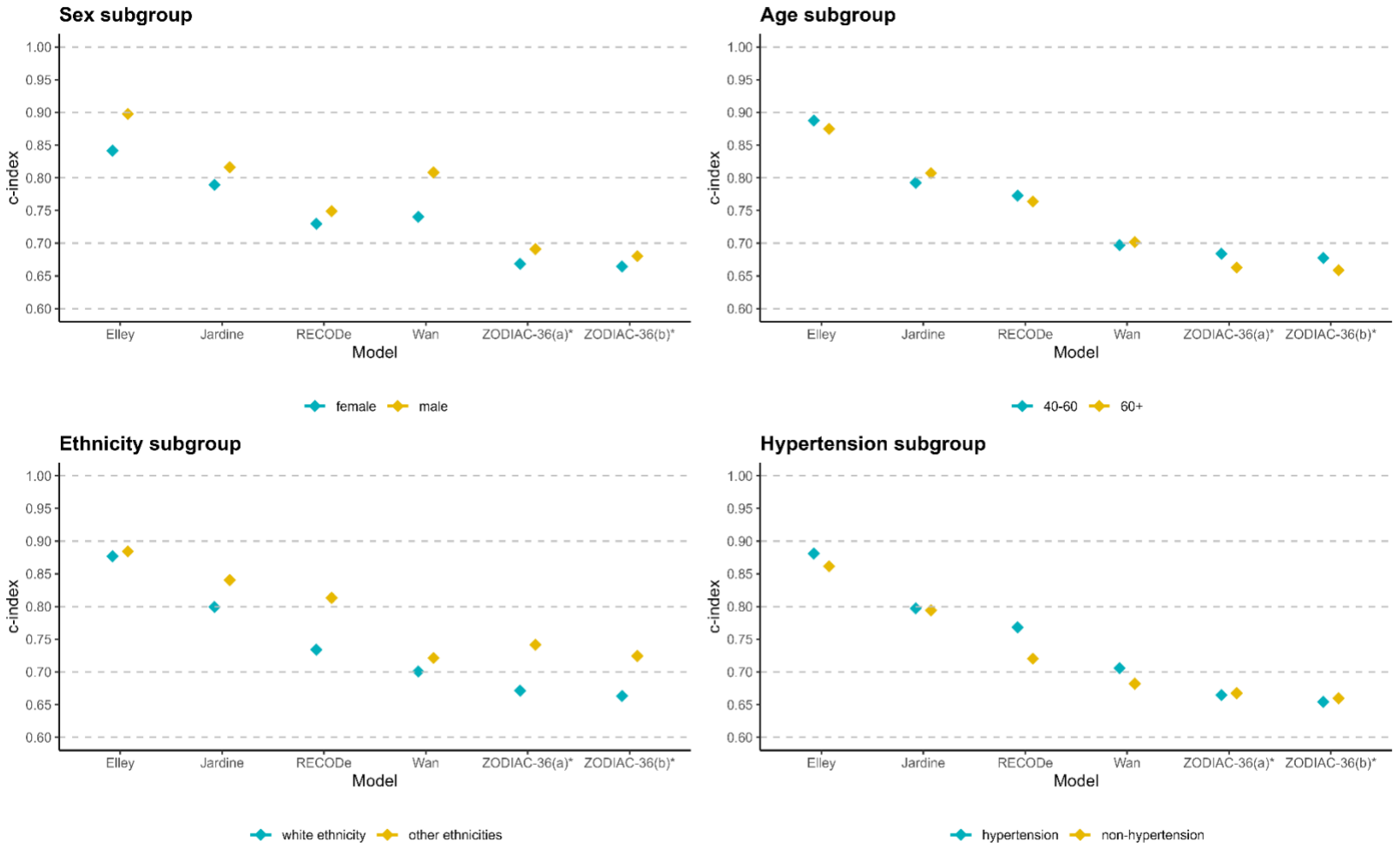
Figure S7. Discriminative performance for models predicting chronic kidney disease among people with type 2 diabetes by subgroup



* ZODIAC-36 (a): ZODIAC-36 (cox regression model), ZODIAC-36 (b): ZODIAC-36 (competing risk model)

