Diabetes and End-Stage Renal Disease Synergistically Contribute to Increased Incidence of Cardiovascular Events: A Nationwide Follow-up Study During 1998–2009

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OBJECTIVE

This study aimed to investigate the effect of interaction of diabetes and end-stage renal disease (ESRD) on the risks of cardiovascular (CV) events.

RESEARCH DESIGN AND METHODS

By using two representative national cohorts, we determined the age- and sex-specific incidences and 20-year risks of incident CV events, including acute myocardial infarction (AMI), stroke, and congestive heart failure (CHF), stratified by the presence of diabetes, de novo diabetes after ESRD, or ESRD. Individuals were excluded if age <18 years or if previous CV events or malignancies were present before enrollment. Cox proportional hazards models were also constructed with adjustments for competing risk of mortality.

RESULTS

A total 648,851 non-ESRD individuals and 71,397 ESRD patients, including 53,342 and 34,754 diabetic patients, respectively, were followed up during 1998–2009. A monotonic risk pattern of CV-related incidences was noted with the presence of diabetes, ESRD, or both, respectively, after stratification by age and sex. De novo diabetes showed similar increased risks for CV incidences, especially AMI and stroke. There is a multiplicatively synergistic effect of diabetes and ESRD for CV-related risks, especially for AMI and stroke, of which the adjusted hazard ratios (aHRs) were 5.24 (95% CI 4.83–5.68) and 2.43 (2.32–2.55), respectively, in comparison with people without diabetes or ESRD; de novo diabetes after ESRD had similar effects with aHRs of 4.12 (3.49–4.87) and 1.75 (1.57–1.95), respectively.

CONCLUSIONS

Diabetes and ESRD synergistically increase risks of CV events. Proactive screening and control for diabetes in patients with ESRD should be built into our daily practice.

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In recent years, noncommunicable diseases (NCDs) are becoming responsible for more morbidity and premature death than communicable disease worldwide (1), and this has lead to enormous losses of human capital and high health care expenditure. It is estimated that cardiovascular (CV) disease and diabetes together will reduce global gross domestic product by 5% in 2015 (1). Chronic kidney disease (CKD), another NCD, is also prevalent worldwide (2,3), and its most severe form, end-stage renal disease (ESRD), accounts for ~2–6% of the global annual health care budget, although affected patients represent only 0.02–0.2% of the total population (4,5). More efforts should thus be expended on controlling NCDs, including diabetes, ESRD, and the related complications. This is not only a health care issue but also a financial one, especially for countries that have a policy of universal health care coverage, such as Taiwan.

In fact, CV disease is a frequent complication of ESRD and diabetes and is responsible for high mortality and morbidity in these two patient populations (6–9). Although considerable resources have been spent on efforts to reduce the incidence of CV events in patients with diabetes and ESRD in recent decades, such individuals still face poor outcomes of CV events compared with the general population (10,11). To date, most previous studies exploring CV events in ESRD patients have been based on mortality rates rather than counting the new incidence of CV events (5,11–13), which usually underestimate such events because of coding only one underlying cause of death (14). Furthermore, data on the excess risks of combination of diabetes or de novo diabetes after ESRD and ESRD on the composite or different types of CV events, which are important for designing primary prevention strategies, are limited. In this study, we aimed to determine and compare the age- and sex-specific incidence rates and hazard ratios of individual CV events, including acute myocardial infarction (AMI), stroke, and congestive heart failure (CHF) or the composite CV events (either AMI, stroke, or CHF), among patients with or without diabetes, de novo diabetes after ESRD, or ESRD who never had a previous CV event, by using two sets of national cohorts derived from the National Health Insurance (NHI) Research Database in Taiwan. We also estimated the 20-year risks of various CV events by calculating their cumulative incidence rates (CIRs) for patients at various age intervals.

