

SUPPLEMENTAL MATERIAL

Supplemental Table 1: Comparison of AASK and VA NEPHRON-D participants who were included vs. excluded from primary analyses.

Supplemental Table 2: Number of ESKD events and participants by subgroups of GFR slope and biomarker slope in AASK.

Supplemental Table 3: Comparison of models by Harrell's C Statistic and Brier Score in AASK and VA NEPHRON-D.

Supplemental Table 4: Number of kidney function decline events and participants by subgroups of eGFR change and biomarker change in VA NEPHRON-D.

Supplemental Figure 1: Flowchart of study population for primary analyses in a) AASK and b) VA NEPHRON-D.

Supplemental Figure 2: Pearson's correlation coefficients of TNFR1 and TNFR2 slopes with biomarker levels and kidney function measures in AASK.

Supplemental Figure 3: Distributions of baseline TNFR1 and TNFR2 in AASK and VA NEPHRON-D, by outcome.

Supplemental Figure 4: Calibration plots of observed vs. predicted 5-year risk for ESKD in AASK and 2-year risk for kidney function decline in VA NEPHRON-D.

Supplemental Figure 5: Pearson's correlation coefficients of TNFR1 and TNFR2 change with biomarker levels and kidney function measures in VA NEPHRON-D.

CKD Biomarkers Consortium Collaborators: Phase II: Group Members and Affiliations

Supplemental Table 1: Comparison of AASK and VA NEPHRON-D participants who were included vs. excluded from primary analyses.

AASK					
Characteristic		All (n=1094)	Excluded (n=676)	Included (n=418)	p-value
Age, years		54.6 ± 10.7	54.9 ± 10.7	54.2 ± 10.7	0.28
Female		425 (39%)	265 (39%)	160 (38%)	0.76
European ancestry, %**		16.7 ± 13.3	16.9 ± 13.7	16.4 ± 12.8	0.63
APOL1**	Low-risk	533 (77%)	302 (78%)	231 (75%)	0.35
	High-risk	160 (23%)	84 (22%)	76 (25%)	
Systolic blood pressure, mm Hg		150 ± 24	150 ± 23	151 ± 25	0.39
Body mass index, kg/ m ²		30.6 ± 6.6	30.3 ± 6.6	31.0 ± 6.5	0.08
Smoking		321 (29%)	215 (32%)	106 (25%)	0.02
GFR, ml/min/1.73 m ²		45.6 ± 13.0	45.7 ± 13.5	45.5 ± 12.3	0.85
UPCR, g/g Cr		0.08 (0.03, 0.36)	0.08 (0.03, 0.41)	0.08 (0.03, 0.32)	0.27
Blood pressure goal	MAP ≤92	540 (49%)	329 (49%)	211 (50%)	0.56
	MAP 102-107	554 (51%)	347 (51%)	207 (50%)	
Blood pressure drug	Ramipril	436 (40.0%)	273 (40%)	163 (39%)	0.78
	Metoprolol	441 (40%)	267 (39%)	174 (42%)	
	Amlodipine	217 (20%)	136 (20%)	81 (19%)	
VA NEPHRON-D					
Characteristic		All (n=1448)	Excluded (n=694)	Included (n=754)	p-value
Age, years		64.6 ± 7.8	64.4 ± 8.1	64.8 ± 7.6	0.40
Male		1436 (99%)	688 (99%)	748 (99%)	0.89
Race	Black	345 (24%)	183 (26%)	162 (21%)	0.06
	White	1051 (73%)	490 (71%)	561 (74%)	
	Other***	52 (4%)	21 (3%)	31 (4%)	
Systolic blood pressure, mm Hg		137 ± 16	138 ± 17	136 ± 16	0.01
Body mass index, kg/m ²		34.6 ± 6.9	34.6 ± 7.1	34.6 ± 6.7	0.94
Smoking		284 (20%)	132 (19%)	152 (20%)	0.04
Hemoglobin A1c, %		7.8 ± 1.3	7.8 ± 1.2	7.8 ± 1.3	0.35
eGFR, ml/min/1.73 m ²		56.1 ± 18.7	55.6 ± 18.6	56.6 ± 18.8	0.27
UACR, g/g Cr		0.84 (0.42, 0.17)	0.93 (0.44, 0.20)	0.80 (0.42, 0.16)	0.05
Randomized group	Losartan	724 (50%)	346 (50%)	378 (50%)	0.92
	Losartan + lisinopril	724 (50%)	348 (50%)	376 (50%)	

*p-values comparing included vs. excluded (missing biomarker specimen or had event prior to 12 months) and determined using ANOVA, Wilcoxon rank-sum, and Pearson's chi-squared tests in AASK and Wilcoxon rank-sum and chi-squared tests in VA NEPHRON-D.

