PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Early Chronic Kidney Disease Care Program delays kidney function deterioration in patients with Stage I–IIIa chronic kidney disease: An observational cohort study in Taiwan
AUTHORS	Niu, Shu-Fen; Wu, Chung-Kuan; Chuang, Nai-Chen; Yang, Ya-Bei; Chang, Tzu-Hao

VERSION 1 – REVIEW

REVIEWER	Benjamin Bowe Clinical Epidemiology Center, VA St. Louis Health Care System, United States
REVIEW RETURNED	03-Jul-2020

GENERAL COMMENTS	This study by Niu et al looks at the effect of an early CKD care program on the progression of CKD in those with earlier stage CKD in a Taiwanese population. Identification of interventions to slow the progression of CKD is important, and what is optimal may be different for different populations, and so should be appropriately tailored. Overall, I found myself wondering about how the care program had an effect, which I think is important to contributing to the novelty of this study. Below are my comments for the author's consideration. Comments: -The care program was multifaceted in its design on intervening in CKD, including aspects of education, medication management, lifestyle consultation, involvement of family, and routine follow-up, all things known to improve health outcomes. It would be informative to (and I think necessary), as possible, delve into what of these aspects served as the main drivers for differences in progression. For instance, did the lifestyle consultation affect the trajectory of BMI in the case group, and this contributed to the slow of progression? Were those in the case group more commonly prescribed medications for their risk factors like DM or HTN? -Further subgroup analyses by major comorbidities might shed additional light on where the program was effective. Did the program make a difference in those with DM, or HTN, or hyperlipidemia, etc? -Another thing that may be interesting would be to plot out adjusted trajectories of eGFR, and calculate the effect of the program on slope. Comparatively, how much did it slow progression? -The methodology used in adjustment for confounding was not very clear to me until I looked at table one. Maybe clarify in abstract and methods that the models are adjusted by comorbidities.

	-Comparability of the two groups is not clear; sensitivity analyses to enhance confidence in their comparison should be considered. For instance, a negative outcome control might provide some insight (see Lipsitch). The authors also seem to suggest in their discussion that there may be differences in assessment of comorbidity burden, that is there is more measurement error in the control group. Another concern might be that there are differences in the frequency of measurements between the two groups. -Possibility of residual confounding should be further considered. Identification for inclusion in the care program may also have been related to other comorbidities not considered here, degree of severity of comorbidities, prior treatment history, etc. Minor: -The results section is one giant paragraph, gets a bit hard to follow. Sub-sections would help a lot with organization for the reader, and likely help with the flow of the results. -Index date is not explicitly defined. -Matching details are a bit limited. Was a caliper used? Greedy or optimal? -Large amounts of focus (such as in the discussion) on established risk factors didn't really add much for me.

REVIEWER	Harris University of Sydney Australia
REVIEW RETURNED	05-Jul-2020

GENERAL COMMENTS	This is a large observational cohort study examining progression to stage 111b CKD among urban chinese adults with stage 1-111a CKD who voluntarily took part in an Early CKD Care Program (ECKDCP), or received routine care (control). Progression to stage 111b CKD was greater in controls, even though comorbidities were greater at baseline in those taking part ion the ECKDCP. The result was maintained after adjustment for risk variables and propensity matching for age, sex, eGFR and CKD stage. However, the protective effect of the ECKDCP was only seen for baseline CKD stage 111a, and not stages 1-11. As expected, progression was greater for those with diabetes or heart disease, including from stages 1 & 11. Major comments: 1.The strengths of the study include its large size. The major limitations are acknowledged by the authors: lack of generalisability beyond the study population and importantly the likelihood that patients taking part in the voluntary intervention were more motivated and compliant with treatment. 2. However, the outcome requires greater definition. Was it defined by the first eGFR reading <45? Was a single reading of eGFR <45 sufficient? What happened if a subsequent measurement was >45? This is important because the control group many have had fewer measurements of eGFR. Outcome eGFR data should be provided. 3. How do the authors explain the fact that the protective effect was seen early on, and did not increase further with longer follow-up? (Figure 2.) Minor comments: 1. Greater explanation is needed in the headings to tables 2 & 3. 2. page 11/34, ln 52, should be a heading.

