Association and risk factors of chronic kidney disease and incident diabetes: a nationwide population-based cohort study

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Abstract

Aims/hypothesis Chronic kidney disease (CKD) is a known complication of diabetes mellitus, and insulin resistance is a well-known complication of CKD. However, there is no consensus in the published data on the association of CKD with incident diabetes.

Methods A total of 15,403 people with CKD were identified from the Taiwan National Health Insurance Research Database to determine their risk of incident diabetes compared with that of 15,403 matched individuals without CKD. Fine and Gray regression models using death as a competing risk were performed to calculate adjusted HRs and 95% CIs. Risk factors for incident diabetes in people with CKD were also determined.

Results The CKD cohort had a higher incidence rate of diabetes compared with the non-CKD cohort (11.23/1000 person-years vs 8.93/1000 person-years). In the fully adjusted model, CKD was a significant and independent predictor of incident diabetes (adjusted HR 1.204; 95% CI 1.11, 1.31). The influence of CKD on incident diabetes showed consistent results in three levels of sensitivity analysis. In the CKD cohort, the significant risk factors for incident diabetes included increased age, geographical location, hypertension, hyperlipidaemia and gout. Of these, hypertension was associated with the highest risk of developing incident diabetes (adjusted HR 1.682; 95% CI 1.47, 1.93).

Conclusions/interpretation People with CKD were at higher risk of developing incident diabetes. People with CKD and hypertension, hyperlipidaemia, increased age or gout and who lived in certain geographical regions of Taiwan were more likely to develop diabetes as a complication compared with people without those characteristics.

Keywords Chronic kidney disease · CKD · Competing-risk regression · Incident diabetes mellitus · Insulin resistance · New-onset diabetes mellitus

Abbreviations

CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
NHI	National Health Insurance
NHIRD	National Health Insurance Research Database

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Introduction

With advancements in medical treatment and increasing life expectancy, the prevalence of chronic kidney disease (CKD) has increased worldwide and has had a profound impact on healthcare systems and socioeconomic institutions [1]. Similarly, the increasing prevalence of type 2 diabetes mellitus has also had a great influence on public health. The leading cause of CKD is diabetes; diabetic nephropathy accounts for approximately 40% of the population undergoing dialysis in Taiwan [2]. However, little attention been given to renal failure as a possible cause of diabetes.

Diabetes is known to complicate myocardial infarction, cerebrovascular events and kidney failure [3]. Insulin resistance plays a crucial aetiological role in the pathophysiological mechanisms underlying type 2 diabetes. Glucose homeostasis depends on a plentiful secretion of insulin in

Research in context

What is already known about this subject?

- Insulin resistance is known to occur in people with chronic kidney disease (CKD)
- In the presence of insulin resistance, euglycaemia may be still attained through increased secretion of insulin by the pancreatic beta cells
- Approximately half of those with CKD are affected by impaired glucose homeostasis

What is the key question?

- Is CKD associated with incident diabetes?

What are the new findings?

- After adjusting for various well-known risk factors, CKD was found to be a significant risk factor predicting incident diabetes
- Higher age, living in central or southern Taiwan, or having hypertension, hyperlipidaemia or gout, significantly increased the likelihood of developing diabetes in people with CKD
- The presence of hypertension represented the highest additional risk for developing diabetes among people with CKD

How might this impact on clinical practice in the foreseeable future?

- More aggressive medical attention should be paid to individuals with CKD, particularly those with other risk factors, in an attempt to prevent incident diabetes or enable its early detection

combination with appropriate insulin action on peripheral tissues such as adipocytes, skeletal muscle cells and hepatocytes. Euglycaemia may be attained through the augmented secretion of insulin by the pancreatic beta cells in the presence of insulin resistance [4]. CKD is characterised as the progressive retention of toxic uraemic metabolites, many of which adversely influence a number of organs. Approximately half of all people with CKD are affected by impaired glucose homeostasis [5–7]. In addition to end-stage renal disease (ESRD), insulin resistance appears to exist in the early stages of CKD and is exacerbated as renal function declines [8–11]. The causes of insulin resistance in CKD are multifactorial and may include, among other factors, obesity, a sedentary lifestyle and poor diet [12]. At the molecular level, the major abnormality is an acquired defect in the insulin receptor-signalling pathway [13].