**APOL1 risk status and European ancestry were available in 693 of 1094 AASK participants.

***Other defined as American Indian or Alaska Native, Asian, or Native Hawaiian or Other Pacific Islander.

Supplemental Table 2: Number of ESKD events and participants by subgroups of GFR slope and biomarker slope in AASK.

		TNFR1 slope		
		Negative	Positive	Total
GFR slope	Positive	1/55 (1.8%)	2/30 (6.7%)	3/85 (3.5%)
	Stable	6/46 (13.0%)	8/43 (18.6%)	14/89 (15.7%)
	Negative	2/29 (6.9%)	110/215 (51.2%)	112/244 (45.9%)
	Total	9/130 (6.9%)	120/288 (41.7%)	129/418 (30.9%)

		TNFR2 slope		
		Negative	Positive	Total
GFR slope	Positive	2/58 (3.4%)	1/27 (3.7%)	3/85 (3.5%)
	Stable	5/44 (11.4%)	9/45 (20.0%)	14/89 (15.7%)
	Negative	9/48 (18.8%)	103/196 (52.6%)	112/244 (45.9%)
	Total	16/150 (10.7%)	113/268 (42.2%)	129/418 (30.9%)

Data in each cell presented as # of ESKD events/# of participants (% with event).

For GFR slope, positive, stable, and negative are defined as GFR changes of >1 ml/min/1.73 m²/year, -1 to 1 ml/min/1.73 m²/year, and <-1 ml/min/1.73 m²/year, respectively.

Supplemental Table 3: Comparison of models by Harrell's C Statistic and Brier Score in AASK and VA NEPHRON-D.

Model	Harrell's C Statistic (95% CI)	Difference in C Statistics (95% CI)	Brier Score*
AASK			
Clinical Model: Adjusted for age, sex, SBP, BMI, current smoking, GFR, ln(UPCR)	0.836 (0.804 to 0.868)	Ref	0.105
Clinical Model + t_0 ln(TNFR1)	0.844 (0.813 to 0.875)	0.008 (-0.002 to 0.018)	0.106
Clinical Model + t_0 ln(TNFR1) + ln(TNFR1) slope	0.891 (0.866 to 0.916)	0.055 (0.034 to 0.076)	0.085
Clinical Model + t_0 ln(TNFR2)	0.844 (0.814 to 0.874)	0.008 (-0.003 to 0.018)	0.106
Clinical Model + t_0 ln(TNFR2) + ln(TNFR2) slope	0.878 (0.853 to 0.903)	0.042 (0.025 to 0.059)	0.091
VA NEPHRON-D			
Clinical Model: Adjusted for age, sex, race, SBP, BMI, HgbA1c, smoking, eGFR, and ln(UACR) at 0 months.	0.749 (0.699 to 0.799)	Ref	0.101
Clinical Model + t_0 ln(TNFR1)	0.777 (0.733 to 0.820)	0.028 (-0.002 to 0.057)	0.100
Clinical Model + t_0 ln(TNFR1) + ln(TNFR1) change	0.819 (0.780 to 0.858)	0.070 (0.032 to 0.108)	0.101
Clinical Model + t_0 ln(TNFR2)	0.765 (0.719 to 0.811)	0.015 (0.001 to 0.030)	0.100
Clinical Model + t_0 ln(TNFR2) + ln(TNFR2) change	0.804 (0.766 to 0.843)	0.055 (0.024 to 0.086)	0.101

Abbreviations: SBP=systolic blood pressure; BMI=body mass index; HgbA1c=hemoglobin A1c; GFR=measured glomerular filtration rate; eGFR=estimated glomerular filtration rate; UPCR=urine protein-to-creatinine ratio; UACR=urine albumin-to-creatinine ratio; TNFR1=soluble tumor necrosis factor receptor 1; TNFR2=soluble tumor necrosis factor receptor 2; t_0 =measurement at 0 months.