	3. Some data in tables are unnecessarily repeated in the text. 4. English requires some minor attention.

VERSION 1 – AUTHOR RESPONSE

Response to the reviewer #1:
Reviewer Name: Benjamin Bowe
Institution and Country: Clinical Epidemiology Center, VA St. Louis Health Care System, United States
Please state any competing interests or state 'None declared': None declared

Question 1:

The care program was multifaceted in its design on intervening in CKD, including aspects of education, medication management, lifestyle consultation, involvement of family, and routine follow-up, all things known to improve health outcomes. It would be informative to (and I think necessary), as possible, delve into what of these aspects served as the main drivers for differences in progression. For instance, did the lifestyle consultation affect the trajectory of BMI in the case group, and this contributed to the slow of progression? Were those in the case group more commonly prescribed medications for their risk factors like DM or HTN?

Response:

Thank you for these constructive suggestions. Unfortunately, we do not have data on body weight and body height in the control group. Therefore, proving the causality of lifestyle consultation, the trajectory of BMI, and the slow progression of CKD is difficult. In response to the second suggestion, we have analyzed the prescribed medications between case and control group, and the results are shown in following Table 1. Prior to matching, the number of patients who received medication for DM was significantly higher in the case group than in the control group (41.6% vs 25.7%, $p < 0.0001$). After matching, the quantity of patients who received medication for DM was still significantly higher in the case group than in the control group (41.6% vs 34.9%, $p = 0.0003$). For patients who received medication for hypertension, the number in the case group was significantly higher than that in the control group (before matching: 84.7% vs 56.0%, $p < 0.0001$; after matching: 84.7% vs 67.6%, $p < 0.0001$).

Table 1. Difference of prescribed medication between case and control group.

	Before matching			After matching		
	Case	Control	p-value	Case	Control	p-value
	N (%)	N (%)		N (%)	N (%)	
Prescribed medication for DM	431 (41.6)	40813 (25.7)	**< 0.0001**	431 (41.6)	724 (34.9)	**0.0003**
Prescribed medication for HTN	878 (84.7)	88736 (56.0)	**< 0.0001**	878 (84.7)	1401 (67.6)	**< 0.0001**

DM, Diabetes Mellitus; HTN, Hypertension

Boldface was showed as significance difference.

Question 2: *Further subgroup analyses by major comorbidities might shed additional light on where the program was effective. Did the program make a difference in those with DM, or HTN, or hyperlipidemia, etc?*

Response:

In response to the reviewer's suggestion, we performed subgroup analyses and listed the results in the following Table 2. Subgroup univariate and multivariate analyses by major comorbidities showed that the case group had a low risk of deteriorating to CKD stage 3b in both univariate and multivariate analysis. Furthermore, the number of cases with hypertension was associated with a significantly low risk in univariate and multivariate analyses (HR = 0.63, 95% CI = 0.47–0.83, *p* = 0.0011; aHR = 0.63, 95% CI = 0.47–0.86, *p* = 0.0031). By contrast, the case group was associated with a significantly low risk for patients without DM (HR = 0.63, 95% CI = 0.50–0.79, p < 0.0001; aHR = 0.56, 95% CI = 0.42–0.75, *p* = 0.0001), gout (HR = 0.73, 95% CI = 0.60–0.89, *p* = 0.0016; aHR = 0.69, 95% CI = 0.55–0.86, *p* = 0.0010), heart diseases (HR = 0.71, 95% CI = 0.57–0.89, *p* = 0.0025; aHR = 0.67, 95% CI = 0.51–0.87, *p* = 0.0031), hyperlipidemia (HR = 0.69, 95% CI = 0.54–0.89, *p* = 0.0041; aHR = 0.66, 95% CI = 0.50–0.89, *p* = 0.0053), and cerebrovascular diseases (HR = 0.71, 95% CI = 0.59–0.85, *p* = 0.0002; aHR = 0.68, 95% CI = 0.55–0.84, *p* = 0.0004).

Table 2. Univariate and multivariate Cox regression analysis of subgroup by major comorbidities.