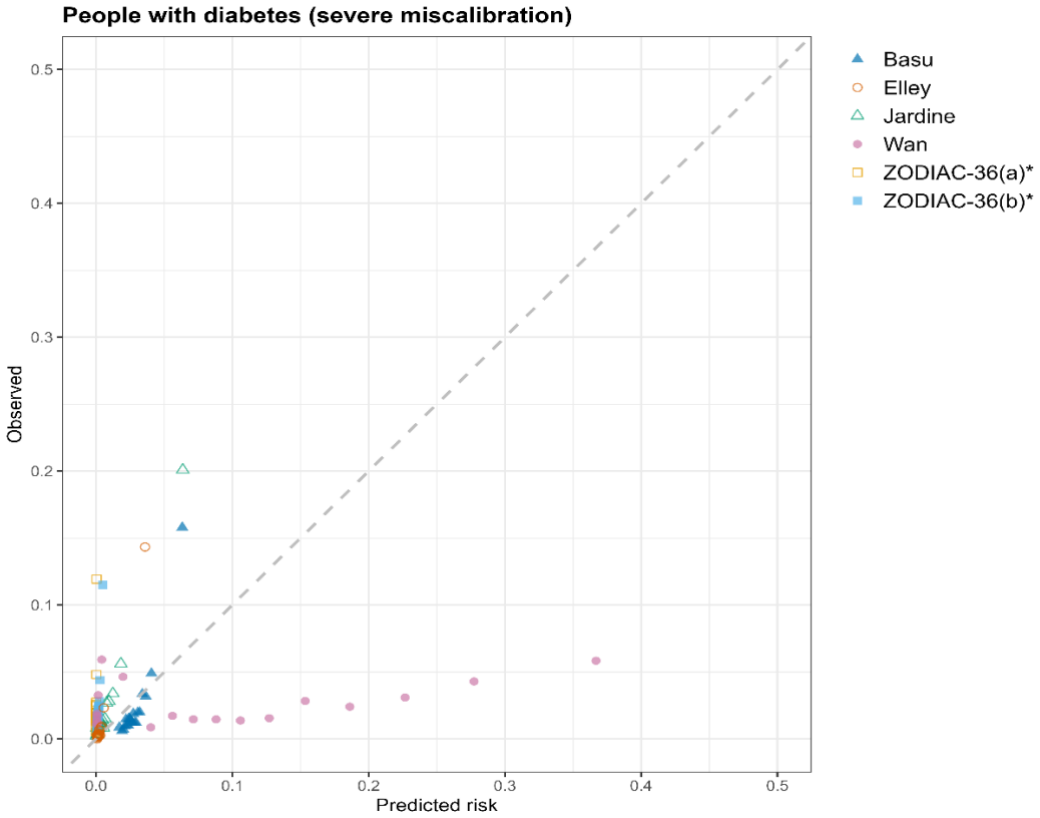
Kshirsagar (a): Kshirsagar (simplified categorical model), Kshirsagar (b): Kshirsagar (best-fitting categorical mode

Figure S8. Discriminative performance for models predicting kidney failure among people with type 2 diabetes by subgroup



* ZODIAC-36 (a): ZODIAC-36 (cox regression model), ZODIAC-36 (b): ZODIAC-36 (competing risk model)

Figure S9. Calibration plots for models predicting kidney failure among people with type 2 diabetes



* ZODIAC-36 (a): ZODIAC-36 (cox regression model), ZODIAC-36 (b): ZODIAC-36 (competing risk model)

Figure S10. Calibration plots for models predicting chronic kidney disease among people with type 2 diabetes by subgroup

