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Research article

Diabetes mellitus is a risk factor for incident chronic kidney disease: A nationwide cohort study

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ABSTRACT

Objective: Diabetes mellitus and chronic kidney disease are multifactorial conditions with multiple etiologies that share similar pathophysiologies. This nationwide cohort study examined the impact of diabetes mellitus on the follow-up development of chronic kidney disease.
Methods: By retrieving the Longitudinal Health Insurance Database 2005, 5121 patients with diabetes mellitus were included in this study and 5121 patients without diabetes mellitus, who were matched according to sex, age, and Charlson comorbidity index made up the control group. The adjusted hazard ratios for chronic kidney disease were calculated using Cox proportional hazards regression analysis. Kaplan–Meier analysis was used to estimate the cumulative incidence of chronic kidney disease rate in the diabetes mellitus and control groups.
Results: After adjusting for sex, age, and Charlson comorbidity index score, the diabetes mellitus group had a 1.380 times higher (95% CI: 1.277–1.492) risk of developing chronic kidney disease than the control group. Further stratified analysis showed that patients with diabetes mellitus had a significantly higher risk of developing chronic kidney disease regardless of their sex, age, and Charlson comorbidity index score, compared to those without diabetes mellitus.
Conclusions: There is a possibility that diabetes mellitus serves as an independent risk factor for chronic kidney disease development. Early screening and monitoring of diabetes mellitus appear to be of great importance in the prevention of chronic kidney disease.

1. Introduction

Diabetes mellitus (DM) is a condition with metabolic abnormalities, featuring hyperglycemia caused by islet impairment and insulin resistance [1]. It can produce many marked symptoms, such as polyuria, polydipsia, hyperphagia, weight loss, diabetic ketoacidosis, and hyperosmolar coma; and various long-term complications, including diabetic retinopathy, nephropathy, and diabetic

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neuropathy, diabetic foot, and recurrent infections [2]. DM, one of the most common metabolic disorders, affected over 463 million people globally in 2019, and its prevalence is anticipated to reach 700 million by 2045 [3]. Effective diabetes management is crucial for preventing the progression of complications and alleviating clinical and financial loads [4].

Chronic kidney disease (CKD) is a secondary clinical syndrome that refers to abnormal renal structure and/or function with various causes, including infection and autoimmune diseases [5]. It is an increasingly prominent global public health issue, accompanied by a high incidence of disease and a high fatality rate [6]. A meta-analysis showed that the worldwide prevalence of CKD was approximately 13.4% [7]. According to the World Health Organization, the number of deaths caused by CKD annually is 5–10 million [8].

DM is highly correlated with the risk of CKD and is recognized as a primary contributor of CKD in developed and developing countries [8]. Researchers consider CKD to be one of the most prevalent comorbidities resulting from DM [9]. Compared with non-diabetic patients, patients with DM have a higher rate of CKD development [10]. However, most previous studies have ignored the impact of sex, age, and comorbidities which may exaggerate the effects of DM on CKD [11,12]. Male sex is a contributing factor to the onset of diabetic nephropathy [13,14]. A meta-analysis indicated that women have faster renal disease progression after menopause [15]. A study drawing data from the Global Burden of Disease Study found that type 2 diabetes-associated CKD has the highest prevalence in people >80 years of age, worldwide [16]. It has been confirmed that the association between diseases (such as hypertension) and CKD is strong and graded [17]. There are also several studies summarizing the risk factors for CKD due to diabetes [18,19]. However, real-world longitudinal cohort studies investigating the association between DM and CKD are lacking. Few studies have investigated the impact of DM on the development of CKD after exclusion of the effects of sex, age, and comorbidities. Consequently, we carried out this study to explore the connection between DM and CKD by utilizing data from Taiwan National Health Insurance Research Database (NHIRD). We examined the risk of CKD in diabetic and non-diabetic individuals and adjusted for the influences of sex, age, and comorbidities. This study provides an evidence-based and updated reference for the clinical management of diabetes and kidney diseases [20].