	Univariate		Multivariate*		Univariate		Multivariate*	
	HR (95%CI)	p value	aHR (95%CI)	p value	HR (95%CI)	p value	aHR (95%CI)	p value
Hypertension	**Without Hypertension**				**With Hypertension**			
Group								
Control	ref		ref		ref		ref	
Case	0.69 (0.47, 1.01)	0.0569	0.73 (0.46, 1.15)	0.1707	0.63 (0.47, 0.83)	**0.0011**	0.63 (0.47, 0.86)	**0.0031**
DM	**Without DM**				**With DM**			
Group								
Control	ref		ref		ref		ref	
Case	0.63 (0.50, 0.79)	**< 0.0001**	0.56 (0.42, 0.75)	**0.0001**	0.70 (0.43, 1.13)	0.1458	0.71 (0.41, 1.23)	0.2219
Gout	**Without Gout**				**With Gout**			
Group								
Control	ref		ref		ref		ref	

Case	0.73 (0.60, 0.89)	**0.0016**	0.69 (0.55, 0.86)	**0.0010**	0.35 (0.09, 1.30)	0.1161	0.06 (0.01, 2.66)	0.1476
Heart diseases	**Without Heart diseases**				**With Heart diseases**			
Group								
Control	ref		ref		ref		ref	
Case	0.71 (0.57, 0.89)	**0.0025**	0.67 (0.51, 0.87)	**0.0031**	0.71 (0.43, 1.16)	0.1665	0.79 (0.42, 1.49)	0.4713
Hyperlipidemia	**Without Hyperlipidemia**				**With Hyperlipidemia**			
Group								
Control	ref		ref		ref		ref	
Case	0.69 (0.54, 0.89)	**0.0041**	0.66 (0.50, 0.89)	**0.0053**	0.74 (0.44, 1.25)	0.2578	0.75 (0.43, 1.30)	0.3076
Cerebrovascular diseases	**Without Cerebrovascular diseases**				**With Cerebrovascular diseases**			
Group								
Control	ref		ref		ref		ref	
Case	0.71 (0.59, 0.85)	**0.0002**	0.68 (0.55, 0.84)	**0.0004**	0.44 (0.14, 1.40)	0.1623	0.08 (0.01, 1.36)	0.0800

DM, Diabetes Mellitus; aHR, adjusted Hazard ratio.

*Multivariable model was adjusted by all variables.

Boldface was showed as significance difference.

Question 3:

Another thing that may be interesting would be to plot out adjusted trajectories of eGFR, and calculate the effect of the program on slope. Comparatively, how much did it slow progression?

Response:

In response to the reviewer's suggestion, we plotted the distribution of eGFR over time in our study, and listed the results in the following Table 3. eGFR was significantly lower in the case group than in the control group during study period on 1 year (63.3 ± 17.9 vs 67.0 ± 26.0, $p = 0.0122$). At 2–5 years, the eGFR in the case group was higher than that in the control group, but no significant difference was found.

Table 3. Distribution of eGFR by case and control during follow-up time

	eGFR				
	Control (n = 2076)		Case (n = 1038)		p-value
	N	Mean ± SD	N	Mean ± SD	
Follow-up time					
Baseline	2076	62.2 ± 13.3	1038	62.2 ± 12.9	0.8842
1 year	479	67.0 ± 26.0	398	63.3 ± 17.9	**0.0122**
2 years	385	65.4 ± 24.5	239	65.5 ± 19.6	0.9406
3 years	301	63.0 ± 24.1	143	66.5 ± 19.3	0.0970
5 years	181	56.7 ± 20.9	17	59.1 ± 13.9	0.6338

Question 4:

The methodology used in adjustment for confounding was not very clear to me until I looked at table one. Maybe clarify in abstract and methods that the models are adjusted by comorbidities.

Response:

As per the reviewer's suggestion, we revised the abstract and methods as follows: In the abstract section, we have revised the sentence (Page 2, Lines 10 to 12) as "The models were adjusted by age, sex, estimated glomerular filtration rate, and CKD stage with 1:2 propensity score to reduce bias between two groups." In the method section, we have revised the sentence (Page 8, Lines 15 to 17) as "The models were adjusted by age, sex, estimated glomerular filtration rate, and CKD stage with 1:2 propensity score to reduce bias between the case group and the control group."

Question 5:

Comparability of the two groups is not clear; sensitivity analyses to enhance confidence in their comparison should be considered. For instance, a negative outcome control might provide some insight (see Lipsitch). The authors also seem to suggest in their discussion that there may be differences in assessment of comorbidity burden, that is there is more measurement error in the control group. Another concern might be that there are differences in the frequency of measurements between the two groups.

Response:

In response to the reviewer's suggestion, we established cause-specific Cox models and included all candidate variables to determine the risk factors for patients developing CKD stage 3b. In the Cox model observations, failures from other causes (death or loss to follow-up respectively in this study) are defined as censor and observations with CKD stage 3b was defined as event.

