Author's response to reviews

Title: Risk factors and their interaction on chronic kidney disease: A multi-centre case control study in Taiwan

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Author's response to reviews: see over
Response to reviewer comments

Revised Title: Risk factors and their interaction on chronic kidney disease: A multi-centre case control study in Taiwan.


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Dear Sir,

Thank you for giving us an opportunity to respond to the reviewers’ comments. The responses to the points raised by reviewers are indicated below. We have made appropriate changes to the manuscript as indicated.
Editorial Request:

Comments to the Author

1. Copyediting - We recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/authors/authorfaq/editing.

Response

We had used the BioMed Central-recommended language editing company, Edanz, to review and edit our manuscript.

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Part 2:

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Sincerely,

Megumi Hara (Ms)

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4 個附件
Reviewer 1:

Comments to the Author

1. The spelling issue seemed to persist. In the abstract, abbreviations “CKD”, “ESRD”, “OR”, and “CI” were not spelled in full at first mention. Also, redundant sentences also needed polishing. Ex. page 6, line 7, “Previous studies also…”, but in line 10, again “Previous studies had shown…”. Similarly, in page 5, line 11, “systematic evidence that has confirmed that a screening…”. In page 6, line 11, “that the effects of some factors…that means that some risk factors…” Page 6, line 13, “it might be change our clinical…”, and more in discussion section.

Response
Thank you for pointing this out. We re-edited our manuscript and highlight the full spelled name at first mention whether in abstract or this article.

Page 3 Lines 52-54 (Abstract)
Chronic kidney disease (CKD) is highly prevalent in Taiwan. More than two-thirds of end-stage renal disease is associated with diabetes mellitus (DM) or hypertension (HTN).

Page 3 Lines 67-69 (Abstract)
Patients with anaemia had a higher risk when associated with HTN [odds ratio (OR) = 6.75, 95% confidence limit (95% CI) 4.76–9.68] but had a smaller effect in people without HTN (OR 2.83, 95% CI 2.16–3.67).

Page 5 Lines 84-85 (Article)
Chronic kidney disease (CKD) is an important public health issue because these patients have an increased risk of end-stage renal disease (ESRD).

Page 5 Lines 88-91 (Article)
A previous study has shown that screening people with hypertension (HTN), diabetes mellitus (DM) or age >55 years is the most effective strategy to detect patients with CKD [5].

2. The introduction section should display manuscript flow like the following: CKD as a public health threat DM, HTN, and other traditional factors as historical focuses inconsistency in results or heterogeneity exists focusing on
**Response**

Thank you for your variable comment. We had re-written the introduction as following.

**Page 5 Line 84-Page 6 Line 121**

Chronic kidney disease (CKD) is an important public health issue because these patients have an increased risk of end-stage renal disease (ESRD). Taiwan has a high prevalence of CKD [1] and ESRD [2]. These patients are at increased risk for cardiovascular events and progression to kidney failure [3]. The benefits of screening at-risk populations and estimating progression of CKD are well established [4]. A previous study has shown that screening people with hypertension (HTN), diabetes mellitus (DM) or age >55 years is the most effective strategy to detect patients with CKD [5]. Therefore, planning a specific population screening/prevention strategy for people with HTN or DM is a major public health challenge. To our knowledge, there is no systematic evidence at present to confirm that a screening/prevention strategy for the general population would apply to high risk groups.

CKD is a complex disease that has complex aetiologies, but the effects of these factors are mild. The traditional factors that have an effect on CKD are primarily divided into three parts: demographic characteristics (gender [6], age [7], obesity [8] and social economic [9]), comorbidity [hepatitis B (HB) [10], hepatitis C (HC) [11], hyperuricemia [7], anaemia [12] and hyperlipidaemia [7]) and lifestyles (smoking status [13], alcohol intake [14], betel nut chewing [15], exercise habits [16, 17] and groundwater use [18]). Foregoing factors have been extensively investigated and some studies have investigated their effects in populations. However, these reported effects are inconsistent in different populations. For example, obesity had a significant effect in the general population [8] but not in patients with DM [19]. This suggests that the effects of obesity on CKD may be associated with DM. In addition, several studies have investigated the interaction between some of these factors and HTN/DM on CKD. Other studies have reported an interaction between HTN and smoking [20] and between DM and...
hyperuricemia [21] on renal outcomes. As a result of these various reports, we suspected that the effect of each factor on CKD may be different in healthy populations and in patients with DM/HTN.