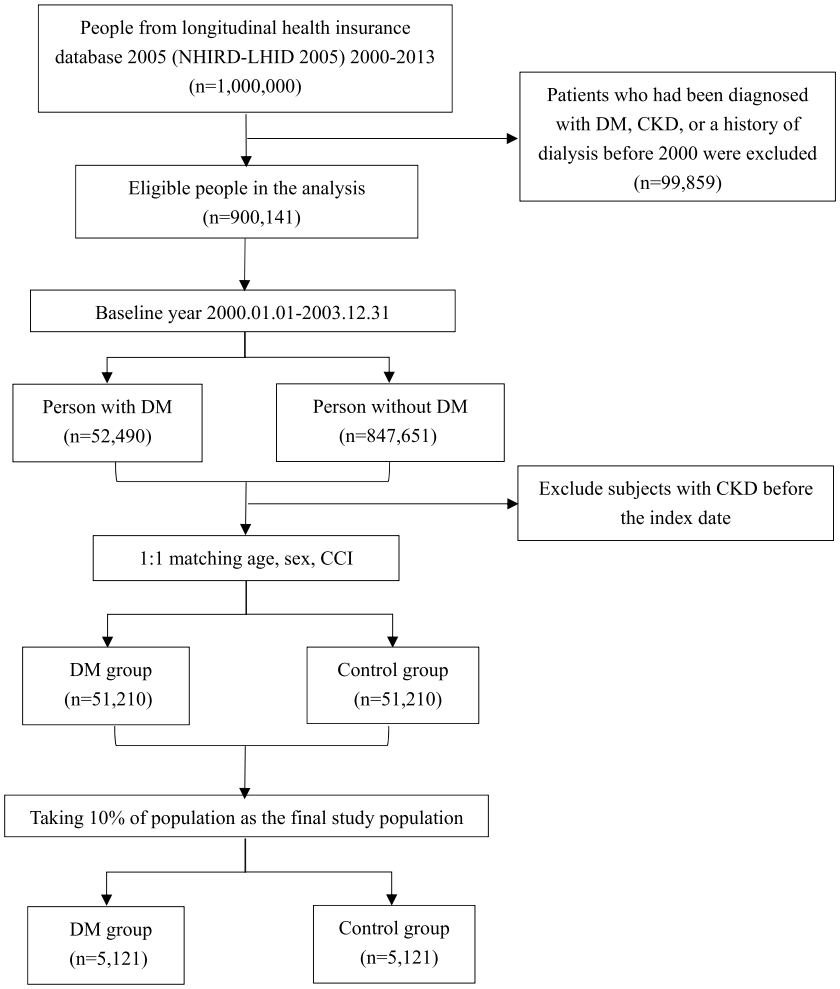

Fig. 1. Flowchart demonstrating the enrollment process for patients with DM and the controls.

2. Materials and methods

2.1. Data sources

The NHIRD was established by the National Health Research Institutes (NHRI) and contains claims data for all in- and out-patient medical services from the Taiwan National Health Insurance (NHI) program. Implemented in 1995, the NHI program in Taiwan serves as a mandatory single-payer healthcare system, covering the vast majority of Taiwan's population, more than 99.9% to be exact. In this study, the Longitudinal Health Insurance Database 2005 (LHID 2005) was employed, which incorporates longitudinally connected data of 1 million enrollees randomly selected from the NHIRD. In order to protect patients privacy, all personal identification of each insured patient was encrypted with a scrambled random identification number by the NHRI before being made available for public access. The LHID 2005 diagnostic codes were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The Institutional Review Board of Kaohsiung Veterans General Hospital approved this study, with the approval number KSVGH21-CT5-06.