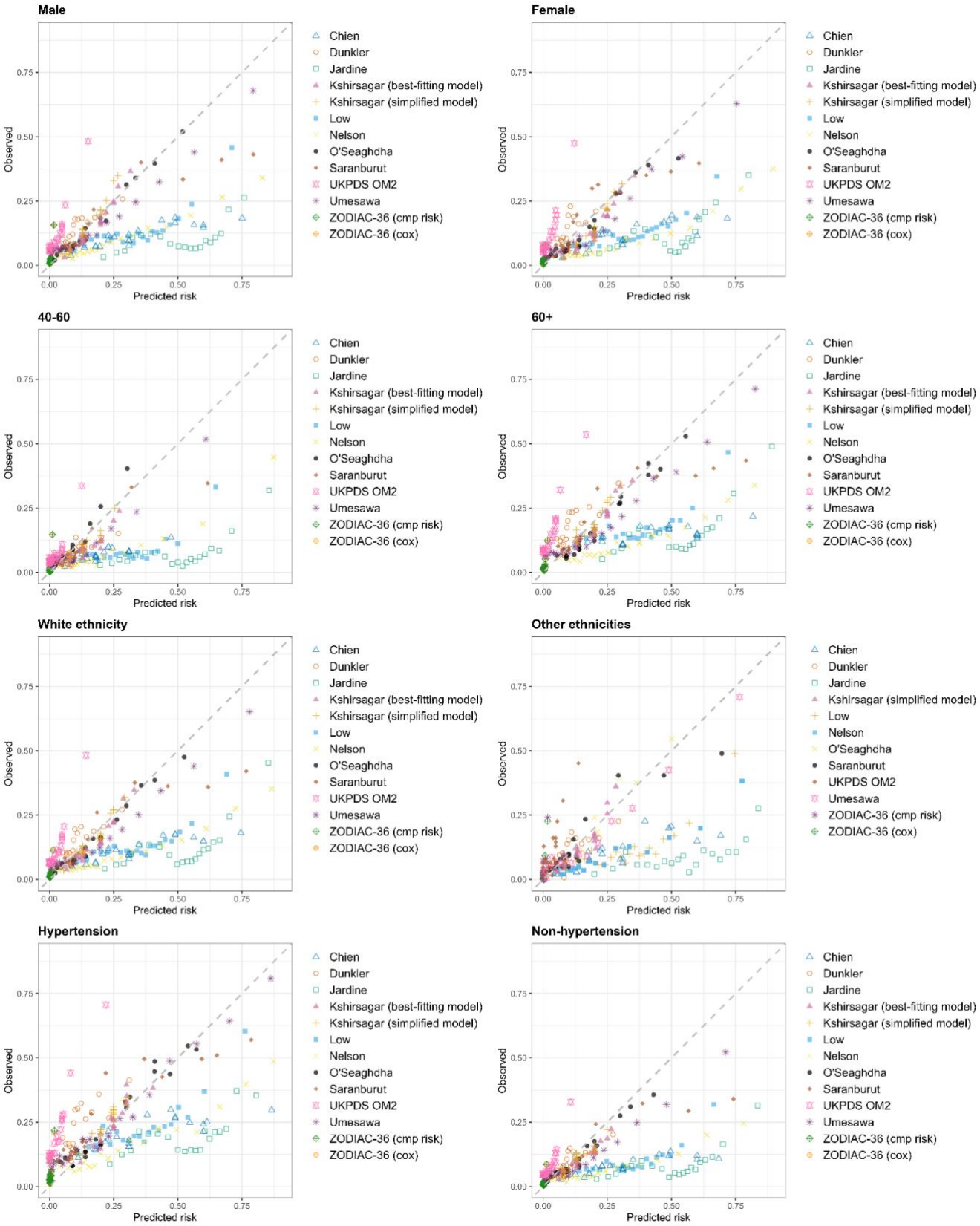


Figure S11. Calibration plots for models predicting kidney failure among people with type 2 diabetes by subgroup