*5-year risk for ESKD in AASK and 2-year risk for kidney function decline in VA NEPHRON-D.

Supplemental Table 4: Number of kidney function decline events and participants by subgroups of eGFR change and biomarker change in VA NEPHRON-D.

		TNFR1 change		
		Negative	Positive	Total
eGFR change	Positive	3/66 (4.5%)	3/83 (3.6%)	6/149 (4.0%)
	Stable	5/39 (12.8%)	7/52 (13.5%)	12/91 (13.2%)
	Negative	21/149 (14.1%)	72/336 (21.4%)	93/485 (19.2%)
	Total	29/254 (11.4%)	82/471 (17.4%)	111/725 (15.3%)

		TNFR2 change		
		Negative	Positive	Total
eGFR change	Positive	4/78 (5.1%)	2/71 (2.8%)	6/149 (4.0%)
	Stable	5/42 (11.9%)	7/49 (14.3%)	12/91 (13.2%)
	Negative	15/172 (8.7%)	78/313 (24.9%)	93/485 (19.2%)
	Total	24/292 (8.2%)	87/433 (20.1%)	111/725 (15.3%)

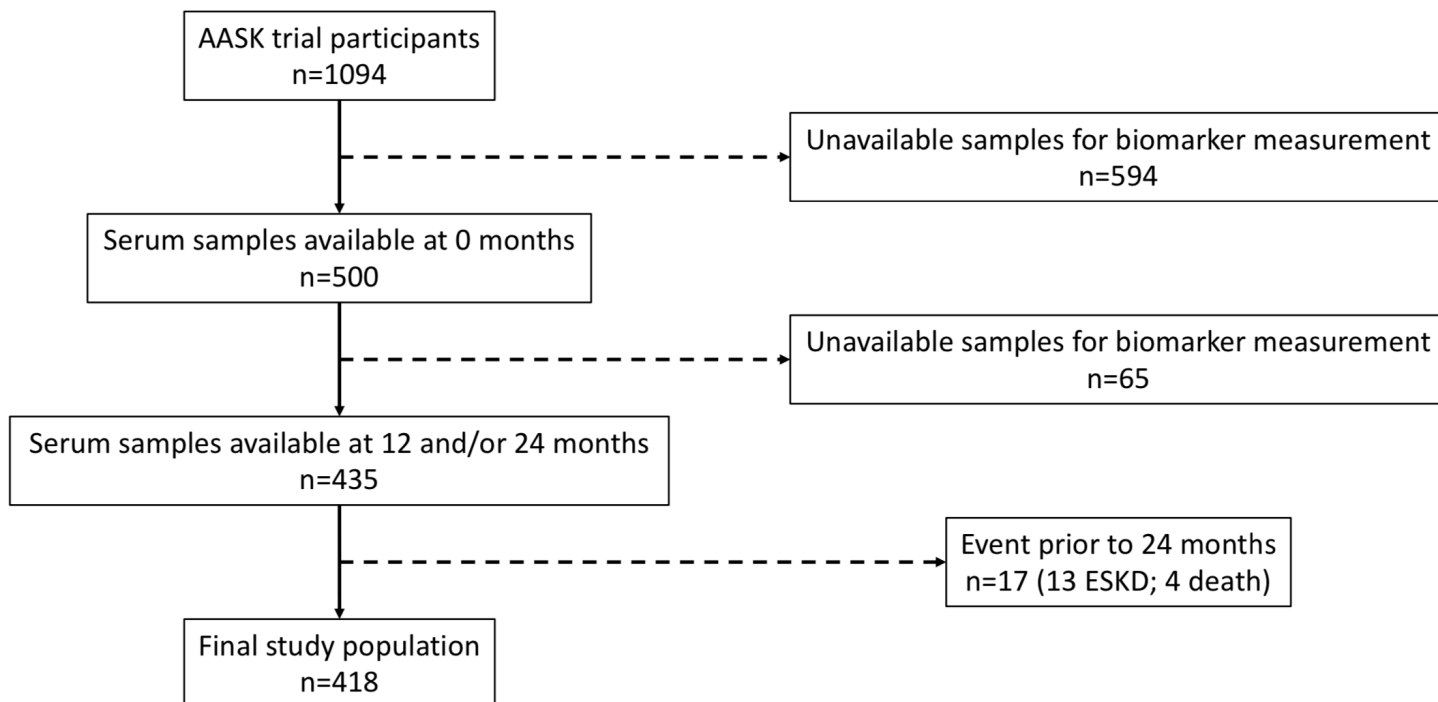
Data in each cell presented as # of kidney function decline events/# of participants (% with event).