CKD is an established complication of diabetes. However, there is no consensus regarding the association of CKD with incident diabetes in the published data. Whether insulin resistance contributes to the development of overt type 2 diabetes in CKD has not been well addressed. We hypothesise that CKD may be associated with an increased risk of incident diabetes through a variety of pathophysiological factors. The present research was designed as a nationwide population-based study to assess the association between CKD and incident diabetes, and evaluate the risk factors for incident diabetes among people with CKD.

Methods

Data source and study population The National Health Insurance (NHI) scheme, in which 99% of the 23 million population are enrolled, was launched in 1995 to provide healthcare insurance in Taiwan. In order to have their expenses reimbursed, medical facilities that have contracted in to the NHI system must provide computerised data on all medical care provided. The NHI Research Database (NHIRD) is run by the Taiwan National Health Research Institute to enable medical research. It contains comprehensive medical information, including data on demographics, medical procedures, pharmacotherapy, residency and medical diagnoses, gathered from both inpatient and outpatient settings. The ICD-9-CM (www.icd9data.com/2007/Volume1) is used for diagnostic coding in the NHIRD. Previous studies indicated that the diagnostic coding in the database was highly accurate for many major diseases [1, 14, 15].

The study population was a large-scale cohort of ~1,000,000 people that was a subset randomly sampled from the NHIRD and contained patient information from 1996 to 2013. The study project was reviewed and approved by the Institutional Review Board of Changhua Christian Hospital. The requirement for informed consent from each individual was waived because all data in the NHIRD were de-identified according to personal data protection law in Taiwan.

Study design The study was carried out to investigate whether CKD was a risk factor for the occurrence of incident diabetes, and also to identify the predictors of incident diabetes among the CKD population using data from the NHIRD between 1995 and 2013. Individuals with incident CKD (ICD-9 codes 580–589) were selected from inpatient and outpatient claims between 1 January 2000 and 31 December 2013, after excluding those diagnosed with CKD between 1995 and 1999. The index date was defined as the date of incident CKD. Those with CKD who had undergone permanent renal replacement therapy (haemodialysis, peritoneal dialysis or kidney transplant) before the index date or who had type 1 diabetes (ICD-9 codes 250.x1, 250.x3) throughout the study period were excluded. People with type 2 diabetes before the index date were also excluded, as well as those aged <18 or >100 years and those undergoing bariatric surgery, or those who were followed for <1 year. The control non-CKD cohort was derived from the NHIRD using similar criteria to those used to select the CKD cohort, except that the control cohort had no CKD throughout the study period. For each CKD case, one non-CKD case was selected by matching for age, sex and calendar year of index date and propensity scores. Both cohorts were followed from the index date to the date of first diagnosed diabetes, death, withdrawal from the NHI, or the end of 2013.

Definition of CKD, diabetes and other comorbidities Cases of CKD, diabetes and other comorbidities were considered if they met one of the following criteria: (1) at least two diagnostic codes at outpatient visits within 1 year, and an interval between the first and last diagnosis of at least 30 days (to avoid miscoding problems); (2) one diagnostic code in the hospitalisation database. In addition to ICD-9 code 250, the diagnosis of diabetes also required the prescription of glucose-lowering agents (insulin preparations [A10A] or oral glucose-lowering agents [A10B]).

Potential confounders Other comorbid conditions as potential confounders included hypertension (ICD-9 codes 401–405), hyperlipidaemia (ICD-9 code 272), ischaemic heart disease (ICD-9 codes 410–414), congestive heart failure (ICD-9 code 428), cerebrovascular disease (ICD-9 codes 430–438), rheumatoid disease (ICD-9 codes 446.5, 710.0–710.4, 714.0–714.2, 714.8, 725.x), gout (ICD-9 code 274), obesity (ICD-9 codes 278, 783.1, V77.8), and Charlson's comorbidity index, which did not consider CKD, cerebrovascular disease, rheumatoid disease, ischaemic heart disease and diabetes, to avoid double-counting and overestimation of those variables. The data were also adjusted for geographical region, monthly income, number of medical visits after study entry and medications (statins, antihypertensive drugs, erythropoiesis-stimulating agents and glucocorticoids). The use of a medication was defined as continuous use of certain drugs for a minimum of 3 consecutive months.

Statistical analysis Data are presented as number (percentage) or the mean $\pm$ SD. Comparisons of the differences in the covariates were made between the control cohort and the CKD cohort using standardised differences to assess the balance of covariate distribution, where an absolute value >0.1 was considered a significant imbalance between the two groups.