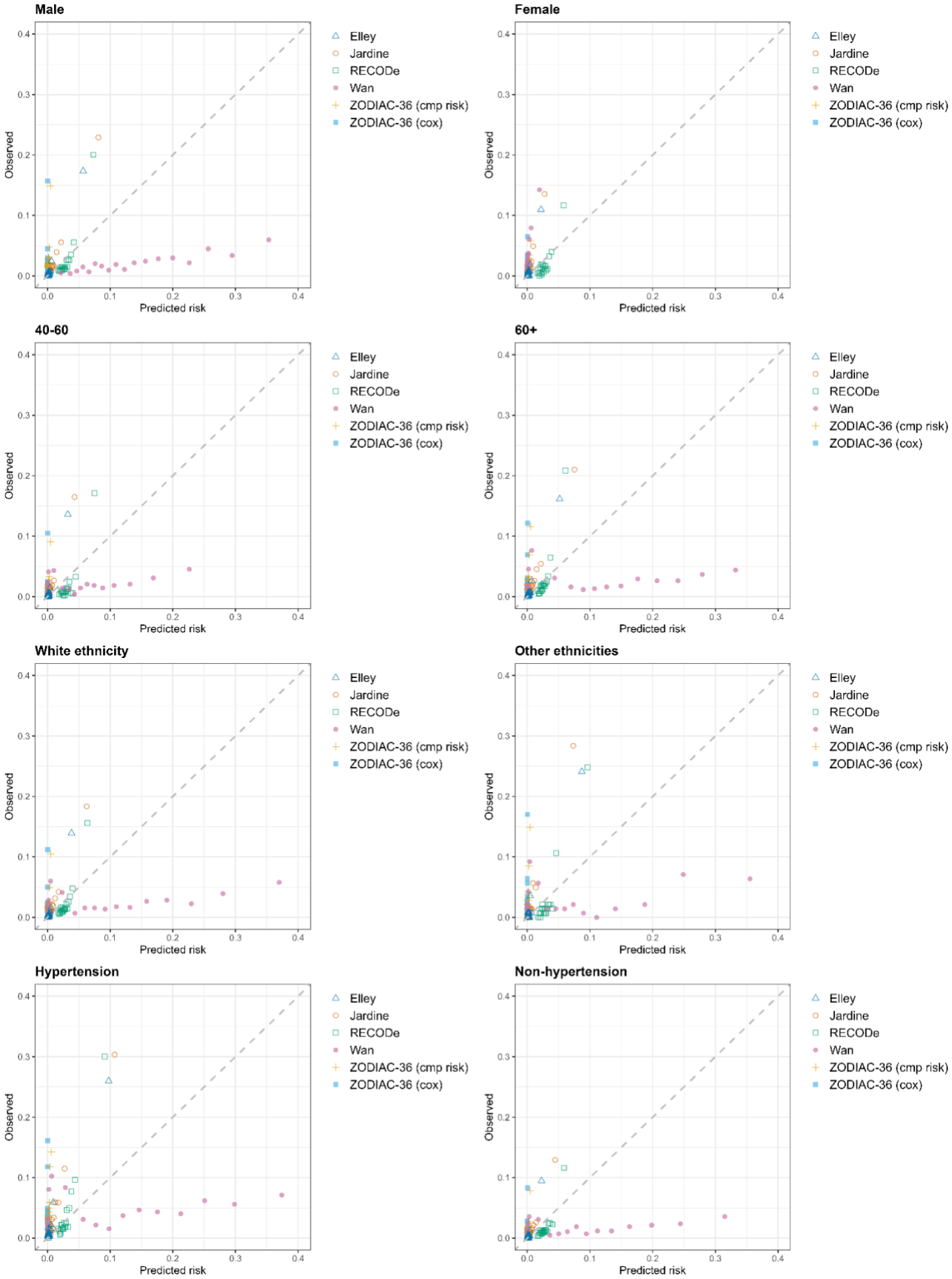