RESEARCH DESIGN AND METHODS

Sources of Data Files

This study was approved by the ethics review board of the National Cheng Kung University Hospital (A-ER-101-089). This work uses the data collected from the reimbursement records of the NHI program in Taiwan, in which the personal identification information is encrypted, and these data are maintained by the National Health Research Institutes for research purposes (15). The NHI has been established since March 1995 and covered >98% inhabitants in Taiwan (16). Most importantly, the NHI has a list of catastrophic illnesses, of which all registered cases are waived for all copayment, and ESRD is included as one of them. In this study, two sets of databases were used for analysis. The first one originated from the representative database of 1 million beneficiaries, named by Longitudinal Health Insurance Database 2000, which was constructed by systematic sampling from >23 million beneficiaries within the registry during 1996–2000. There were no statistically significant differences in sex and age distribution, as reported by the National Health Research Institutes (15). The second is a specific database that recruited all ESRD patients who started maintenance dialysis during 1998–2009. Individuals would be recognized as patients on maintenance dialysis if they had the order codes directly related to hemodialysis and peritoneal dialysis in their inpatient or ambulatory care for more than three consecutive months. Both databases contained detailed information of each enrolled individual about the date of admission or discharge, time of visits for ambulatory care, and up to five hospital discharge or three ambulatory care diagnostic codes (in accordance with the regulations of the ICD-9) when he or she sought medical services. Besides, peer reviews of randomly selected cases and concomitant penalties for any false reports provide support for the accuracy of this data claim system, and it has been used in a number of high-quality research projects (17–19).

Study Design and Identification of the Study Population

To identify new-onset CV events, including AMI, stroke, and CHF, we excluded patients with previous diagnoses of AMI (coded as ICD-9 410.X), stroke (ICD-9 430–438), and CHF (ICD-9 398.91, 425, 428, 402.X1, 404.X1, and 404.X3) before 1998 or before the diagnosis of diabetes or ESRD. To ensure the above requirements, we examined the inpatient claim data for 1997 and 1998 for each study subject in the non-ESRD cohort and before the enrolled date of identified individuals in the ESRD cohort. We also excluded individuals aged <18 years at enrollment. Those who received maintenance dialysis during 1998–2009 were also excluded in the non-ESRD cohort. Moreover, we excluded individuals who had been admitted to hospital for malignancy (ICD-9 140–208, 230–234, and V10) in the period 1996–1997 or before the identification of diabetes or dialysis to avoid confounding in the results. ICD-9 codes 250, 357.2, 362.0X, and 366.41 were included as diabetes-related diagnoses. Patients were thus recognized as having diabetes if any of these codes were found in their discharge summary or if they had two separate ambulatory care visits for diabetes-related diagnoses within 1 year and the interval between these two visits was >30 days apart. In the Longitudinal Health Insurance Database 2000, individuals with newly diagnosed diabetes during 1998–2009 were classified into the diabetes/non-ESRD group. The onset of diabetes in this group was recorded as the date of the first visit for diabetes care during 1998–2009. Individuals without any diabetes-related diagnoses during the follow-up period were classified into the nondiabetes/non-ESRD group. In the ESRD cohort, patients with diabetes-related diagnoses before or after initiating dialysis were classified into the diabetes/ESRD and de novo diabetes/

ESRD groups, respectively, in order to more specifically identify the effects of prevalent or incident diabetes with regard to further CV risks. The detailed enrollment process used for our study cohort is shown in Fig. 1.

End Point of the Study

We defined a new diagnosis of any of AMI, stroke, or CHF from the inpatient claim data as the end point of the follow-up of composite CV events. The date of reaching the end point would be the first day of hospitalization. However, subjects with any one or two of the above three diagnoses were still considered eligible for follow-up with regard to the development of the other event(s) in the period 1998–2009. The inpatient claims contain the data of date of birth, sex, geographic area, dates of admission and discharge, a maximum of five leading discharged diagnoses, and up to four operation procedure codes, which make such observations possible. The total follow-up period was 12 years, from 1 January 1998 to 31 December 2009. The date of censoring would be the end of the study (31 December 2009) or the date of last withdrawal from the NHI. We defined the date of mortality as the individual withdrew from the NHI program due to death in non-ESRD population and one month after the last medical visit in ESRD population if they stopped receiving medical services from the NHI.

Identification of Comorbidities and Other Data

We identified the following major comorbidities as risk factors for our study subjects: CKD (ICD-9 016.0, 095.4, 189.0, 189.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403.X1, 404.X2, 404.X3, 440.1, 442.1, 447.3, 572.4, 580–588, 591, 642.1, 646.2, 753.12–753.17, 753.19, 753.2, and 794.4), liver disease (ICD-9 570, 571, and 572.4), hypertension (ICD-9 401–402 and 405), anemia (ICD-9 280–285), hyperlipidemia (ICD-9 272.0–272.4), coronary artery disease (ICD-9 414.8 and 414.9), chronic obstructive pulmonary disease (ICD-9 491–494, 496, and 510), gastrointestinal bleeding (ICD-9 456.0–456.2, 530.7, 531–534, 569.84, 569.85, and 578), peripheral artery occlusive disease (ICD-9 440–444, 447, and 557), and malignancy. Patients would be treated as having a comorbidity if any of these diseases occurred before censoring or the development of the CV events of interest. The age of each individual was calculated by the difference between the index date and the date of birth.