Studies have shown evidence that the effects of some factors on CKD may depend on the presence of DM or HTN, which means that some risk factors may or may not be important in patients with HTN/CKD. This information may be important for clinical decision making for CKD patients with HTN/CKD. However, to our knowledge, no study has systematically investigated the potential factors which may have a DM- or HTN-dependent effect on CKD. Therefore, the aim of this study was to investigate different targets for screening/prevention strategies between healthy people and patients with HTN or DM that may aid in planning most effective prevention strategies for patients with DM and HTN.

3. Following the 2nd comment, I suggest the authors re-write the discussion section in a softer tone and try to avoid descriptions regarding the choice of targets for CKD prevention. This study essentially investigated the heterogeneity of CKD associations between different factors (based on the study results), but not prevention or intervention strategies (the latter issue need medical economical analyses, not just risk estimation among subgroups).

Response
Thank you for your variable comment. We had re-written the discussion as following.

Discussion
The results of this study found that male, ageing, low income, hyperuricemia and lack of exercise habits were risk factors for CKD. The effects of anaemia and hyperlipidaemia on CKD in patients with or without HTN were different. We also found that HB, HC, smoking, alcohol intake, betel nut chewing and groundwater use may not be associated with CKD. Among males, ageing and lack of exercise habits were the traditional risk factors for CKD [6, 7, 16, 17]. In our study, we also observed a significant association between these risk factors and CKD, and we did not find high heterogeneity among the four groups. The discussion that follows divides the associations between other variables and
CKD into three parts: socioeconomic status-related factors, possible reasons for the high prevalence of ESRD in Taiwan and the interactive effects between anaemia/hyperlipidaemia and HTN on CKD.

Low income was an important predictive factor for CKD, and it was characteristic of people with a low socioeconomic status. Socioeconomic status may be related to many risk factors, such as second-hand tobacco smoke [30] and unhealthy diets [31]. In this study, we investigated some socioeconomic status-related factors (smoking status [32], alcohol intake [33], betel nut chewing [34] and groundwater use [18]), and we found that the association between smoking status/groundwater use and CKD may be related to income level. Their effects were significant before the adjustment of income but not after this adjustment.

The ORs of alcohol intake and betel nut chewing in the univariate and multivariate analyses also presented a similar phenomenon. Previous studies that had investigated the above factors did not adjust for socioeconomic status. Thus, they may have overrated their risk on CKD [14, 15, 18]. Based on the power of this study, further research is needed concerning the association between betel nut chewing and CKD. With smoking status, alcohol intake and groundwater use, these may have a smaller impact on CKD. Intervention for these small impact factors may not be effective, and therefore, we determined that smoking status, alcohol intake and betel nut chewing were not the best targets for CKD prevention.

The prevalence of HB [35] and HC [36] in Taiwan is higher than in most other countries, and Taiwan has the highest prevalence and third highest incidence of ESRD in the world [2]. Previous studies have reported the association between HC and CKD [11], so we suspected that the high prevalence of hepatitis might be the main reason for the high prevalence of ESRD. However, our study showed the nonsignificance of these factors. Therefore, we determined that HB and HC were not the main reason for the high prevalence and incidence of ESRD in Taiwan, but the power of HC may be insufficient and needs further research.

People with hyperuricemia have a higher risk of ESRD than those without it, and the association was found to be very high in this study. Despite the lack of detailed statistics worldwide, we believe that the prevalence of hyperuricemia in Taiwan may be higher than in many other countries [37, 38], and this may also
play a key role in ESRD in Taiwan. However, our study might have overrated the risk of hyperuricemia in CKD. Previous studies presented a significant association between hyperuricemia and CKD, but the relative risks in these studies were <2 [7, 21]. Therefore, we determined that hyperuricemia might be associated with CKD, but the effect of intervention for hyperuricemia-related factors on CKD might not be very effective.

Anaemia is a likely complication in patients with CKD, but this is not a cause [39]. Therefore, it is not a good target for the prevention of CKD. However, this study was not only concerned with prevention strategies but also with screening strategies for CKD. Previous studies have demonstrated that awareness of CKD in patients is very low [40, 41]. Therefore, physicians might have to help them with monitoring the CKD. This study showed a strong association between anaemia and CKD in patients with HTN but not in the general population. This result helps to better pinpoint CKD high risk groups. Patients with both anaemia and HTN are a newly discovered high risk group for CKD, and physicians in outpatient clinics need to recognise that patients with anaemia accompanied with HTN might be latent CKD cases.