Abbreviations: eGFR=estimated glomerular filtration rate; TNFR1=soluble tumor necrosis factor receptor 1; TNFR2=soluble tumor necrosis factor receptor 2.

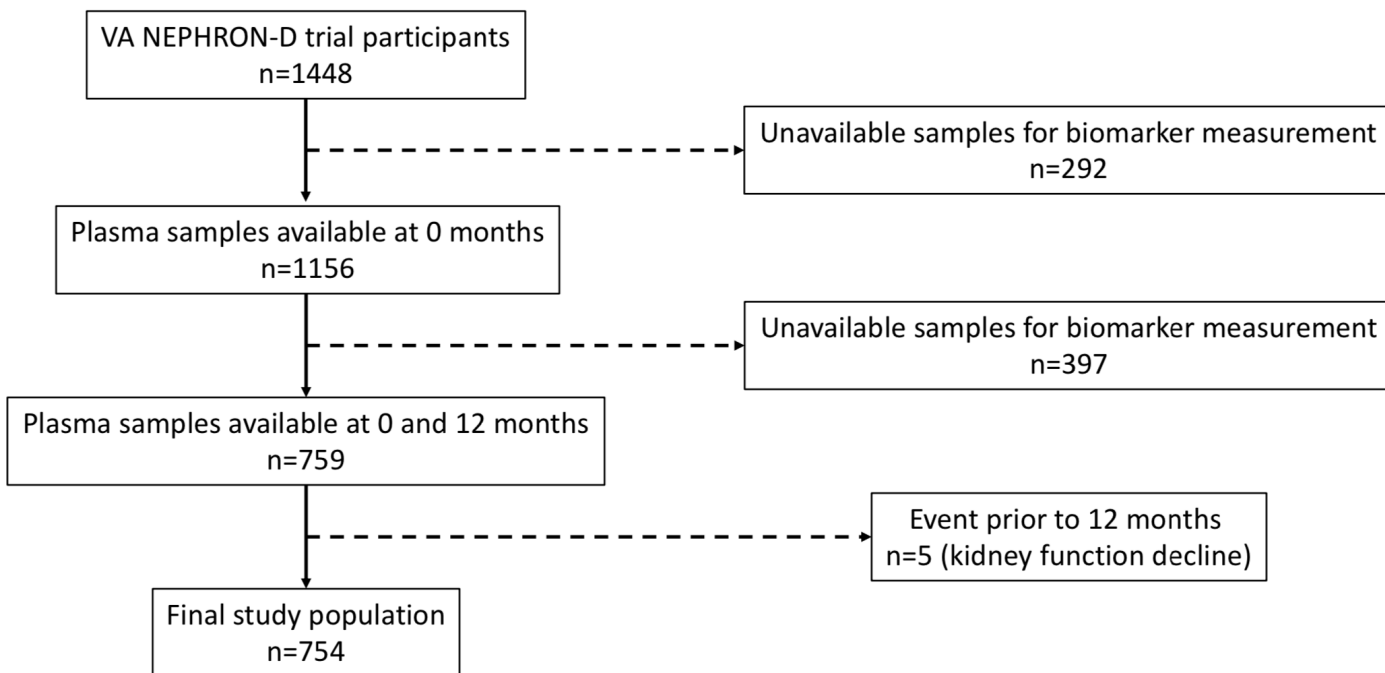
For eGFR change, positive, stable, and negative are defined as eGFR changes of >1 ml/min/1.73 m²/year, -1 to 1 ml/min/1.73 m²/year, and <-1 ml/min/1.73 m²/year, respectively.

Supplemental Figure 1: Flowchart of study population for primary analyses in a) AASK and b) VA NEPHRON-D.

a)



b)



Abbreviations: AASK=African American Study of Kidney Disease and Hypertension; ESKD=end-stage kidney disease; VA NEPHRON-D=Veterans Affairs Nephropathy in Diabetes.