The outcome of the cause-specific Cox models is summarized in the following Table 4. Univariate and multivariate analyses revealed that the case group was associated with a low risk of deteriorating to CKD stage 3b (hazard ratio [HR] = 0.75, 95% confidence interval [CI] = 0.64–0.89, p = 0.0010; adjusted HR [aHR] = 0.67, 95% CI = 0.55–0.82, p < 0.0001). However, DM (HR = 1.36, 95% CI = 1.12–1.67, p = 0.0024; aHR = 1.64, 95% CI = 1.16–2.31, p = 0.0051), heart diseases (HR = 1.33, 95% CI =

1.08–1.64, *p* = 0.0085; aHR = 1.57, 95% CI = 1.10–2.23, *p* = 0.0129), and cerebrovascular disease (HR = 1.33, 95% CI = 1.01–1.77, *p* = 0.0448; aHR = 1.45, 95% CI = 1.01–2.10, *p* = 0.0455) were the risk factors for deteriorating to CKD stage 3b.

Table 4. Univariate and multivariate cause specific cox model of all population (n = 3,114).

	Univariate		Multivariate*	
	HR (95%CI)	p value	aHR (95%CI)	p value
Group				
Control	ref		ref	
Case	0.75 (0.64, 0.89)	**0.0010**	0.67 (0.55, 0.82)	**< 0.0001**
Comorbidity number				
0	ref		ref	
1	1.08 (0.82, 1.41)	0.5921	0.91 (0.61, 1.36)	0.6479
2	1.06 (0.82, 1.38)	0.6587	0.68 (0.35, 1.30)	0.2390
3+	1.31 (1.03, 1.66)	**0.0290**	0.59 (0.21, 1.62)	0.3041
Hypertension				
No	ref		ref	
Yes	1.05 (0.87, 1.25)	0.6235	1.17 (0.79, 1.73)	0.4350
DM				
No	ref		ref	
Yes	1.36 (1.12, 1.67)	**0.0024**	1.64 (1.16, 2.31)	**0.0051**
Gout				
No	ref		ref	
Yes	0.91 (0.70, 1.18)	0.4760	1.20 (0.83, 1.73)	0.3246
Heart diseases				
No	ref		ref	
Yes	1.33 (1.08, 1.64)	**0.0085**	1.57 (1.10, 2.23)	**0.0129**
Hyperlipidemia				
No	ref		ref	
Yes	1.08 (0.89, 1.32)	0.4275	1.30 (0.90, 1.88)	0.1649

Cerebrovascular diseases				
No	ref		ref	
Yes	1.33 (1.01, 1.77)	**0.0448**	1.45 (1.01, 2.10)	**0.0455**

DM, Diabetes Mellitus; aHR, adjusted Hazard ratio.

*Multivariable model was adjusted by all variables.

Boldface was showed as significance difference.

Question 6:

Possibility of residual confounding should be further considered. Identification for inclusion in the care program may also have been related to other comorbidities not considered here, degree of severity of comorbidities, prior treatment history, etc.

Response:

We agree with the reviewer that some residual confounding factors should also be considered. Although we did not match the degree of severity of comorbidities and prior treatment history to reduce bias, the case group with severe comorbidities and prior treatment had better outcome than the control group. This result can explain that the Early Chronic Kidney Disease Care Program can delay that deterioration of renal function.

Minor:

Question 7:

The results section is one giant paragraph, gets a bit hard to follow. Sub-sections would help a lot with organization for the reader, and likely help with the flow of the results.

Response:

We thank the reviewer for this suggestion and added subsection title “Association of Early CKD Care Program and risk factors between CKD stage I-II and CKD stage IIIa with Early CKD Progression” in Page 11, Lines 13-14.

Question 8:

Index date is not explicitly defined.

Response:

We thank the reviewer for allowing us to further explain. We recruited adult nonpregnant patients with CKD stage I–IIIa, and had more than two medical return visits from Taipei Medical University Research Database (TMURD) between January 1, 2012 and August 31, 2017. Therefore, the index date of the patients in our study is between January 1, 2012 and August 31, 2017.

Question 9:

Matching details are a bit limited. Was a caliper used? Greedy or optimal?