The risk effect of hyperlipidaemia on CKD was only found to be in the general population, but not in patients with HTN as reported in an earlier study [7]. Male subjects had a higher prevalence of HTN than females, and the hazard ratio of hyperlipidaemia on CKD in males was lower than in females [7]. Obesity was a hyperlipidaemia-related factor, and the risk effects of obesity presented similar results (Appendix Table 1 and Appendix Table 2). Although the results were not significant, we still found that the ORs in patients with HTN were lower than those in people without HTN. In addition, the heterogeneity of obesity was 39.0% in the multivariate analysis, which implies that HTN might be a moderate factor in the association between obesity-related factors and CKD. It has been reported that renal lipid accumulation is nephrotoxic and could play a role in CKD [42], but we are unable to explain why the association between hyperlipidaemia and CKD in patients with HTN has a negative impact. Further research is required to understand the basic mechanism.

This study has two limitations. First, a cross-sectional study is not the way to distinguish whether correlations were causative or not, and time relationships were not confirmed in this study. Most of our discussion has focused on this issue, and we surmised that associations between some factors and CKD might
not be causative. Although these may not help prevent CKD, they are useful for planning a screening strategy. Low awareness of CKD is an important issue, and a good outpatient screening strategy is urgently needed. Second, the risk factors assessment was based on a structured questionnaire rather than on the laboratory data. This may have caused some misclassification. However, Taiwan has good medical accessibility and most people can easily obtain medical resources and understand their disease status. In addition, our interviewers were highly trained, and we regularly held meetings for feedback from the interviewers. This ensured the quality of our research and reduced the possibility of misclassification.

Conclusions
Gender, age, income, hyperuricemia, anaemia, hyperlipidaemia and exercise habits were good targets for planning a screening/prevention strategy for CKD in healthy populations and in patients with DM. In addition, the important evidence from this study confirmed that HB, smoking status, alcohol intake and groundwater use were not good targets for CKD prevention. They were not associated with CKD or only had a low impact on the condition. We believe that intervention for related factors might not be an efficient method based on the strong statistical power in this study. The associations between HC/betel nut chewing and CKD require further research because they were underpowered in this study. Finally, this study suggested that a specific CKD screening/prevention strategy for patients with DM might not be efficient without laboratory data analyses, and the strategy for the general population could be used in patients with DM. Furthermore, we determined that a screening/prevention strategy for CKD in patients with HTN might differ from that of a healthy population. Hyperlipidaemia-related factors might not be a good target for patients with HTN, and physicians need to recognise that patients with HTN in anaemia outpatient clinics might be potential CKD patients. In addition, there is a need for better care in patients with anaemia and HTN and timely intervention is required when there are signs of deterioration.

4. In Table 3, please consider to remove the description “…(X is ref.)” following every variable. Other better wordings for this statistical issue are available.

Response
Thank you for your variable comment. We had changed the wording in Table 3
and supplementary file to “$X_1$ versus $X_2$” as following.
TABLE 3: Pooled data showing effect of each risk factor on CKD and heterogeneity between the four groups§.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariable analyses</th>
<th>Multivariable analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>I^2</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Gender (Male versus Female)</td>
<td>1.65 (1.49 to 1.82)*</td>
<td>25.5%</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.19 (1.09 to 1.29)*</td>
<td>85.7%*</td>
</tr>
<tr>
<td>Obesity (Abnormal versus Normal)</td>
<td>1.14 (0.93 to 1.40)</td>
<td>43.9%</td>
</tr>
<tr>
<td>Income (Median versus Low)</td>
<td>0.57 (0.45 to 0.72)*</td>
<td>80.8%*</td>
</tr>
<tr>
<td>Obesity (High versus Low)</td>
<td>0.50 (0.38 to 0.67)*</td>
<td>82.3%*</td>
</tr>
<tr>
<td>HB (Abnormal versus Normal)</td>
<td>1.08 (0.88 to 1.33)</td>
<td>21.6%</td>
</tr>
<tr>
<td>HC (Abnormal versus Normal)</td>
<td>1.29 (0.93 to 1.79)</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hyperuricaemia (Abnormal versus Normal)</td>
<td>4.56 (3.96 to 5.26)*</td>
<td>0.0%</td>
</tr>
<tr>
<td>Anaemia (Abnormal versus Normal)</td>
<td>4.89 (2.76 to 8.66)*</td>
<td>88.5%*</td>
</tr>
<tr>
<td>Hyperlipidaemia (Abnormal versus Normal)</td>
<td>1.48 (1.17 to 1.88)*</td>
<td>80.5%*</td>
</tr>
<tr>
<td>Smoking status (Abnormal versus Normal)</td>
<td>1.45 (1.28 to 1.64)*</td>
<td>26.6%</td>
</tr>
<tr>
<td>Alcohol intake (Abnormal versus Normal)</td>
<td>1.15 (1.00 to 1.33)</td>
<td>22.3%</td>
</tr>
<tr>
<td>Betel nut chewing (Abnormal versus Normal)</td>
<td>1.35 (1.03 to 1.77)</td>
<td>29.0%</td>
</tr>
<tr>
<td>Exercise habits (Abnormal versus Normal)</td>
<td>0.74 (0.65 to 0.85)*</td>
<td>50.9%</td>
</tr>
<tr>
<td>Groundwater using (Abnormal versus Normal)</td>
<td>1.44 (1.13 to 1.83)</td>
<td>24.1%</td>
</tr>
</tbody>
</table>

