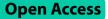
# **MATTERS ARISING**



# Correspondence: insulin resistance and chronic kidney disease in patients without diabetes

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## Abstract

Future investigations on the association between insulin resistance in people without diabetes and chronic kidney disease (CKD) should consider the following aspects to facilitate causal inference and provide more robust findings. The study design should have an adequate follow-up period to rule out reverse causation and pre-existing diabetes, as well as to confirm the diagnosis of CKD. Known causes of CKD and relevant covariates should be identified where possible. Homeostasis model assessment of insulin resistance (HOMA-IR), being an indirect measure of insulin resistance, has limited sensitivity and specificity compared to direct methods like the hyperinsulinaemic-euglycaemic clamp. Regression modelling with HOMA-IR quartiles instead of continuous form may have masked more nuanced relationships. Sensitivity analyses, such as spline regression, could provide more insights about the association and mechanism. Propensity score methods could help address the inadequate overlap in covariate distributions, if present, by ensuring covariate balance. When investigating the CKD diagnostic performance of HOMA-IR, its cut-off for clinically meaningful insulin resistance should be well justified or comprehensively explored to improve the reliability of the results.

Keywords Insulin resistance, Chronic kidney disease, Reverse causation, Prediabetes, Metabolic disease

To the Editor,

We read with great interest, and we would like to congratulate Li et al. on their study entitled "Association of insulin resistance with chronic kidney disease in individuals without diabetes in a community population in South China," published in the BMC Nephrology [1]. Their results present new insights into the association

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between homeostasis model assessment of insulin resistance (HOMA-IR) and chronic kidney disease (CKD), emphasising the importance of further research into these interconnected conditions. Nonetheless, we have identified several concerns regarding the study's design, statistical methods, and interpretation of findings that were not adequately addressed. We believe the following recommendations could strengthen the rigour of future investigations and contribute to a deeper understanding of the underlying pathological mechanisms.

For the study design, given its cross-sectional nature, the authors did not account for the potential of reverse causation, where CKD could have caused insulin resistance instead of vice versa. CKD diagnosis usually requires  $\geq$  3 months of monitoring to confirm [2], but such follow-up durations were not feasible due to the



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cross-sectional design in this study. We suggest designing a longitudinal study in future investigations to avoid these critical issues. Additionally, the authors did not consider patients' comorbidities, especially the primary cause of CKD. If there is a causal relationship between insulin resistance and CKD, the direct effect of insulin resistance needs to be adjusted for other confounders and separated from the primary cause of CKD to confirm this hypothesis. There was also a chance that some of the included patients already had diabetes that was undetected, as the authors did not rule out this possibility during data collection. In these cases, diabetes could partially block the effect of insulin resistance and directly cause CKD. We suggest measuring all relevant covariates and actively screening for existing diabetes where possible to facilitate causal inference.

For the statistical analysis, in addition to the lack of adjustment for potential confounders (as discussed above) in the multivariable regression, the use of HOMA-IR quartiles could also mask non-linear relationships. In case a normal reference range of HOMA-IR is not established, conducting sensitivity analyses, e.g., continuous analyses or spline regressions, may provide more nuanced insights [3]. More importantly, HOMA-IR, as an indirect measure of insulin resistance, has limited sensitivity and specificity compared to direct methods like hyperinsulinaemic-euglycaemic clamp [4, 5]. If the study setting does not facilitate such techniques, this limitation should be acknowledged to avoid misunderstanding for general readers. Another issue is an inadequate overlap of the covariates in the regression models, particularly with body mass index and serum triglycerides. Failing to address this assumption could bias the results and preclude causal inference [6, 7]. We suggest using propensity score methods to ensure the covariates are balanced.

For the data interpretation/reporting, as the study design could not identify the temporal relationship between insulin resistance and CKD, interpreting HOMA-IR as a predictor of CKD is inappropriate. The 2.5 cut-off value of HOMA-IR for estimating the area under the curve of CKD diagnosis was also not justified. This minor detail can mislead the general readers about an established threshold for HOMA-IR. We suggest being cautious in analysis and interpretation when evidence of temporality is not clear. Categorising a continuous variable without a predefined cut-off is also not recommended [8]. Noteworthily, the prevalences of CKD in the four quartiles were miscalculated, i.e., the prevalence of CKD in each quartile was not equal to the proportion between the number of cases with CKD and the sample size. This has raised a strong concern about whether the subsequent findings were accurate. We suggest the authors revise their results to address this issue.

## Abbreviations

CKD Chronic kidney disease HOMA-IR Homeostasis model assessment of insulin resistance

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## Author contributions

HTP, K-HT-N, and M-HT reviewed the literature and this paper, drafted and revised the manuscript, read, and agreed to the final manuscript.

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#### Data availability

No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate** Not applicable.

## **Consent for publication**

Not applicable.

## **Competing interests**

HTP reported receiving speaking fees and travel reimbursement from Servier Vietnam Ltd and Pfizer Vietnam Ltd, grants from Servier Vietnam Ltd, and speaking fees from Aguettant Asia Pacific Pte Ltd outside the submitted work. K-HT-N reported receiving travel reimbursement from Pierre Fabre Vietnam Ltd outside the submitted work. M-HT reported receiving travel reimbursement from Pizer Vietnam Ltd and Viatris Vietnam Ltd, speaking fees and grants from Servier Vietnam Ltd, and speaking fees from Aguettant Asia Pacific Pte Ltd outside the submitted work.

## **Registry, trial registration number, and data of registration** Not applicable.

#### **Clinical trial number**

Not applicable.

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