Supplemental Figure 2: Pearson's correlation coefficients of TNFR1 and TNFR2 slopes with biomarker levels and kidney function measures in AASK.

TNFR1								
	ln(TNFR1) slope	t ₀ ln(TNFR1)	t ₀ GFR	t ₀ ln(UPCR)	Last ln(TNFR1)	Last GFR	Last ln(UPCR)	GFR slope
ln(TNFR1) slope	1.00							
t ₀ ln(TNFR1)	0.44	1.00						
t ₀ GFR	-0.44	-0.74	1.00					
t ₀ ln(UPCR)	0.49	0.57	-0.45	1.00				
Last ln(TNFR1)	0.85	0.85	-0.69	0.62	1.00			
Last GFR	-0.71	-0.74	0.75	-0.55	-0.85	1.00		
Last ln(UPCR)	0.55	0.49	-0.39	0.70	0.61	-0.50	1.00	
GFR slope	-0.68	-0.51	0.39	-0.45	-0.70	0.85	-0.39	1.00

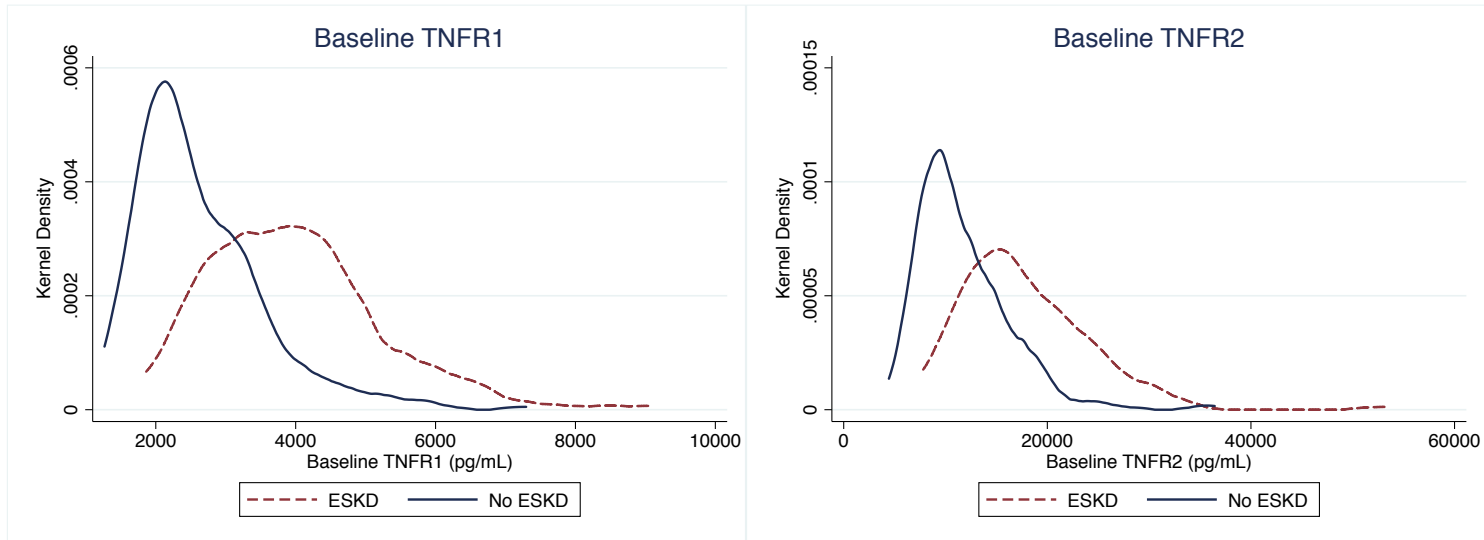
TNFR2								
	ln(TNFR2) slope	t ₀ ln(TNFR2)	t ₀ GFR	t ₀ ln(UPCR)	Last ln(TNFR2)	Last GFR	Last ln(UPCR)	GFR slope
ln(TNFR2) slope	1.00							
t ₀ ln(TNFR2)	0.40	1.00						
t ₀ GFR	-0.42	-0.66	1.00					
t ₀ ln(UPCR)	0.47	0.53	-0.45	1.00				
Last ln(TNFR2)	0.81	0.86	-0.65	0.59	1.00			
Last GFR	-0.64	-0.65	0.75	-0.55	-0.77	1.00		
Last ln(UPCR)	0.49	0.46	-0.39	0.70	0.57	-0.50	1.00	
GFR slope	-0.61	-0.45	0.39	-0.45	-0.62	0.85	-0.39	1.00

Abbreviation: t₀=measurement at 0 months; Last=measurement at 24 months or last available visit; TNFR1=soluble tumor necrosis factor receptor 1; TNFR2=soluble tumor necrosis factor receptor 2; GFR=glomerular filtration rate; UPCR=urine protein-to-creatinine ratio.