2.2. Study population

We carried out a nationwide cohort study consisting of DM and non-DM groups. The process of selecting the study population is depicated in Fig. 1. Patients with DM (ICD-9-CM 250.0), CKD (ICD-9-CM 403. xx, 404. xx, 580. xx–587. xx, 250.4, 274.1, 274.10, 440.1, 442.1, 572.4, 753.1), or a history of dialysis (ICD-9-CM D8, D9 (cure item)) before 2000 were excluded (n = 99,859). Overall, 900,141 eligible people were included in the analysis. We identified 52,490 new DM patients between January 1, 2000 and December 31, 2003. The onset date of DM was taken as the index date for the DM group. DM patients who were identified as having CKD prior to the index date were all ruled out. People in the non-DM (control) group had no history of DM diagnosis. To guarantee comparable fundamental traits and alleviate the possibility of selection bias, for each patient with DM, an individual without a DM diagnosis was chosen from the non-DM population and matched based on sex, age, and Charlson comorbidity index (CCI) score. The index date for the non-DM control group was determined by the index date of the DM patients they were paired with. All controls with CKD histroy were excluded. Altogether, there were 51,210 patients in the DM group and 51,210 people in the control group. We randomly selected 10% of the population for the final analysis, of which 5121 patients with DM comprised the DM group, and 5121 patients without DM comprised the control group. The follow-up of both groups started from the DM diagnosis date and ended on December 31, 2013, after 10-years follow up, quit from the NHI, the date of CKD diagnosis, or died due to severe diseases or any other reasons, whichever occurred first.

2.3. Covariates and outcomes

The demographic characteristics taken into account were sex and age ($\leq$39, 40–49, 50–59, 60–69, and $\geq$70 years). The CCI was used to evaluate comorbidities, which were considered confounding factors [21,22]. The CCI is a scoring system used to measure patients' comorbidities in terms of the amount and severity of their diseases. The original version of the CCI, developed by Charlson, consists of 19 items corresponding to different comorbid medical conditions [22]. Each comorbid condition was allocated a weight, and the CCI scores were derived by adding up the weighted scores of the patients' comorbidities, as indiacted by their inpatient diagnoses. Regarding the CCI score, 19 comorbidities were categorized into four classes, as shown in Supplementary Table 1. To identify the severity of comorbid conditions among patients, the sum of the CCI scores was divided into five levels: CCI = 0 for healthy, 1–2 for mild comorbid conditions, 3–4 for moderate comorbid conditions, and $\geq$5 for severe comorbid conditions [23]. The main outcome measure was CKD, which was identified using the ICD-9-CM code (ICD-9-CM 403. xx, 404. xx, 580. xx-587. xx,250.4, 274.1, 274.10, 440.1, 442.1, 572.4, 753.1).

2.4. Statistical analysis

Data analysis was carried out using Statistical Package for Social Sciences (SPSS) version 23 (IBM). Continuous variables were described by means and standard deviations (SD), and categorical variables by frequencies and percentages. To compare the differences in the demographic factors between the DM and non-DM groups, continuous variables were tested with the Student's t-test, while categorical factors were examined using the Pearson chi-squared test. By means of Kaplan–Meier (KM) analysis, the cumulative incidence curves of CKD in the DM and non-DM groups were determined, and the log-rank test was employed to compare the discrepancies between the two groups. The risks of CKD and CKD-associated risk factors were calculated via univariate and multivariate Cox proportional hazards regression models. The multivariate model was modified by sex, age, and CCI score. By stratifying according to sex, age, and CCI score, the hazard ratios (HR) of CKD in the DM and non-DM groups were contrasted. Before constructing the Cox proportional-hazards regression model, we assess the proportional hazards (PH) assumption by the method of visual assessment of KM curves. By plotting survival function against time, if the KM survival curves follow a similar trend without crossing, the PH assumption holds; if the survival curves are unparallel and cross, indicating PH violation [24]. The threshold for statistical significance was $P < 0.05$.

3. Results

Overall, 5121 participants with DM and 5121 participants without DM comprised the study population. In Table 1, it can be seen that 53.9% of the participants in the non-DM group were female, while 52.7% of the participants in the DM group were female. The mean ages of the non-DM and DM were 55.05 (SD = 14.73) and 55.58 (SD = 14.82) years, respectively. The mean CCI scores of non-DM and DM were 3.10 (SD = 1.87) and 3.19 (SD = 1.96). The distributions of sex, age, and CCI score group did not differ significantly between groups ($P > 0.05$).

The average follow-up periods were 8.35 years (SD = 0.05 years) for the DM group and 8.70 years (SD = 0.04 years) for the non-DM group. As shown in Fig. 2, the log-rank test demonstrated that the cumulative incidence of CKD was notably higher in the DM group compared to the non-DM group ($P < 0.001$).