The incidence rate of diabetes was calculated from the total number of new-onset diabetes cases divided by the total person-years during the follow-up period for each cohort. Since death may preclude the occurrence of incident diabetes, a multivariate-adjusted Cox proportional hazards regression model, where death was considered the competing risk (Fine and Gray regression models), was conducted to calculate HRs and 95% CIs, with adjustments for all the characteristics listed in Table 1. Propensity scores were calculated from logistic regression analysis and used to adjust the Cox regression models to reduce bias from unmeasured confounders.

Pharmacotherapy might have changed during the follow-up period, so medical treatment was also adjusted as a time-dependent covariate in addition to baseline status. The renal function status of individuals with CKD was determined at their time of study entry; it might have progressed to advanced CKD (equivalent to CKD stage 5, eGFR <15 ml min⁻¹ 1.73 m⁻²) or to ESRD requiring dialysis treatment during the study period [14, 15].

Type 1 diabetes is most common in childhood; however, it is sometimes diagnosed in adults. Patients with diabetes who are diagnosed at an older age may have type 1 diabetes. Diabetic individuals who receive insulin as their first therapy or within a year of diagnosis are also likely to have type 1 diabetes. To eliminate the misclassification of type 1 diabetes as type 2 diabetes, those who had type 1 diabetes diagnosed by the ICD-9 throughout the entire study period were excluded. After excluding individuals who were <20 or <30 years of age when they were diagnosed with diabetes, as well as those who received insulin as their first therapy within a year of diagnosis, the data were reanalysed to check whether the results were consistent with those in the main analysis.

Three sensitivity tests were carried out to evaluate the validity of the results: (1) individuals whose renal status changed were censored; (2) time-dependent Cox regression analysis was used to adjust for the change in renal status; and (3) the diagnosis of diabetes was redefined on the basis of ICD-9 codes at three or more outpatient visits. Risk factors associated with new-onset diabetes in those with CKD were examined using Cox regression models. The influence of CKD on diabetes risk was also examined by performing subgroup analyses for different strata, including sex, age, comorbidities and frequency of medical visits. Data analyses were carried out using IBM SPSS Statistics for Windows, version 22.0 (IBM, Armonk, NY, USA). A *p* value <0.05 was considered to indicate a statistically significant difference.

Table 1 Baseline characteristics and clinical outcomes between the cohorts with and without CKD before and after matching