Response:

A total of 159,774 patients with stage I–IIIa CKD, including 1,038 in the case group and 158,736 in the control group, were enrolled from the participating hospitals. We conducted 1:2 propensity score matching with age, sex, estimated glomerular filtration rate, and CKD stage to reduce selection bias in the control group. Considering that the number of participants in the case group was substantially smaller than that in the control group, we chose a greedy and nearest neighbor matching for propensity score matching algorithm. After matching, 1,038 cases and 2,076 controls remained.

Question 10:

Large amounts of focus (such as in the discussion) on established risk factors didn't really add much for me.

Response:

We thank the reviewer for this suggestion and simplified the discussion on established risk factors (Page 13, Line 19 to Page 14, Line 19).

Response to the reviewer #2:
Reviewer Name: Harris
Institution and Country: University of Sydney, Australia
Please state any competing interests or state 'None declared': none declared

Question 1:

The strengths of the study include its large size. The major limitations are acknowledged by the authors: lack of generalisability beyond the study population and importantly the likelihood that patients taking part in the voluntary intervention were more motivated and compliant with treatment.

Response:

We thank the reviewer for summarizing the major limitations of our study. We discussed these limitations in our paper.

Question 2:

However, the outcome requires greater definition. Was it defined by the first eGFR reading <45? Was a single reading of eGFR <45 sufficient? What happened if a subsequent measurement was >45? This is important because the control group many have had fewer measurements of eGFR. Outcome eGFR data should be provided.

Response:

We thank the reviewer for pointing out this important issue. The outcome of progression of CKD stage I-IIIa to CKD stage IIIb is defined as the level of eGFR decline to the range between 30 and 45. We were unable to consider reversible acute kidney injury. Therefore, we added the following sentence "Fourth, the study did not take reversible acute kidney injury into account." (Page 16, Lines 16-17) into

the limitation of our study. We provided the distribution of eGFR by case and control during follow-up time as the following Table.

Table. Distribution of eGFR by case and control during follow-up time

	eGFR				
	Control (n = 2076)		Case (n = 1038)		p-value
	N	Mean ± SD	N	Mean ± SD	
Follow-up time					
Baseline	2076	62.2 ± 13.3	1038	62.2 ± 12.9	0.8842
1 year	479	67.0 ± 26.0	398	63.3 ± 17.9	**0.0122**
2 years	385	65.4 ± 24.5	239	65.5 ± 19.6	0.9406
3 years	301	63.0 ± 24.1	143	66.5 ± 19.3	0.0970
5 years	181	56.7 ± 20.9	17	59.1 ± 13.9	0.6338

Question 3:

How do the authors explain the fact that the protective effect was seen early on, and did not increase further with longer follow-up? (Figure 2)

Response:

We thank the reviewer for pointing out this important issue and allowing us to further explain. Cumulative incidence rate of CKD stage IIIb among the control and case groups at 1-, 3-, and 5-year periods are 0.18, 0.27, and 0.31, respectively, and 0.13, 0.21, and 0.23, respectively, as shown in Figure 2. The protective effect of Early Chronic Kidney Disease Care Program was sustained during the follow-up period, and the difference of cumulative incidence rate between two groups still increased. However, the slope decreasing over time may be attributed to the fact that patients who overcome the decline of eGFR to less than 45 more than 1 year had good compliance or few comorbidities.

Minor comments:

Question 4:

Greater explanation is needed in the headings to tables 2 & 3.

Response:

We thank the reviewer for this suggestion and revised the headings in Tables 2 and 3. The heading of Table 2 is " Univariate and multivariate Cox regression analysis for the risk of CKD I-IIIa progression to CKD IIIb among the Early Chronic Kidney Disease Care Program and other risk factors" and that of Table 3 is "Univariate and multivariate Cox regression analysis for the risk of baseline stage < 3a progression to stage 3b and stage 3a progression to stage 3b among the Early Chronic Kidney Disease Care Program and other risk factors."

Question 5:

page 11/34, ln 52, should be a heading.

Response:

In response to this suggestion, we added the heading “Association of Early CKD Care Program and risk factors between CKD stage I-II and CKD stage IIIa with Early CKD Progression.”

Question 6:

Some data in tables are unnecessarily repeated in the text.

Response:

We deleted unnecessarily repeated data in the results.

Question 7:

English requires some minor attention.