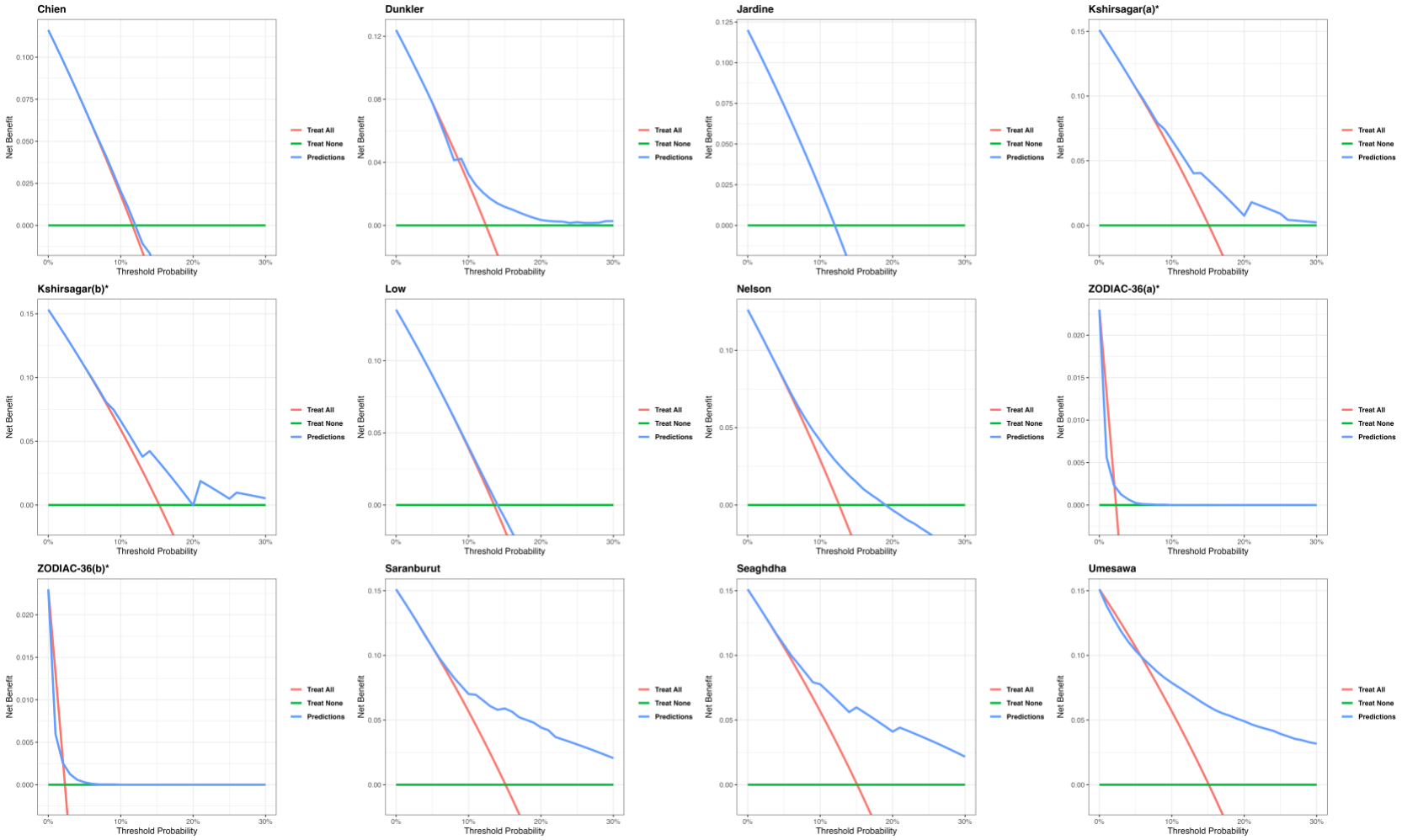