Characteristic	Before matching			After matching		
	Non-CKD cohort (<i>n</i> =529,883)	CKD cohort (<i>n</i> =18,667)	StD ^a	Non-CKD cohort (<i>n</i> =15,403)	CKD cohort (<i>n</i> =15,403)	StD ^a
Demographics						
Age, years	39.45 ± 14.95	55.77 ± 17.61	0.999	53.47 ± 17.06	53.47 ± 17.05	0.000
Male sex	255,280 (48.18)	10,952 (58.67)	0.212	8834 (57.35)	8834 (57.35)	0.000
Monthly income, NTD	18,923.33 ± 16,057.40	16,746.80 ± 15,569.54	0.138	17,719.50 ± 16,308.28	17,695.04 ± 15,916.63	0.002
Geographical location						
Northern Taiwan	268,628 (50.70)	8387 (44.93)	0.116	7047 (45.75)	6979 (45.31)	0.009
Central Taiwan	98,106 (18.51)	3489 (18.69)	0.005	2867 (18.61)	2883 (18.72)	0.003
Southern Taiwan	151,341 (28.56)	6339 (33.96)	0.117	5060 (32.85)	5206 (33.80)	0.020
Eastern Taiwan and islands	11,808 (2.23)	452 (2.42)	0.013	429 (2.79)	335 (2.17)	0.039
Annual frequency of medical visits	14.29 ± 12.85	26.56 ± 19.28	0.749	25.14 ± 18.42	23.83 ± 16.60	0.075
Comorbidities						
CCI score ^b	0.39 ± 0.77	1.11 ± 1.25	0.701	0.94 ± 1.13	0.95 ± 1.14	0.013
Hypertension	38,268 (7.22)	7873 (42.18)	0.887	5334 (34.63)	5124 (33.27)	0.029
Hyperlipidaemia	15,090 (2.85)	3394 (18.18)	0.516	1854 (12.04)	2183 (14.17)	0.063
Ischaemic heart disease	10,661 (2.01)	2608 (13.97)	0.452	1587 (10.30)	1511 (9.81)	0.016
Congestive heart failure	2669 (0.50)	1346 (7.21)	0.354	461 (2.99)	553 (3.59)	0.033
Gout	9042 (1.71)	3545 (18.99)	0.592	1417 (9.20)	1745 (11.33)	0.070
Cerebrovascular disease	7235 (1.37)	1710 (9.16)	0.355	1066 (6.92)	976 (6.34)	0.023
Rheumatoid disease	1092 (0.21)	206 (1.10)	0.111	99 (0.64)	113 (0.73)	0.011
Obesity	481 (0.09)	56 (0.30)	0.047	40 (0.26)	38 (0.25)	0.003
Long-term medications						
Antihypertensive drugs	29,205 (5.51)	5408 (28.97)	0.653	3470 (22.53)	3445 (22.37)	0.004
ACEIs/ARBs	12,418 (2.34)	3025 (16.21)	0.492	1686 (10.95)	1823 (11.84)	0.028
Diuretics	6993 (1.32)	2034 (10.90)	0.408	996 (6.47)	1146 (7.44)	0.038
Beta-blockers	18,292 (3.45)	3046 (16.32)	0.441	2025 (13.15)	1916 (12.44)	0.021
Statins	6281 (1.19)	1317 (7.06)	0.299	720 (4.67)	831 (5.40)	0.033
Erythropoiesis-stimulating agents	0 (0)	28 (0.15)	0.055	0 (0)	23 (0.15)	0.055
Glucocorticoids	3103 (0.59)	648 (3.47)	0.206	323 (2.10)	387 (2.51)	0.028
Propensity score	0.03 ± 0.05	0.15 ± 0.19	0.874	0.09 ± 0.11	0.09 ± 0.11	0.001
Outcomes						
Diabetes	15,004 (2.83)	1654 (8.86)***		1060 (6.88)	1284 (8.34)***	
Death	29,050 (5.48)	2456 (13.16)***		1645 (10.68)	1695 (11.00) [†]	
Duration of follow-up, years	6.88 ± 3.55	7.27 ± 3.94***		7.71 ± 3.94	7.42 ± 3.93***	

Values are expressed as mean ± SD or number (%)

^a StD, standardised difference >0.1 is considered an important imbalance

^b CCI score, Charlson's comorbidity index did not consider CKD, cerebrovascular disease, ischaemic heart disease, rheumatoid disease and diabetes as a comorbidity, to prevent double-counting and over-adjustment in multivariate regressions

****p*<0.001

[†] *p*=non-significant

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NTD, New Taiwan Dollar

Results

Baseline characteristics As shown in Fig. 1, a total of 15,403 CKD cases and 15,403 control subjects were enrolled in the

study. The baseline sociodemographic data, comorbidities and use of medications for the two cohorts before and after the matching process are shown in Table 1. Before matching, the CKD cohort was more likely to be older and male, have a

Fig. 1 Flow chart of selection process for CKD and non-CKD cohorts

lower monthly income, a higher frequency of medical visits, more comorbidities and increased use of medications, and live in southern Taiwan, compared with the non-CKD cohort. After matching in a 1:1 ratio, the differences between the two cohorts were non-significant in terms of all subject characteristics (standardised difference <0.1 for each covariate).

Prevalence of incident diabetes in the CKD and non-CKD cohorts

The mean duration of follow-up was 7.42 years for the CKD cohort and 7.71 years for the non-CKD cohort. The prevalence rate of incident diabetes for the CKD and non-CKD cohorts was 1.1% and 0.8% at 1 year, 3.5% and 2.5% at 3 years, 5.7% and 4.6% at 5 years, and 8.3% and 6.5% at 7 years, respectively. After taking the competing risk of death into account, the cumulative incidence of diabetes was significantly higher in the CKD cohort compared with the non-CKD cohort (Fig. 2; Gray's test, $p < 0.001$). At the end of the study period, the prevalence rate of diabetes was 1.21-fold higher in the CKD cohort compared with the non-CKD cohort (8.34% vs 6.88%; $p < 0.0001$).