Response:

The revised manuscript has been edited by a professional English editing service and the certificate of this English editing service has been uploaded along with the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Benjamin Bowe VA St. Louis Health Care System
REVIEW RETURNED	14-Oct-2020

GENERAL COMMENTS	The authors have done much work to conduct several additional analyses, and I believe they shed some additional light on what is going on with the study. I have a few minor comments. -If the authors did not consider the additional information gained something to include in the manuscript, they could consider suggesting that future research is needed in understanding in what participants the interventions was effective, and which aspects of the intervention were effective. -It is a bit interesting that the trajectory of average eGFR mostly increases in the case group (actually in the control group too); not typical to see improvement in eGFR given known average age related declines (independent of disease). Adjusted eGFR would be a step towards a clearer picture. Selection bias may occur for a large number of reasons, including differential rates of death, and cause-specific models make their own set assumptions which do not necessarily resolve competing risk issues. If analyses to reduce concerns of selection are not available, I think the discussion in the limitations needs to be expanded here, and also

	in residual confounding; focusing on “motivation” does not recognize the many other potential explanations for why the results appeared as they did. -Thank you for clarifying the variables included in the PS matching. Would suggest “matched by” instead of “adjusted by.” You may want to consider adding the small bit of additional detail about how the matching was done. Also, the multivariable models were, beyond the matching, additionally adjusted for diabetes, hypertension, etc., correct? Please detail this in the methods. -I would suggest univariable and multivariable, or unadjusted and adjusted. Multivariate statistically implies modeling multiple outcomes simultaneously, so I believe the other terms may be more appropriate.

REVIEWER	David Harris AUSTRALIA, SYDNEY UNIVERSITY
REVIEW RETURNED	26-Oct-2020

GENERAL COMMENTS	Here is my review. 1. There are long explanations and several tables in the response to reviewers, but from the track changes relatively minor changes in the new manuscript. (I have relied on the tracked changes to compare the original and revised manuscript.) Most of these changes have English errors, despite the authors having employed a professional English editing service. It is not easy to see where repeated data have been deleted (my question #6). 2. I'll leave it to the first reviewer to comment on the responses to his criticisms of the original manuscript. However, I don't think the long paragraph added into the Discussion is particularly useful. 3. My question #2 hasn't been answered satisfactorily. Small changes in eGFR, reflecting the (in)accuracy of the estimate rather than an episode of AKI, may result in a change in CKD stage if they occur around the estimate of the eGFR that defines a stage transition. Outcome eGFR data should be presented in the revised manuscript, not just the response to reviewer. 4. The response to my question #3 could occur briefly in the text.

VERSION 2 – AUTHOR RESPONSE

Response to the reviewer #1:
Question 1:
-If the authors did not consider the additional information gained something to include in the manuscript, they could consider suggesting that future research is needed in understanding in what participants the interventions was effective, and which aspects of the intervention were effective.
Response:
We thank the reviewer for this suggestion. We have added the sentence “More research is needed to understand what type of participants in the Early Chronic Kidney Disease Care Program and which aspects of the Program yield the more effective results.” in page 17, line 19 to page 18, lines 1-2.

Question 2:
-It is a bit interesting that the trajectory of average eGFR mostly increases in the case group (actually

in the control group too); not typical to see improvement in eGFR given known average age-related declines (independent of disease). Adjusted eGFR would be a step towards a clearer picture. Selection bias may occur for a large number of reasons, including differential rates of death, and cause-specific models make their own set assumptions which do not necessarily resolve competing risk issues. If analyses to reduce concerns of selection are not available, I think the discussion in the limitations needs to be expanded here, and also in residual confounding; focusing on "motivation" does not recognize the many other potential explanations for why the results appeared as they did.
Response:
Unfortunately, our data could not accurately reveal average age-related eGFR declines between the control and case groups in Table S2, especially at 1-year follow-up, because a large number of baseline patients enrolled in this study had no available eGFR data or were lost to follow-up at the 1-year mark. Thus, we could only calculate age-related eGFR declines by using the eGFR data of the remaining participants. According to the reviewer's suggestion, we have modified the sentence "Second, participation in the care program was voluntary; therefore, patients' motivation and the encouragement of medical personnel possibly played a role, and thus, selection bias should be considered." into "Second, our study cannot completely eliminate concerns related to selection bias because this phenomenon may be attributed to multiple reasons, including differential rates of death, and cause-specific models could feature assumptions that do not necessarily resolve competing risk issues." in page 17, lines 6-10.
Table S2. Distribution of eGFR amongst cases and controls during the follow-up period

eGFR					
	Control (n = 2076)		Case (n = 1038)		p-value
	N	Mean ± SD	N	Mean ± SD	
Follow-up time					
Baseline	2076	62.2 ± 13.3	1038	62.2 ± 12.9	0.8842
1 year	479	67.0 ± 26.0	398	63.3 ± 17.9	0.0122
2 years	385	65.4 ± 24.5	239	65.5 ± 19.6	0.9406
3 years	301	63.0 ± 24.1	143	66.5 ± 19.3	0.0970
5 years	181	56.7 ± 20.9	17	59.1 ± 13.9	0.6338