Statistical Methods

The estimation of the age- and sex-specific incidence rates of newly developed CV events (AMI, stroke, and CHF or composite events) was determined by the Poisson assumption or accumulated follow-up person-years. CIRs between indicated age intervals ($CIR_{t1–t2}$) were calculated to estimate the occurrence of CV events in non-ESRD and ESRD patients with or without diabetes by using the following formula: $CIR_{t1-t2} = 1 - e^{-\Sigma_1(IRi)(ti)}$ (20,21). For example, $CIR_{40–59}$ indicates the CIR of target events in individuals survived from 40 to 59 years of age. The Kaplan-Meier method was performed to reveal the CV event–free survival rate, and we selected the log-rank test to examine whether there were any differences in the risk of CV events in the five study groups. Since patients under dialysis are at much higher risk of mortality than is the general population (22), we might overestimate the CV-related risks if the computation does not account for competing risk of death. Thus, we analyzed the risks of CV diseases by CIR and Cox proportional hazards model after allowing for competing risk of death. Most statistical analyses were performed with SAS, version 9.2 (SAS Institute, Cary, NC), except the analysis

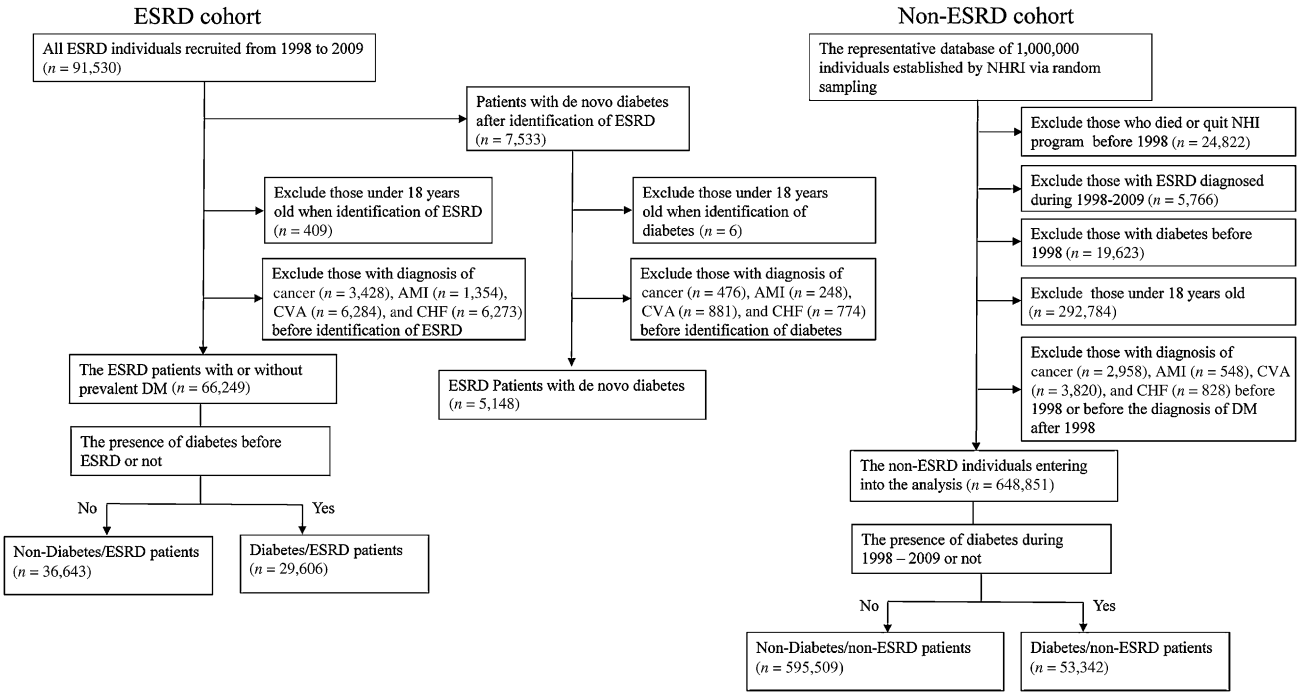

Figure 1—Flowchart of the establishment of the cohort in this study. CVA, cerebrovascular accident; DM, diabetes.