Role of CKD as an independent risk factor for incident diabetes Table 2 shows the unadjusted and adjusted HRs for CKD in the development of incident diabetes, where death was

considered as a competing event. In model 1 (unadjusted), CKD was significantly associated with incident diabetes (HR 1.256; 95% CI 1.16, 1.36). The significant risk for incident diabetes in the CKD cohort remained after adjusting for propensity score in model 2 (adjusted HR 1.254; 95% CI 1.16, 1.36). After adjusting for all the variables in Table 1 (model 3), CKD was still significantly associated with the development of incident diabetes (adjusted HR 1.257; 95% CI 1.16, 1.36).

Fig. 2 Cumulative incidence rate of diabetes in CKD and non-CKD cohorts (Gray's test, $p < 0.001$)

Table 2 Incidence and risk of diabetes in the CKD cohort compared with the non-CKD cohort

Cohort	Non-CKD	CKD
No. of events	1060	1284
Person-years	118,760	114,306
Incidence ^a	8.93 (8.39, 9.46)	11.23 (10.62, 11.85)
Model 1		
HR (95% CI)	Reference	1.256 (1.16, 1.36)
<i>p</i> value	–	<0.0001
Model 2		
Adjusted HR (95% CI)	Reference	1.254 (1.16, 1.36)
<i>p</i> value	–	<0.0001
Model 3		
Adjusted HR (95% CI)	Reference	1.257 (1.16, 1.36)
<i>p</i> value	–	<0.0001
Model 4		
Adjusted HR (95% CI)	Reference	1.204 (1.11, 1.31)
<i>p</i> value	–	<0.0001

All analyses considered death as a competing risk

Model 1, unadjusted model; model 2, adjusted for propensity score; model 3, adjusted for all variables listed in Table 1; model 4, adjusted for all variables listed in Table 1 and medication use treated as a time-dependent covariate

^a Per 1000 person-years

compared with the non-CKD cohort. Similarly, the independent and significant association continued when medication use was treated as a time-dependent variable (model 4).

Risk factors for incident diabetes among individuals with CKD

The risk factors associated with incident diabetes among the CKD cohort (Table 3) were further analysed. Being older, living in central or southern Taiwan and having hypertension, hyperlipidaemia or gout significantly increased the likelihood of developing diabetes. Among these risk factors, the presence of hypertension represented the highest risk factor for developing incident diabetes (adjusted HR 1.682; 95% CI 1.47, 1.93) compared with those without hypertension.

Association of CKD with incident diabetes according to sex, age, frequency of medical visits and comorbidities In the analysis stratified by age, sex, annual frequency of medical visits and number of comorbidities, the adjusted HR of incident diabetes associated with CKD vs without CKD was significantly higher in people who were younger (<50 years), male, with no comorbidities and a lower frequency of medical visits (Table 4).

Sensitivity analysis Of the 2344 individuals with new-onset diabetes, none (0%) were aged <20 years and eight (0.34%) were aged <30 years at the time of onset. Therefore, the

impact of diabetes classification errors is relatively small in the present study. In addition, when the study data were reanalysed after deleting the eight individuals with diabetes diagnosed when they were aged <30 years, as well as those who received insulin as their first therapy or within a year of diagnosis, the results were similar to those in the primary analyses (Table 5).

Three levels of sensitivity testing were performed (Table 6). CKD remained a significant risk factor for incident diabetes even when censoring individuals or using time-dependent Cox regression models for those with CKD whose renal status had changed. In addition, the significant association between CKD and diabetes remained when the diabetes diagnosis was defined by three or more ICD-9 codes.

Discussion

Using the well-established, large dataset of the Taiwan NHIRD, it was found that CKD was a significant risk factor for the development of incident diabetes, after adjusting for various well-known risk factors. In subgroup analyses, the risk of incident diabetes associated with CKD was significant in both sexes and in all age groups, while the risk was higher in younger people (<50 years) and in men, compared with their respective counterparts. In the CKD cohort, being older, living in central or southern Taiwan, or having hypertension, hyperlipidaemia or gout, significantly increased the likelihood of developing diabetes. Among these risk factors, the presence of hypertension was associated with the highest risk of developing incident diabetes (adjusted HR 1.682; 95% CI 1.47, 1.93) compared with no hypertension.