§: The four groups were Group I (participants without DM and HTN), Group II (participants with HTN without DM), Group III (participants with DM without HTN) and Group IV (participants with DM and HTN).

HB: hepatitis B; HC: hepatitis C.

OR: pooled odds ratio for variation groups compared with reference groups on CKD; 95% CI: 95% confidence interval of OR.

I^2: heterogeneity between four groups in each variable; Q test: the significant test of I^2 using Cochrane Q test.

Boldface & *: significance after Bonferroni adjustment: p value < 0.05/14 = 0.0036.

£: The pooled results were unreliable because the difference between coefficients in four group were significant. Please refer to the results of stratified analyses in Supplementary File (univariable analyses: Appendix Table 1; multivariable analyses: Appendix Table 2).
### TABLE S1. Effect of risk factors on CKD by hierarchical generalized linear models.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (Male versus Female)</strong></td>
<td>1.83 (1.60 to 2.11)*</td>
<td>1.62 (1.41 to 1.87)*</td>
<td>1.51 (1.15 to 1.97)*</td>
<td>1.50 (1.25 to 1.81)*</td>
</tr>
<tr>
<td><strong>Age (per 10 years)</strong></td>
<td>1.24 (1.18 to 1.29)*</td>
<td>1.06 (1.01 to 1.11)*</td>
<td>1.29 (1.15 to 1.45)*</td>
<td>1.21 (1.12 to 1.31)*</td>
</tr>
<tr>
<td><strong>Obesity (Abnormal versus Normal)</strong></td>
<td>1.20 (0.90 to 1.60)</td>
<td>0.90 (0.70 to 1.15)</td>
<td>1.29 (0.81 to 2.06)</td>
<td>1.34 (1.00 to 1.80)</td>
</tr>
<tr>
<td><strong>Income (Median versus Low)</strong></td>
<td>0.46 (0.39 to 0.54)*</td>
<td>0.76 (0.65 to 0.90)*</td>
<td>0.49 (0.35 to 0.67)*</td>
<td>0.58 (0.46 to 0.72)*</td>
</tr>
<tr>
<td><strong>Income (High versus Low)</strong></td>
<td>0.37 (0.31 to 0.44)*</td>
<td>0.65 (0.54 to 0.79)*</td>
<td>0.43 (0.29 to 0.64)*</td>
<td>0.61 (0.46 to 0.82)*</td>
</tr>
<tr>
<td><strong>HB (Abnormal versus Normal)</strong></td>
<td>1.07 (0.83 to 1.38)</td>
<td>1.36 (1.00 to 1.85)</td>
<td>0.75 (0.39 to 1.45)</td>
<td>0.88 (0.55 to 1.40)</td>
</tr>
<tr>
<td><strong>HC (Abnormal versus Normal)</strong></td>
<td>1.56 (0.87 to 2.80)</td>
<td>1.37 (0.81 to 2.32)</td>
<td>0.85 (0.30 to 2.35)</td>
<td>1.06 (0.52 to 2.18)</td>
</tr>
<tr>
<td><strong>Hyperuricaemia (Abnormal versus Normal)</strong></td>
<td>5.35 (4.00 to 7.16)*</td>
<td>4.50 (3.66 to 5.53)*</td>
<td>2.91 (1.78 to 4.75)*</td>
<td>4.72 (3.44 to 6.47)*</td>
</tr>
<tr>
<td><strong>Anaemia (Abnormal versus Normal)</strong></td>
<td>2.88 (2.23 to 3.72)*</td>
<td>9.23 (6.50 to 13.09)*</td>
<td>3.11 (1.62 to 5.96)*</td>
<td>6.58 (4.30 to 10.06)*</td>
</tr>
<tr>
<td><strong>Hyperlipidaemia (Abnormal versus Normal)</strong></td>
<td>2.08 (1.70 to 2.55)*</td>
<td>1.25 (1.06 to 1.47)</td>
<td>1.41 (1.03 to 1.93)</td>
<td>1.31 (1.07 to 1.60)</td>
</tr>
<tr>
<td><strong>Smoking status (Abnormal versus Normal)</strong></td>
<td>1.68 (1.39 to 2.03)*</td>
<td>1.33 (1.12 to 1.58)*</td>
<td>1.37 (1.01 to 1.85)</td>
<td>1.39 (1.11 to 1.74)</td>
</tr>
<tr>
<td><strong>Alcohol intake (Abnormal versus Normal)</strong></td>
<td>1.25 (0.99 to 1.58)</td>
<td>1.05 (0.86 to 1.29)</td>
<td>0.93 (0.65 to 1.33)</td>
<td>1.36 (1.05 to 1.76)</td>
</tr>
<tr>
<td><strong>Betel nut chewing (Abnormal versus Normal)</strong></td>
<td>2.02 (1.26 to 3.22)*</td>
<td>1.11 (0.74 to 1.67)</td>
<td>1.10 (0.65 to 1.87)</td>
<td>1.35 (0.88 to 2.07)</td>
</tr>
<tr>
<td><strong>Exercise habits (Abnormal versus Normal)</strong></td>
<td>0.86 (0.74 to 0.99)</td>
<td>0.67 (0.57 to 0.78)*</td>
<td>0.78 (0.58 to 1.04)</td>
<td>0.69 (0.56 to 0.84)*</td>
</tr>
<tr>
<td><strong>Groundwater using (Abnormal versus Normal)</strong></td>
<td>1.83 (1.26 to 2.67)*</td>
<td>1.22 (0.90 to 1.64)</td>
<td>1.16 (0.61 to 2.19)</td>
<td>1.61 (0.99 to 2.64)</td>
</tr>
</tbody>
</table>