of the Kaplan-Meier estimates, competing risk-adjusted CIRs, and Cox proportional hazards model, which were carried out by the R statistical program. A P value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of the Study Subjects

A total of 648,851 non-ESRD individuals and 71,397 ESRD patients including 53,342 and 34,754 prevalent and incident diabetic patients, respectively, were enrolled into the final analysis. The median follow-up periods were 12.0, 4.9, 3.7, 2.4, and 1.7 years in the nondiabetes/non-ESRD, diabetes/non-ESRD, nondiabetes/ESRD, diabetes/ESRD, and de novo diabetes/ESRD groups, respectively. Table 1 reveals the demographic characteristics and the comorbidities in the population when considering the composite CV events as the end point. Because we are estimating the incidence rates for AMI, stroke, and CHF, there are minor differences in counting the presence of comorbidities for the above three specific events. The prevalence rates of comorbidities for various CV outcomes are summarized in Supplementary Tables 1–3. ESRD patients were found to show higher proportions of hypertension, anemia, gastrointestinal bleeding, and peripheral artery disease than non-ESRD individuals, while diabetic patients showed higher proportions of hyperlipidemia among the five study populations (Table 1).

Incidence Rates and 20-Year Risks of Composite or Separate CV Events in the Stratified Populations

The age- and sex-specific incidence rates and CIRs with various age intervals of each CV event are presented in Table 2. For AMI, the crude incidence rates of men were 0.67, 2.97, 6.63, 18.72, and 20.97 per 1,000 person-years in the nondiabetes/non-ESRD, diabetes/non-ESRD, nondiabetes/ESRD, diabetes/ESRD, and de novo diabetes/ESRD groups, respectively, while the corresponding figures for women were 0.19, 1.54, 2.88, 16.46, and 14.87. The incidence rates generally increase along with age. However, the increased risks in patients with diabetes and/or ESRD for AMI diminished as people aged. For example, within the 18- to 39-year-old male group, individuals in the diabetes/non-ESRD, nondiabetes/ESRD, diabetes/ESRD, and de novo diabetes/ESRD groups were associated with 8.13-, 10.47-, 65.33- and 69.80-fold increases in incidence rates compared with the nondiabetes/non-ESRD groups. However, when individuals were >80 years old, diabetes, ESRD, the presence of both, or de novo diabetes/ESRD only increased the risks by 1.44-, 3.56-, 6.34-, and 7.46-fold, respectively. Similar findings were also observed among the females, and such a trend also persisted for stroke and CHF. Moreover, the magnitude of the increased risk of AMI and stroke among patients in the diabetes/ESRD group is almost equal or even higher than the direct multiplication product of the associated risks of two factors independently, except in subjects aged <40 years. This implies that the disease processes of diabetes and ESRD may independently and synergistically contribute to the occurrence of AMI and stroke. A similar phenomenon could also be observed in the de novo diabetes/ESRD group after stratification by age (Table 2). In contrast, this synergistic and multiplicative effect was attenuated upon analysis of the risk of CHF.

To estimate the effect of diabetes and ESRD on risks of CV events, we calculated the CIR within specific time intervals, which assumed that the interested subjects had not died of

Table 1—Demographic and clinical characteristics of ESRD and non-ESRD populations stratified by diabetes