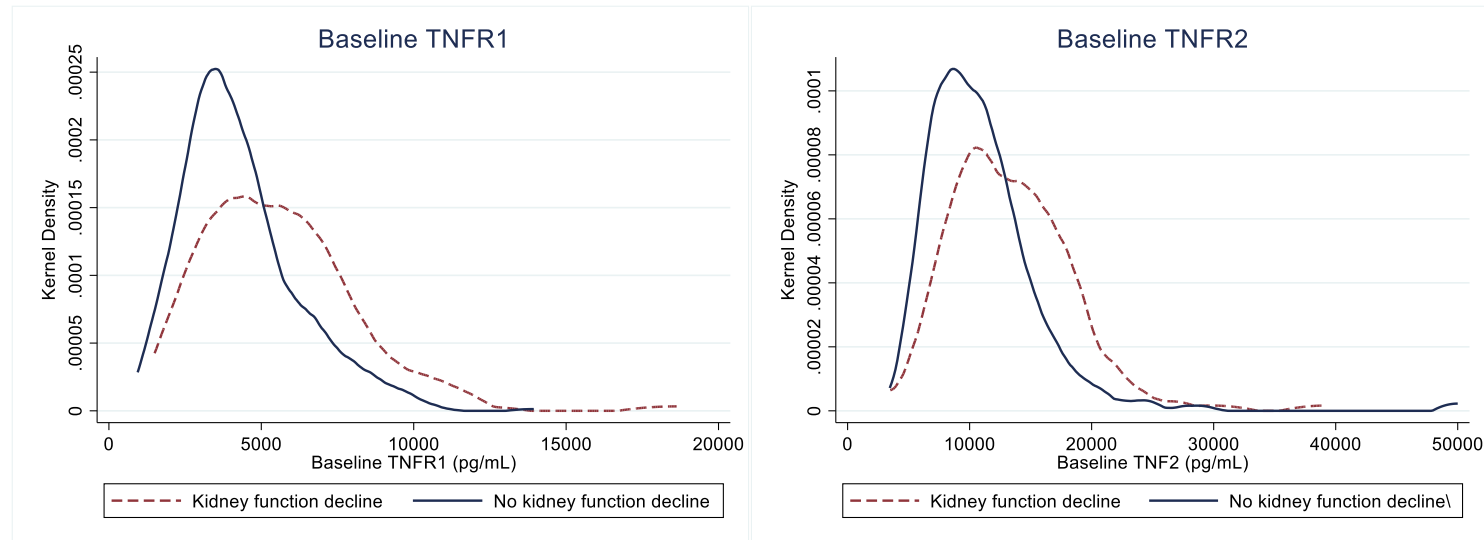
Red denotes negative correlation; green denotes positive correlation; intensity of shading reflects degree of correlation.

Supplemental Figure 3: Distributions of baseline TNFR1 and TNFR2 in AASK and VA NEPHRON-D, by outcome.