**Group I**: participants without DM and HTN; **Group II**: participants with HTN without DM; **Group III**: participants with DM without HTN; **Group IV**: participants with DM and HTN. **HTN**: hypertension; **DM**: diabetes mellitus; **HB**: hepatitis B; **HC**: hepatitis C. **OR**: odds ratio for variation groups compared with reference groups on CKD; **95% CI**: 95% confidence interval; **ref.**: reference groups; **p**_{interaction}: p value of interaction between each factor and groups on CKD. ***: significance after Bonferroni adjustment: p value < 0.05/14 = 0.0036. **£**: the ORs in four groups had significant heterogeneity.
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Group I (OR, 95% CI)</th>
<th>Group II (OR, 95% CI)</th>
<th>Group III (OR, 95% CI)</th>
<th>Group IV (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male versus Female)</td>
<td>1.61 (1.36 to 1.91)*</td>
<td>1.62 (1.36 to 1.93)*</td>
<td>1.72 (1.22 to 2.42)*</td>
<td>1.51 (1.19 to 1.92)*</td>
</tr>
<tr>
<td>Age (per 10 years) £</td>
<td>1.12 (1.07 to 1.18)*</td>
<td>1.02 (0.96 to 1.09)</td>
<td>1.28 (1.12 to 1.46)*</td>
<td>1.19 (1.09 to 1.31)*</td>
</tr>
<tr>
<td>Obesity (Abnormal versus Normal)</td>
<td>1.15 (0.83 to 1.58)</td>
<td>0.83 (0.63 to 1.10)</td>
<td>1.20 (0.72 to 1.99)</td>
<td>1.27 (0.92 to 1.77)</td>
</tr>
<tr>
<td>Income (Median versus Low)</td>
<td>0.52 (0.44 to 0.63)*</td>
<td>0.77 (0.63 to 0.93)</td>
<td>0.45 (0.31 to 0.64)*</td>
<td>0.59 (0.45 to 0.76)*</td>
</tr>
<tr>
<td>(High versus Low)</td>
<td>0.42 (0.34 to 0.52)*</td>
<td>0.65 (0.52 to 0.82)*</td>
<td>0.54 (0.35 to 0.84)</td>
<td>0.65 (0.47 to 0.71)</td>
</tr>
<tr>
<td>HB (Abnormal versus Normal)</td>
<td>1.29 (0.98 to 1.70)</td>
<td>1.43 (1.01 to 2.02)</td>
<td>0.87 (0.42 to 1.83)</td>
<td>1.00 (0.60 to 1.68)</td>
</tr>
<tr>
<td>HC (Abnormal versus Normal)</td>
<td>1.54 (0.79 to 2.99)</td>
<td>1.12 (0.63 to 1.99)</td>
<td>0.80 (0.26 to 2.43)</td>
<td>1.26 (0.57 to 2.79)</td>
</tr>
<tr>
<td>Hyperuricaemia (Abnormal versus Normal)</td>
<td>3.72 (2.72 to 5.10)*</td>
<td>3.69 (2.95 to 4.63)*</td>
<td>2.80 (1.63 to 4.80)*</td>
<td>3.76 (2.68 to 5.26)*</td>