	Non-ESRD		ESRD			
Categories	Nondiabetes	Diabetes	Nondiabetes	Diabetes	De novo diabetes	*P*
Age (years), *n*						<0.0001
18–39	363,185	5,521	5,567	1,072	205	
40–49	110,223	11,397	6,932	3,607	640	
50–59	51,483	15,233	6,903	7,860	1,351	
60–69	38,785	11,868	7,160	8,929	1,320	
70–79	23,866	7,403	7,192	6,530	1,239	
≥80	7,967	1,920	2,889	1,608	393	
Sex, *n*						<0.0001
Male	303,272	27,930	17,256	15,189	2,547	
Female	292,237	25,412	19,387	14,417	2,601	
Comorbidities (%)						
CKD	2.98	16.11	100	100	100	<0.0001
Liver disease	8.92	28.77	16.80	16.51	17.41	<0.0001
Hypertension	15.99	56.78	71.40	88.14	81.50	<0.0001
Anemia	3.29	5.38	43.18	29.31	33.76	<0.0001
Hyperlipidemia	8.18	51.70	23.10	47.41	40.10	<0.0001
Coronary artery disease	3.36	13.97	14.11	21.63	21.91	<0.0001
Chronic obstructive pulmonary disease	9.13	20.34	17.02	17.46	19.10	<0.0001
Gastrointestinal bleeding	15.00	28.17	34.19	35.09	39.51	<0.0001
Peripheral vascular disease	1.82	6.59	12.33	16.64	20.90	<0.0001
Cancer	5.13	6.41	11.18	6.61	5.92	<0.0001
Total subjects, *n*	595,509	53,342	36,643	29,606	5,148	

Table 2—Incidence rates (per 1,000 patient-years) of AMI, stroke, and CHF in the study population stratified by ESRD and diabetes

	Non-ESRD						ESRD								
	Nondiabetes			Diabetes			Nondiabetes			Diabetes			De novo diabetes		
Variables	AMI	Stroke	CHF	AMI	Stroke	CHF	AMI	Stroke	CHF	AMI	Stroke	CHF	AMI	Stroke	CHF
Male															
Age (years)															
18–39	0.15	0.53	0.09	1.22	2.38	0.45	1.57	7.14	7.97	9.80	27.44	12.05	10.47	31.75	5.24
40–49	0.63	2.63	0.34	1.84	6.01	1.07	3.52	12.11	7.88	10.04	38.67	16.32	8.26	33.78	12.82
50–59	1.48	6.50	0.94	2.93	11.67	2.37	6.28	16.22	11.53	17.05	50.21	19.97	20.09	45.88	14.74
60–69	2.57	13.24	2.75	3.64	20.69	4.80	8.15	27.11	15.00	22.69	53.49	24.35	24.41	65.41	23.00
70–79	3.55	21.41	7.57	5.34	28.96	9.00	14.27	27.42	25.89	27.09	53.31	33.87	30.69	54.38	21.36
≥80	5.09	27.28	15.96	7.34	43.31	19.40	18.13	10.28	37.05	32.29	44.70	56.49	37.97	43.48	30.49
$CIR_{40–59}$	0.02	0.09	0.01	0.05	0.16	0.03	0.09	0.25	0.18	0.24	0.59	0.30	0.25	0.55	0.24
$CIR_{50–69}$	0.04	0.18	0.04	0.06	0.28	0.07	0.13	0.35	0.23	0.33	0.65	0.36	0.36	0.67	0.31
$CIR_{60–79}$	0.06	0.29	0.10	0.09	0.39	0.13	0.20	0.42	0.34	0.39	0.66	0.44	0.42	0.70	0.36
Female															
Age (years)															
18–39	0.01	0.26	0.04	0.33	1.07	0.41	0.70	5.30	6.27	7.11	12.93	12.16	0.00	28.37	6.33
40–49	0.08	1.27	0.18	0.49	3.87	0.62	0.77	8.37	6.39	10.74	33.95	16.31	5.80	17.75	4.27
50–59	0.29	3.49	0.67	1.09	7.22	1.87	1.97	11.99	8.09	12.65	41.18	18.61	13.06	36.79	11.46
60–69	0.86	8.96	2.49	1.83	14.04	4.31	3.38	18.47	14.88	17.04	49.84	24.02	18.18	44.38	24.02
70–79	2.22	18.76	8.39	3.44	25.60	9.61	8.82	36.71	21.53	24.03	56.89	32.61	19.25	55.07	28.05
≥80	3.41	29.23	18.66	7.03	37.51	21.12	10.90	52.90	43.11	31.18	55.02	52.43	21.65	44.25	38.79
$CIR_{40–59}$	0.00	0.05	0.01	0.02	0.10	0.02	0.03	0.18	0.13	0.21	0.53	0.29	0.17	0.42	0.15
$CIR_{50–69}$	0.01	0.12	0.03	0.03	0.19	0.06	0.05	0.26	0.21	0.26	0.60	0.35	0.27	0.56	0.30
$CIR_{60–79}$	0.03	0.24	0.10	0.05	0.33	0.13	0.11	0.42	0.31	0.34	0.66	0.43	0.31	0.63	0.41