Question 3:
Thank you for clarifying the variables included in the PS matching. Would suggest "matched by" instead of "adjusted by." You may want to consider adding the small bit of additional detail about how the matching was done. Also, the multivariable models were, beyond the matching, additionally adjusted for diabetes, hypertension, etc., correct? Please detail this in the methods.
Response:
We thank the reviewer for these suggestions. We have changed the phrase 'adjusted by' to 'matched by' (page 2, line 9 and page 8, line 15). We have also added the details of the procedures for propensity score matching and multivariable models in the Methods section of our manuscript (page 8, line 17 to page 9, line 1 and page 9, lines 6-9).

Question 4:
I would suggest univariable and multivariable, or unadjusted and adjusted. Multivariate statistically implies modeling multiple outcomes simultaneously, so I believe the other terms may be more appropriate.
Response:
We appreciate the reviewer's recommendations. We have changed the terms 'univariate' and 'multivariate' to 'univariable' and 'multivariable' (page 27-28).

Response to the reviewer #2:
Question 1:
There are long explanations and several tables in the response to reviewers, but from the track

changes relatively minor changes in the new manuscript. (I have relied on the tracked changes to compare the original and revised manuscript.) Most of these changes have English errors, despite the authors having employed a professional English editing service. It is not easy to see where repeated data have been deleted (my question #6).
Response:
We thank the reviewer for this suggestion. We have deleted the redundant data and relabeled the track changes to improve the clarify of the revised manuscript. We have also corrected language issues in the manuscript.

Question 2:
I'll leave it to the first reviewer to comment on the responses to his criticisms of the original manuscript. However, I don't think the long paragraph added into the Discussion is particularly useful.
Response:
We appreciate the reviewer' s helpful suggestion. We have modified some sentences in the Discussion section of the revised manuscript to reduce the length of the paragraphs.

Question 3:
My question #2 hasn't been answered satisfactorily. Small changes in eGFR, reflecting the (in)accuracy of the estimate rather than an episode of AKI, may result in a change in CKD stage if they occur around the estimate of the eGFR that defines a stage transition. Outcome eGFR data should be presented in the revised manuscript, not just the response to reviewer.
Response:
We thank the reviewer for allowing us to elaborate on this important issue. The outcome of the progression of CKD stage I-IIIa to stage IIIb is defined as the level of eGFR decline to the range of 30-45 at first time. A change in eGFR may result in a change in CKD stage. Therefore, we calculated the number of patients with stage reversal relative to the total number of cases and controls during the follow-up period; the corresponding results are shown in the following table. We found that the total number of patients showing stage reversal is less than 6% of the total number of cases and controls at all timepoints considered. We will add the table "Distribution of eGFR amongst cases and controls during the follow-up period" to the supplementary materials.
Table. Distribution of stage reversal compared with the total number of cases and controls during the follow-up period

	Control (n = 2076)	Case (n = 1038)
	N of reverse/N (%)	N of reverse/N (%)
Follow-up time		
Baseline	-	-
1 year	12/479 (2.5)	11/398 (2.8)
2 years	9/385 (2.3)	7/239 (2.9)
3 years	5/301 (1.7)	4/143 (2.8)
5 years	3/181 (1.7)	1/17 (5.9)

Question 4:
The response to my question #3 could occur briefly in the text.
Response:
We thank the reviewer for the suggestion. We have added part of our response to the reviewer's question #3 to the Discussion section of our revised manuscript as follows: "Figure 2 illustrates that the protective effect of the Early Chronic Kidney Disease Care Program was sustained over the follow-up period, although the difference in cumulative incidence rate between the two groups gradually increased. The decrease of the slope over time may be attributed to the fact that patients who overcame the decline of their eGFR to less than 45 for over 1 year had good compliance or few comorbidities." This addition was made in pages 16, lines 7-12