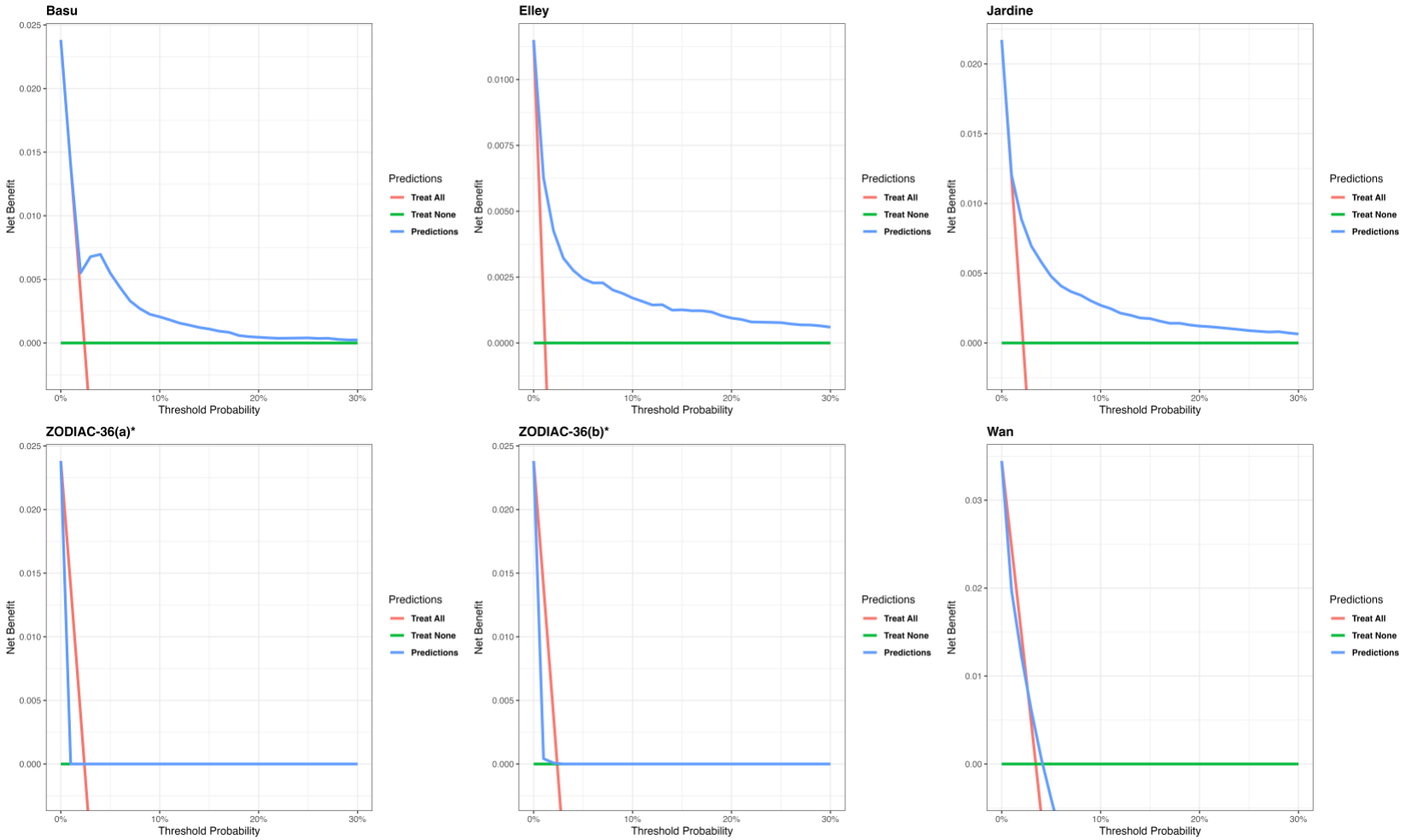
Figure S12. DCA curve for models predicting chronic kidney disease among people with type 2 diabetes