Factors entered into the Cox proportional hazards model had to satisfy the PH assumption. Our results showed that the KM survival curves for DM group, sex, age and CCI score showed similar trends and didn't cross, which indicated that the PH assumption was met. In the DM group, the CKD incidence rate was 3.73 per 100 person-years, which was 1.404 times greater than the non-DM group (2.65 per 100 person-years), and the adjusted HR of 1.380 (95% CI: 1.277–1.492). Multivariate analysis indicates that males are more likely to develop CKD than females (adjusted HR: 1.142, 95% CI: 1.058–1.234). Age ≥70 years (adjusted HR: 1.813, 95% CI: 1.486–2.211) and a CCI score of ≥5 (adjusted HR: 2.931, 95% CI: 2.111–4.070) were strongly linked to a greater risk of CKD (Table 2).

In the analysis stratified by sex, both sexs with DM had a greater likelihood of CKD development compared to those without DM, with adjusted HRs of 1.403 (95% CI: 1.259–1.564) and 1.355 (95% CI: 1.213–1.514) for females and males, respectively. By stratifying patients according to age, a significantly higher risk of CKD was observed in the DM group compared to the non-DM group. The adjusted HRs of CKD were 1.448 (95% CI: 1.074–1.952) in patients aged ≤39 years old, 1.564 among 40–49-year-olds (95% CI: 1.272–1.923), 1.496 among 50–59-year-olds (95% CI: 1.267–1.767), 1.407 among 60–69-year-olds (95% CI: 1.218–1.626), and 1.172 among those aged ≥70 years (95% CI: 1.012–1.357). The risk of developing CKD was higher among patients with DM with all CCI scores than among non-DM patients. The adjusted HRs for CKD were 5.670 (95% CI: 2.530–12.708) in patients with a CCI score of 0, 1.549 (95% CI: 1.323–1.812) in patients with a CCI score of 1–2, 1.304 (95% CI: 1.152–1.477) in patients with a CCI score of 3–4, and 1.271 (95% CI: 1.114–1.450) in patients with a CCI score of ≥5 (Table 3).

4. Discussion

This cohort study revealed that patients with DM had a 1.380-fold increased risk of developing CKD, after considering adjustments for sex, age, and CCI score. Although the mean CCI score were significantly higher in the DM group compare to the non-DM group, the risk of developing CKD remained significantly higher after adjusting for confounding factors. Further stratified analysis indicated that in both males and females, all age groups and all CCI score groups, the likelihood of developing CKD in the DM group was still notably higher than that in the non-DM group.

Many studies have confirmed the association between DM and CKD. Williams believes that diabetes is a major cause of CKD and that patients with diabetes therefore require special monitoring and management [25]. Nordheim et al. considered CKD a common complication and concomitant disease of diabetes and sought to explore drugs to lower glucose levels and benefit the kidneys [25]. Cao et al. concluded that abnormal metabolic factors in type 2 diabetes are closely associated with a microinflammatory state and CKD [26]. This study provides strong evidence for the association between DM and CKD.

Studies have also attempted to analyze the causes of CKD owing to DM. Such studies provide pathological explanatory evidence for the results of the present study. For example, a case-control study by Shestakova et al. found that genetic factors could affect this

Table 1
Baseline demographic factors of study participants according to DM.

	Non-DM group (n = 5121)		DM group (n = 5121)		
Variables	**n**	**%**	**n**	**%**	**P**
Sex					0.205
Female	2762	53.9	2698	52.7	
Male	2359	46.1	2423	47.3	
Age, years					0.306
≤39	724	14.1	701	13.7	
40-49	1060	20.7	1009	19.7	
50-59	1248	24.4	1214	23.7	
60-69	1169	22.8	1231	24.0	
≥70	920	18.0	966	18.9	
Mean (SD)	55.05	(14.73)	55.58	(14.82)	0.071
CCI score					0.065
0	198	3.9	199	3.9	
1-2	1997	39.0	1940	37.9	
3-4	1853	36.2	1797	35.1	
≥5	1073	21.0	1185	23.1	
Mean (SD)	3.10	(1.87)	3.19	(1.96)	0.011

CCI= Charlson comorbidity index, DM = diabetes mellitus.