CKD is a well-known complication of diabetes; however, it is not clear whether CKD is associated with impaired glucose and insulin homeostasis, ultimately resulting in overt diabetes. CKD is reportedly complicated by insulin resistance, which is a key determinant of the onset and progression of diabetes. However, data regarding the association of insulin sensitivity with kidney function are not consistent. People with ESRD had substantially reduced insulin sensitivity compared with healthy control individuals [16]. In a community-based cohort study of 4680 older adults with a normal mean estimated glomerular filtration rate (eGFR) (72.2 ml min⁻¹ 1.73 m⁻²), Pham et al reported that lower eGFR was associated with higher fasting insulin concentrations and a lower insulin sensitivity index [17]. In another community-based cohort study in Sweden of 1015 non-diabetic men aged 70–71 years with a median eGFR of 61.3 ml min⁻¹ 1.73 m⁻², insulin sensitivity was negatively correlated with kidney function quartiles [18]. By contrast, the prevalence of insulin resistance did not differ between people with CKD and BMI-matched control individuals, and insulin resistance was correlated with BMI and fat mass, but not with eGFR, in a study of 95 non-diabetic people

Table 3 Analyses of risk factors by Cox proportional hazards model for incident diabetes in the CKD cohort

Covariate	Adjusted HR (95% CI)	<i>p</i> value
Age (per year)	1.009 (1.00, 1.01)	<0.0001
Male sex	1.010 (0.90, 1.13)	0.8718
Charlson's comorbidity index		
0	1	
1–2	1.051 (0.93, 1.18)	0.4086
≥3	0.794 (0.63, 1.01)	0.0569
Monthly income (NTD)		
<15,840	1	
15,840–25,000	0.944 (0.83, 1.07)	0.3656
>25,000	0.876 (0.74, 1.03)	0.1121
Frequency of medical visits	1.003 (0.99, 1.01)	0.0937
Geographical location		
Northern Taiwan	1	
Central Taiwan	1.243 (1.07, 1.44)	0.0041
Southern Taiwan	1.203 (1.06, 1.37)	0.0047
Eastern Taiwan and islands	1.384 (0.97, 1.97)	0.0699
Hypertension	1.682 (1.47, 1.93)	<0.0001
Hyperlipidaemia	1.418 (1.20, 1.67)	<0.0001
Gout	1.331 (1.13, 1.57)	0.0008
Ischaemic heart disease	1.123 (0.94, 1.34)	0.2050
Congestive heart failure	1.303 (1.00, 1.70)	0.0501
Obesity	2.258 (0.96, 5.30)	0.0615
Cerebrovascular disease	0.809 (0.64, 1.03)	0.0813
Rheumatoid disease	0.628 (0.26, 1.54)	0.3083

All analyses considered death as a competing risk

NTD, New Taiwan Dollar

with stage 3–4 CKD [12]. Beyond low eGFR, alternative candidate factors associated with insulin resistance include mineral metabolism disorders, vitamin D deficiency, acid-base imbalance, medications, physical activity, lifestyle factors, body composition and diet [19].

The balance between beta cell function and insulin resistance is one of the key determinants of glucose homeostasis. In a longitudinal follow-up study of older US adults, beta cell function was increased in the presence of increased insulin resistance inherent to CKD, and the risks of glucose intolerance and incident diabetes were not increased [17]. Similar results were also confirmed by Jia et al, who reported that the net balance between insulin sensitivity and beta cell function was preserved [18]. In those on dialysis, increased beta cell function was observed compared with healthy individuals [20]. By contrast, a study of moderate-to-severe CKD showed that the combination of insulin resistance and inadequate augmentation of insulin secretion led to a high prevalence of impaired glucose tolerance in 65% of study participants with CKD [19]. Sahakyan et al also reported a positive relationship

between serum cystatin C levels and the incidence of type 2 diabetes, independent of confounding risk factors, over a 15 year follow-up period [7]. As these varied results suggest, there are contradicting opinions on whether CKD significantly contributes to the development of diabetes.

There are important differences between risk factors and causal factors. The former may be identified by epidemiological studies, while the latter can only be determined from randomised controlled trials. Observational epidemiological studies are subject to various biases and reverse causation due to unmeasured confounding, while randomised controlled trials cannot be performed to examine genetic factors [21]. Using validated genetic variants from previous studies, the Mendelian randomisation approach has recently been widely used to determine causal inference for diseases. Using an established type 2 diabetes-genetic risk score for Mendelian analysis, Xu et al demonstrated for the first time a causal association between type 2 diabetes and CKD in a Chinese population of 11,502 residents in one community [22]. However, it is not clear whether there is bidirectional causality between CKD and type 2 diabetes. Whether the association between CKD and incident diabetes is causal or non-causal may be examined using the Mendelian randomisation approach and a CKD-genetic risk score as the instrumental variable against diabetes.