a) AASK

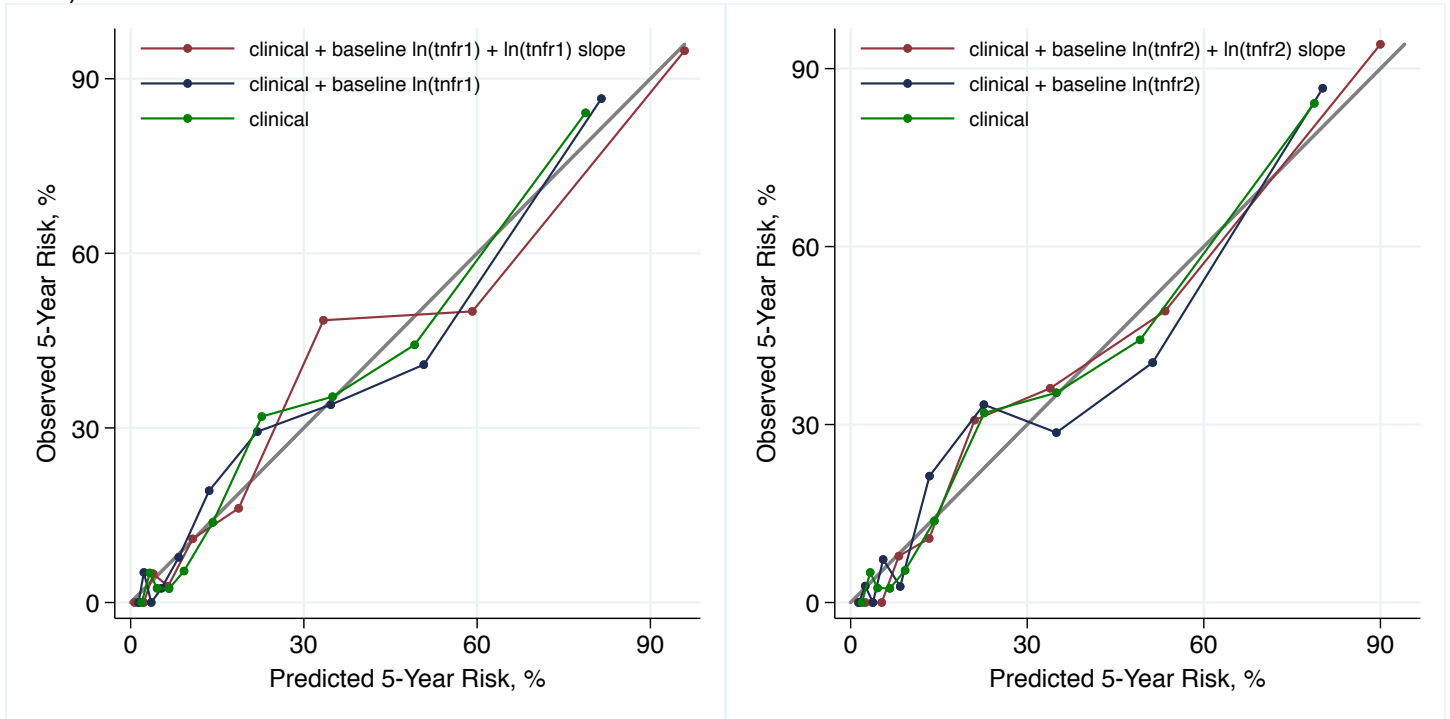


b) VA NEPHRON-D

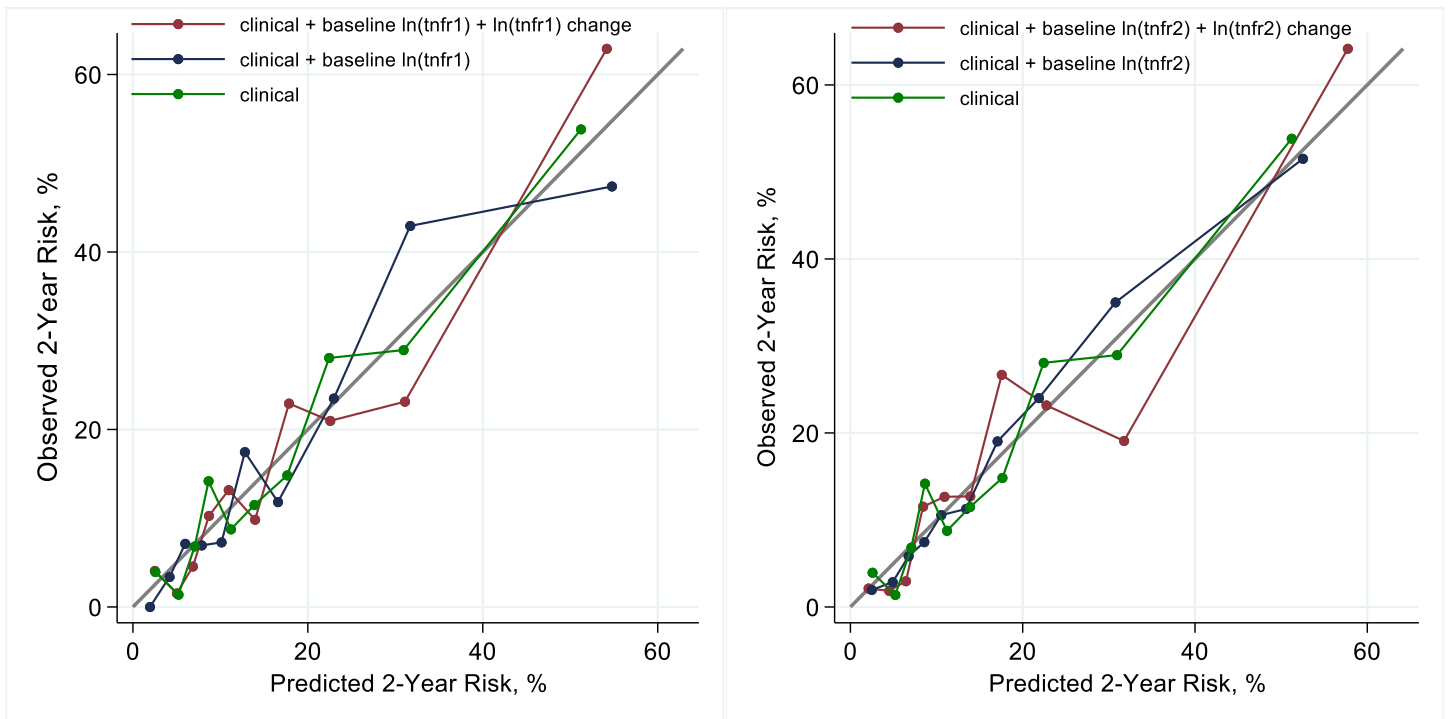


Supplemental Figure 4: Calibration plots of observed vs. predicted 5-year risk for ESKD in AASK and 2-year risk for kidney function decline in VA NEPHRON-D.

a) AASK



b) VA NEPHRON-D



Supplemental Figure 5: Pearson's correlation coefficients of TNFR1 and TNFR2 change with biomarker levels and kidney function measures in VA NEPHRON-D.

TNFR1								
	ln(TNFR1) change	t ₀ ln(TNFR1)	t ₀ eGFR	t ₀ ln(UACR)	t ₁₂ ln(TNFR1)	t ₁₂ eGFR	t ₁₂ ln(UACR)	eGFR change
ln(TNFR1) change	1.00							
t ₀ ln(TNFR1)	-0.35	1.00						
t ₀ eGFR	-0.03	-0.60	1.00					
t ₀ ln(UACR)	0.12	0.31	-0.13	1.00				
t ₁₂ ln(TNFR1)	0.45	0.68	-0.60	0.39	1.00			
t ₁₂ eGFR	-0.16	-0.57	0.82	-0.28	-0.67	1.00		
t ₁₂ ln(UACR)	0.05	0.26	-0.17	0.59	0.29	-0.14	1.00	
eGFR change	-0.25	0.02	-0.22	-0.27	-0.18	0.38	0.03	1.00