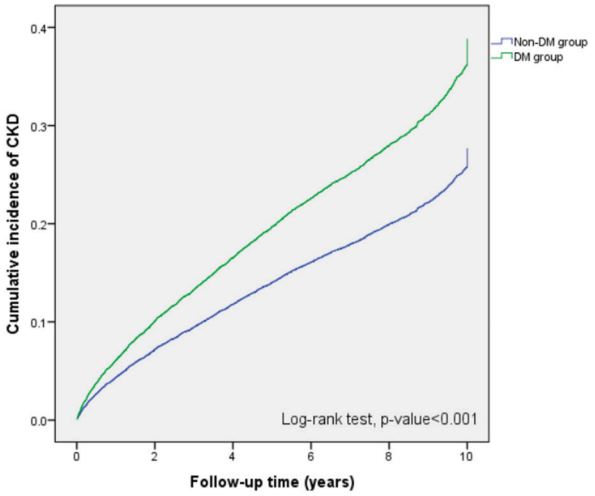

Fig. 2. Cumulative incidence curves of CKD for groups with and without DM.

Table 2
Cox model measured hazard ratios and 95% CI of DM with CKD and covariates.

					Univariate		Multivariate[a]	
Variables	Event No.	All No.	Person-years	IR	HR (95% CI)	P	HR (95% CI)	P
DM						<0.001		<0.001
No	1104	5121	41611	2.65	1		1	
Yes	1512	5121	40538	3.73	1.404 (1.299–1.517)		1.380 (1.277–1.492)	
Sex						0.004		0.001
Female	1335	5460	44213	3.02	1		1	
Male	1281	4782	37986	3.37	1.121 (1.038–1.210)		1.142 (1.058–1.234)	
Age, years								
≤39	180	1425	12162	1.48	1		1	
40-49	376	2069	17213	2.18	1.459 (1.222–1.743)	<0.001	1.399 (1.171–1.671)	<0.001
50-59	571	2462	20224	2.82	1.878 (1.588–2.220)	<0.001	1.500 (1.257–1.791)	<0.001
60-69	764	2400	18801	4.06	2.674 (2.273–3.146)	<0.001	1.690 (1.399–2.042)	<0.001
≥70	725	1886	13800	5.25	3.443 (2.295–4.054)	<0.001	1.813 (1.486–2.211)	<0.001
CCI score								
0	45	397	3476	1.29	1		1	
1-2	648	3937	33429	1.94	1.491 (1.102–2.017)	0.010	1.336 (0.983–1.815)	0.064
3-4	1011	3650	29184	3.46	2.633 (1.953–3.549)	<0.001	1.982 (1.440–2.728)	<0.001
≥5	912	2258	16110	5.66	4.241 (3.144–5.721)	<0.001	2.931 (2.111–4.070)	<0.001

DM = Diabetes mellitus, CKD = chronic kidney disease, CCI= Charlson comorbidity index, CI = confidence interval, HR = hazard ratio, IR = incidence rate per 100 person-years.

[a] Adjusted for DM, sex, age, and CCI score.

process [27]. High blood sugar levels can alter renal haemodynamics and cause metabolic abnormalities, leading to kidney damage. For example, the accumulation of advanced glycation end products is significantly associated with chronic renal processes in diabetes [28]. DM leading to GBM sclerosis is a common cause of proteinuria in patients [29].

In addition, similar to the findings of a meta-analysis by Shen et al. this study showed no sex- or age-specific association between diabetes and CKD [30]. However, some studies have suggested that sex affects the prevalence of CKD due to diabetes. Gembillo et al. concluded that the prevalence of risk factors for diabetic nephropathy (DKD) is higher in women with DM [31], and in the Raile et al. prospective German Diabetes Literature System survey, male sex is a risk factor in the transformation from diabetes to CKD [32]. It is difficult to determine what led to the discrepancies between the studies by Gembillo et al. and Raile et al. and ours. The data used in these studies were obtained from different ethnic groups. Racial differences may account for this discrepancy. Further research is required to figure out if racial disparities contribute to the relationship between DM and CKD.