The strengths of the present investigation included the enrolment of a large nationwide population of individuals with diverse CKD stages, which allows the application of our results to all people with CKD; a long period of longitudinal follow-up, which allowed for tracking of all the incident diabetes events up to 13 years; a representative sample of the entire Taiwanese population, with minimal selection bias as the NHI system covers ~99% of the Taiwanese population; and a homogeneous ethnic population, as >98% of Taiwanese people are of Chinese Han ethnicity. Moreover, the number of annual medical visits for both cohorts was adjusted, as the CKD cohort might have made more visits compared with the non-CKD cohort, and detection bias may exist due to early detection of diabetes events in the CKD cohort. The adjusted HR of incident diabetes for CKD vs non-CKD remained statistically significant after taking the number of annual medical visits into account. This result indicates that the association between CKD and incident diabetes was not merely due to the early detection of diabetes events in the CKD cohort.

There were also several limitations to the present study. First, because laboratory data were not available from the claims data there might have been more prediabetic people at baseline in the CKD group, which would explain the association during follow-up. Second, within the database there is a lack of information on dietary habits, physical activity, BMI and family history, which are all known risk factors that influence the development of diabetes. Obesity is the most

Table 4 Association of CKD with incident diabetes, stratified by sex, age, annual frequency of medical visits and comorbidities

Subgroup	Non-CKD cohort		CKD cohort		CKD vs non-CKD				
	<i>n</i>	No. of events	<i>n</i>	No. of events	Adjusted HR (95% CI) ^a	<i>p</i> value	Adjusted HR (95% CI) ^b	<i>p</i> value	<i>p</i> _{interaction}
Age, years									
<50	6587	315	6586	435	1.419 (1.23, 1.64)	<0.0001	1.338 (1.16, 1.55)	<0.0001	0.0444
≥50	8816	745	8817	849	1.187 (1.08, 1.31)	0.0007	1.152 (1.04, 1.27)	0.0050	
Sex									
Female	6569	471	6569	541	1.196 (1.06, 1.35)	0.0046	1.148 (1.02, 1.30)	0.0276	0.2592
Male	8834	589	8834	743	1.306 (1.17, 1.46)	<0.0001	1.254 (1.13, 1.40)	<0.0001	
Comorbidity									
No	8142	397	7608	500	1.423 (1.25, 1.63)	<0.0001	1.321 (1.16, 1.51)	<0.0001	0.0335
Yes	7261	663	7795	784	1.156 (1.04, 1.28)	0.0063	1.129 (1.02, 1.25)	0.0211	
Annual frequency of medical visits									
≤12	4261	241	4227	318	1.398 (1.18, 1.65)	<0.0001	1.289 (1.09, 1.52)	0.0029	0.1259
>12	11,142	819	11,176	966	1.214 (1.11, 1.33)	<0.0001	1.172 (1.07, 1.29)	0.0008	

All analyses considered death as a competing risk

^a Model was adjusted for all variables listed in Table 1 (model 3)

^b Model was adjusted for all variables listed in Table 1 and medication use as a time-dependent covariate (model 4)

important contributory factor as it can lead to insulin resistance [23]. People with CKD were found to be more likely to have a lower BMI compared with control individuals [19, 24]. Therefore, if CKD is associated with incident diabetes, adjustment for BMI might increase the HR and further strengthen the results. Third, the diagnosis of CKD defined by the study criteria encompassed a variety of diverse CKD entities, and each different disease entity has its unique

pathophysiology and mechanisms of aetiology and outcomes. Different CKD categories may have a distinct impact on the risk of diabetes. It is not possible to solve this problem using the Taiwan NHIRD because of technical limitations. Fourth, the underlying biological mechanisms explaining the association of CKD with incident diabetes cannot be addressed by the present study because of the retrospective design and the registry data used. Fifth, misclassification of medical