</tr>
<tr>
<td>Anaemia (Abnormal versus Normal)</td>
<td>2.69 (2.03 to 3.56)*</td>
<td>7.93 (5.46 to 11.52)*</td>
<td>3.93 (1.89 to 8.18)*</td>
<td>5.51 (3.49 to 8.70)*</td>
</tr>
<tr>
<td>Hyperlipidaemia (Abnormal versus Normal)</td>
<td>1.75 (1.40 to 2.19)*</td>
<td>0.99 (0.82 to 1.19)</td>
<td>1.48 (1.04 to 2.09)</td>
<td>1.09 (0.87 to 1.36)</td>
</tr>
<tr>
<td>Smoking status (Abnormal versus Normal)</td>
<td>1.33 (1.04 to 1.69)</td>
<td>1.04 (0.83 to 1.31)</td>
<td>1.20 (0.79 to 1.82)</td>
<td>1.16 (0.85 to 1.58)</td>
</tr>
<tr>
<td>Alcohol intake (Abnormal versus Normal)</td>
<td>0.82 (0.61 to 1.09)</td>
<td>0.79 (0.61 to 1.02)</td>
<td>0.73 (0.46 to 1.16)</td>
<td>0.99 (0.70 to 1.39)</td>
</tr>
<tr>
<td>Betel nut chewing (Abnormal versus Normal)</td>
<td>1.27 (0.74 to 2.17)</td>
<td>0.97 (0.60 to 1.56)</td>
<td>0.97 (0.51 to 1.85)</td>
<td>1.22 (0.74 to 2.02)</td>
</tr>
<tr>
<td>Exercise habits (Abnormal versus Normal)</td>
<td>0.75 (0.64 to 0.89)*</td>
<td>0.69 (0.58 to 0.81)*</td>
<td>0.70 (0.51 to 0.97)</td>
<td>0.69 (0.55 to 0.86)</td>
</tr>
<tr>
<td>Groundwater using (Abnormal versus Normal)</td>
<td>1.42 (0.94 to 2.14)</td>
<td>1.11 (0.79 to 1.55)</td>
<td>1.19 (0.59 to 2.38)</td>
<td>1.70 (1.02 to 2.86)</td>
</tr>
</tbody>
</table>

Group I: participants without DM and HTN; Group II: participants with HTN without DM; Group III: participants with DM without HTN; Group IV: participants with DM and HTN. HTN: hypertension; DM: diabetes mellitus; HB: hepatitis B; HC: hepatitis C. OR: odds ratio for variation groups compared with reference groups on CKD; 95% CI: 95% confidence interval; ref: reference groups. *: significance after Bonferroni adjustment: p value < 0.05/14 = 0.0036. £: the ORs in four groups had significant heterogeneity.
**Reviewer 2:**

*Comments to the Author*

1. **Risk Factors and Their Interaction on Chronic Kidney Disease: A Multi-Center Case-Control Study in Taiwan**
   *The authors responded to the issues raised and suggestions have been incorporated in the text.*
   *I think the article can be published*

*Response*

   Thank you for your positive response. We would be grateful.