TNFR2								
	ln(TNFR2) change	t ₀ ln(TNFR2)	t ₀ eGFR	t ₀ ln(UACR)	t ₁₂ ln(TNFR2)	t ₁₂ eGFR	t ₁₂ ln(UACR)	eGFR change
ln(TNFR2) change	1.00							
t ₀ ln(TNFR2)	-0.15	1.00						
t ₀ eGFR	0.01	-0.57	1.00					
t ₀ ln(UACR)	0.19	0.33	-0.13	1.00				
t ₁₂ ln(TNFR2)	0.45	0.82	-0.50	0.41	1.00			
t ₁₂ eGFR	-0.15	-0.56	0.82	-0.28	-0.60	1.00		
t ₁₂ ln(UACR)	0.05	0.31	-0.17	0.59	0.31	-0.14	1.00	
eGFR change	-0.29	-0.02	-0.22	-0.27	-0.19	0.38	0.03	1.00

Abbreviation: t₀=measurement at 0 months; t₁₂=measurement at 12 months; TNFR1=soluble tumor necrosis factor receptor 1; TNFR2=soluble tumor necrosis factor receptor 2; eGFR=estimated glomerular filtration rate; UACR=urine albumin-to-creatinine ratio.

Red denotes negative correlation; green denotes positive correlation; intensity of shading reflects degree of correlation.

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