The strengths of this study are its real-world longitudinal cohort design based on a nationwide population, representative cohorts, and a relatively long follow-up period (up to 10 years). However, it has several limitations. First, the NHIRD did not provide the detailed information on patient lifestyle, such as poor diet, alcohol consumption, and smoking, which might increase the risk of CKD. Second, information on medication use for DM was incomplete in the NHIRD, which may have accelerated the development of CKD in this study. Finally, although our study was well designed and adequately controlled for the confounders, there some unkonwn or unmeasured confounders, which may limit the generalizability of the findings. Nevertheless, all medical claims records in the NHI

Table 3
Subgroup analysis of the crude and adjusted hazard ratios (95% CI) of DM for CKD according to sex, age, and CCI.

	Non-DM group				DM group				Compared With non-DM			
									Crude		Adjusted[a]	
Variables	Event No.	All No.	Person-years	IR	Event No.	All No.	Person-years	IR	HR (95% CI)	P	HR (95% CI)	P
Sex												
Female	566	2762	22730	2.49	769	2698	21483	3.58	1.434 (1.287–1.598)	<0.001	1.403 (1.259–1.564)	<0.001
Male	538	2359	18931	2.84	743	2423	19055	3.90	1.368 (1.224–1.528)	<0.001	1.355 (1.213–1.514)	<0.001
Age, years												
≤39	73	724	6170	1.18	107	701	5992	1.79	1.500 (1.114–2.020)	0.008	1.448 (1.074–1.952)	0.015
40-49	153	1060	8848	1.73	223	1009	8365	2.67	1.540 (1.253–1.891)	<0.001	1.564 (1.272–1.923)	<0.001
50-59	238	1248	10446	2.28	333	1214	9778	3.41	1.498 (1.269–1.770)	<0.001	1.496 (1.267–1.767)	<0.001
60-69	313	1169	9391	3.33	451	1231	9410	4.79	1.433 (1.241–1.656)	<0.001	1.407 (1.218–1.626)	<0.001
≥70	327	920	6807	4.80	398	966	6993	5.69	1.182 (1.021–1.368)	0.025	1.172 (1.012–1.357)	0.034
CCI score												
0	7	198	1781	0.39	38	199	1695	2.24	5.737 (2.562–12.849)	<0.001	5.670 (2.530–12.708)	<0.001
1-2	260	1997	17088	1.52	388	1940	16341	2.37	1.554 (1.328–1.818)	<0.001	1.549 (1.323–1.812)	<0.001
3-4	451	1853	14971	3.01	560	1797	14214	3.94	1.308 (1.155–1.480)	<0.001	1.304 (1.152–1.477)	<0.001
≥5	386	1073	7821	4.94	526	1185	8829	5.96	1.276 (1.119–1.456)	<0.001	1.271 (1.114–1.450)	<0.001

DM = Diabetes mellitus, CKD = chronic kidney disease, CCI= Charlson comorbidity index, CI = confidence interval, HR = hazard ratio, IR = incidence rate per 100 person-years.
[a] Adjusted for sex, age, and CCI score.

program were examined and verified by the medical reimbursement specialists, which enhanced the reliability and correctness of the DM and CKD diagnoses. Our findings regarding the association between DM and CKD provide a reliable account based on the validity of the database, the sizable sample size, and the lengthy follow-up duration.

In conclusion, this cohort study determined that DM and CKD were significantly associated and not specific to sex or age. This further confirmed that DM has a significant effect on CKD. Therefore, early screening for diabetes and monitoring for nephropathy are of great interest to healthcare managers. Simultaneously, the link between DM and CKD should be considered in clinical treatment and care. In addition, the development of drugs that lower blood glucose levels and reduce kidney damage is an effective strategy. However, further studies exploring the potential link between DM and CKD are necessary.

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None.

Ethics statement

This study was reviewed and approved by Institutional Review Board of Kaohsiung Veterans General Hospital, with the approval number: KSVGH21-CT5-06.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Ping Tao: Writing – original draft, Resources, Methodology, Formal analysis, Data curation. **Ching-Wen Chien:** Writing – original draft, Methodology, Investigation, Data curation. **Chao Liu:** Writing – original draft. **Jinghang Zheng:** Writing – original draft. **Dongping Sun:** Writing – original draft. **Jibin Zeng:** Writing – original draft. **Qunli Song:** Writing – original draft, Conceptualization. **Yuzhou Liu:** Writing – original draft. **Tao-Hsin Tung:** Writing – review & editing, Writing – original draft, Conceptualization. **Linlin Kang:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28780.

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