* ZODIAC-36 (a): ZODIAC-36 (cox regression model), ZODIAC-36 (b): ZODIAC-36 (competing risk model)

Kshirsagar (a): Kshirsagar (simplified categorical model), Kshirsagar (b): Kshirsagar (best-fitting categorical model)

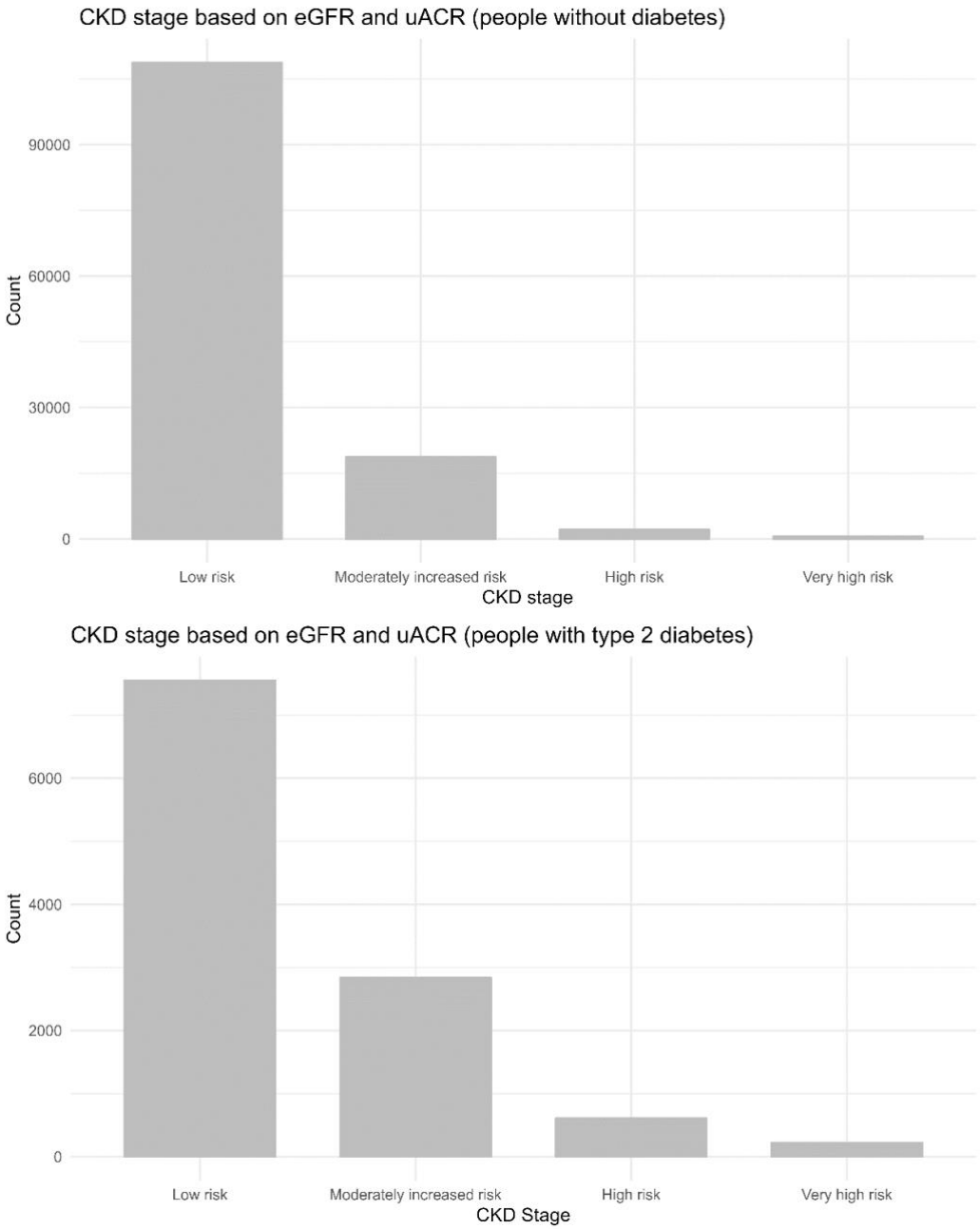
Figure S13. DCA curve for models predicting kidney failure among people with type 2 diabetes



* ZODIAC-36 (a): ZODIAC-36 (cox regression model), ZODIAC-36 (b): ZODIAC-36 (competing risk model)

Kshirsagar (a): Kshirsagar (simplified categorical model), Kshirsagar (b): Kshirsagar (best-fitting categorical model)

Figure S14. Proportion of CKD stage based on the current nomenclature based on GFR and uACR from KDIGO



Low risk: G1-G2 (GFR ≥60 ml/min/1.73m²) with A1 (albumin-creatinine ratio < 30 mg/g)

Moderately increased risk: G3a (GFR 45-59 ml/min/1.73m²) with A1 (albumin-creatinine ratio < 30 mg/g); or G1-G2 (≥60 ml/min/1.73m²) with A2 (albumin-creatinine ratio 30-300 mg/g)

High risk: G1-G2 (≥60 ml/min/1.73m²) with A3 (albumin-creatinine ratio > 300 mg/g); or G3a (45-59 ml/min/1.73m²) with A2 (albumin-creatinine ratio 30-300 mg/g); or G3b (30-44 ml/min/1.73m²) with A1 (albumin-creatinine ratio < 30 mg/g)

Very high risk: G3a (45-59 ml/min/1.73m²) with A3 (albumin-creatinine ratio > 300 mg/g); or G3b (30-44 ml/min/1.73m²) with A2-A3 (albumin-creatinine ratio > 30 mg/g); or G4-G5 (<29 ml/min/1.73m²)