Table 5 Risk of diabetes according to age and insulin use

Variable	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	<i>p</i> value	Adjusted HR (95% CI)	<i>p</i> value	Adjusted HR (95% CI)	<i>p</i> value	Adjusted HR (95% CI)	<i>p</i> value
Excluding those with diabetes onset at age <30 years								
Non-CKD cohort	Reference		Reference		Reference		Reference	
CKD cohort	1.25 (1.15, 1.36)	<0.0001	1.25 (1.15, 1.36)	<0.0001	1.26 (1.16, 1.36)	<0.0001	1.20 (1.11, 1.30)	<0.0001
Excluding those with diabetes onset at age <30 years and those who received insulin as their first treatment								
Non-CKD cohort	Reference		Reference		Reference		Reference	
CKD cohort	1.24 (1.14, 1.35)	<0.0001	1.24 (1.14, 1.35)	<0.0001	1.25 (1.15, 1.35)	<0.0001	1.20 (1.10, 1.30)	<0.0001
Excluding those with diabetes onset at age <30 years and those used insulin within a year of diagnosis								
Non-CKD cohort	Reference		Reference		Reference		Reference	
CKD cohort	1.24 (1.14, 1.34)	<0.0001	1.24 (1.14, 1.34)	<0.0001	1.24 (1.14, 1.35)	<0.0001	1.20 (1.10, 1.30)	<0.0001

All analyses considered death as a competing risk

Model 1, unadjusted model; model 2, adjusted for propensity score; model 3, adjusted for all variables listed in Table 1; model 4, adjusted for all variables listed in Table 1 and medication use treated as a time-dependent covariate

Table 6 Sensitivity analyses

Variable	Adjusted HR (95% CI) ^a	<i>p</i> value	Adjusted HR (95% CI) ^b	<i>p</i> value
Censoring those with changed renal status				
Non-CKD cohort	1		1	
CKD cohort	1.276 (1.18, 1.39)	<0.0001	1.223 (1.13, 1.33)	<0.0001
Time-dependent Cox regression for change in renal status				
Non-CKD cohort	1		1	
CKD cohort	1.309 (1.21, 1.42)	<0.0001	1.252 (1.15, 1.36)	<0.0001
Diabetes diagnosis on basis of ≥3 ICD-9 codes				
Non-CKD cohort	1		1	
CKD cohort	1.366 (1.28, 1.46)	<0.0001	1.314 (1.23, 1.40)	<0.0001

All analyses considered death as a competing risk

^a Model was adjusted for all variables listed in Table 1 (model 3)

^b Model was adjusted for all variables listed in Table 1 and medication use as a time-dependent covariate (model 4)

comorbidities is possible because the diagnoses were based on ICD-9 codes. However, many high-quality studies using the NHIRD have validated the use of the ICD-9 for identifying medical comorbidities [25–27]. The Taiwan NHI Bureau also reviews the medical charts, including the coding of medical illnesses, and imposes heavy fines on institutions with inappropriate charges. In addition, a previous epidemiological study of CKD in Taiwan confirmed that the high prevalence of CKD based on claims data in large administrative datasets provided a reasonable explanation for the subsequent epidemic of ESRD [28]. In the present study the diagnosis of incident diabetes required both the associated ICD-9 codes and a new prescription for glucose-lowering agents; this method was used in previous studies to enhance the diagnostic accuracy. Therefore, we believe that the finding of a positive association between CKD and diabetes is valid.

The development of glucose intolerance or overt diabetes in CKD relies on a combination of factors including insulin resistance, renal insulin clearance, augmented beta cell function, CKD-specific factors (e.g. low eGFR, mineral metabolism disorder), lifestyle factors, the use of specific medications and renal gluconeogenesis. In conclusion, the present national cohort study suggests that CKD is positively associated with incident diabetes, particularly in those living in central or southern Taiwan, who are older and have hypertension, hyperlipidaemia or gout. People with CKD and hypertension had the highest risk of developing incident diabetes. As diabetes has an unfavourable effect on an individual's health, increased medical attention should be paid to those with CKD, especially if they have any of the identified risk factors, in an attempt to prevent the onset of incident diabetes and enable its early detection.

Data availability Data may be obtained from the NHIRD released by the NHI Bureau of Taiwan. Owing to the Personal Information Protection Act implemented by the Taiwanese Government in 2012, the data used in this study may not be made publicly available in manuscripts, supplementary

documents or public repositories. Further information on data acquisition is available at the NHIRD website (<http://nhird.nhri.org.tw>) or via email to nhird@nhri.org.tw.

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