$CIR_{40–59,\ 50–69,\ 60–79}$: CIRs of each indicated CV events in individuals survived from 40–59, 50–69, 60–79 years of age.

other diseases during the same period of time. As most dialysis patients might be deceased within one to two decades (22), we calculated the $CIR_{40–59}$, $CIR_{50–69}$, and $CIR_{60–79}$ of each CV event, which were ~0.15–0.70 and 0.03–0.42 for subjects with and without diabetes in ESRD population, with males always higher than females. The same as before, the difference between $CIR_{40–59}$, $CIR_{50–69}$, and $CIR_{60–79}$ of each CV event between the diabetes/ESRD and de novo diabetes/ESRD groups was minimal. The event numbers of each individual CV outcome are summarized in Supplementary Table 4.

Supplementary Table 5 summarizes the age- and sex-specific incidence rates and CIRs for composite CV events of each stratified group. The CIRs of composite CV events could be up to 0.87 and 0.86 in the male and female dialysis population, respectively. It also shows the stratified rates of the first CV events for AMI, stroke, and CHF. The occurrence of strokes is the highest in all five study cohorts, even after age and sex stratification. ESRD patients seem to be prone to developing CHF first.

Adjusted Hazard Ratios and CIRs of Various CV Outcomes After Adjustment for Competing Risk of Death

During competing risk model construction, we found different magnitudes of interaction of diabetes and ESRD for various CV outcomes, and we were also interested in exploring the potential effect of de novo diabetes. Thus, we stratified the study populations into five distinctive groups. After adjustment for the effect of competing risk of mortality, the pronounced effects of age on the risks of various CV events were revealed (Table 3). The adjusted hazard ratios (aHRs) ranged from 4.28 to 36.03 among groups within different age strata. For AMI and stroke, the monotonic risk patterns presented incrementally from nondiabetes/non-ESRD, diabetes/non-ESRD, nondiabetes/ESRD, de novo diabetes/ESRD, to diabetes/ESRD groups, respectively. For composite CV events and CHF, the risk patterns were similar, but the risks of the de novo diabetes/ESRD group were less than those of the nondiabetes/ESRD group. The results of aHRs also pointed out the synergistic effect of diabetes and ESRD, while the effect was attenuated in the de novo diabetes/ESRD group.

Supplementary Table 6 reveals that patients in the diabetes/ESRD group still had the highest age- and sex-specific CIRs during the study period (1998–2009) after accounting for competing risk of death among all study subpopulations. The CIRs of various CV events in the de novo diabetes/ESRD group were usually similar or slightly higher than those of the nondiabetes/ESRD group, which might be partly attributed to the higher mortality rates (up to four- to fivefold increased risk) in the de novo diabetes/ESRD group than in the nondiabetes/ESRD group (data not shown).

The composite and each separate CV event–free rate, analyzed by the Kaplan-Meier method, are shown in Supplementary Fig. 1. There were statistically significant differences in the incidences of all three CV events among the five study cohorts ($P < 0.0001$ by log rank tests).

Table 3—aHRs (95% CI) of the proportional hazards model for AMI, stroke, CHF, and composite CV events (including AMI, stroke, and CHF) after accounting for competing risk of mortality

	Composite CV events	*P*	AMI	*P*	Stroke	*P*	CHF	*P*
Nondiabetes/non-ESRD	1.00		1.00		1.00		1.00	
Diabetes/non-ESRD	1.60 (1.54–1.66)	<0.0001	1.67 (1.51–1.84)	<0.0001	1.60 (1.54–1.67)	<0.0001	1.52 (1.41–1.65)	<0.0001
Nondiabetes/ESRD	2.27 (2.18–2.36)	<0.0001	2.72 (2.47–2.99)	<0.0001	1.63 (1.55–1.72)	<0.0001	3.72 (3.47–3.99)	<0.0001
Diabetes/ESRD	3.25 (3.12–3.39)	<0.0001	5.24 (4.83–5.68)	<0.0001	2.43 (2.32–2.55)	<0.0001	4.12 (3.85–4.41)	<0.0001
De novo diabetes/ESRD	2.19 (2.00–2.39)	<0.0001	4.12 (3.49–4.87)	<0.0001	1.75 (1.57–1.95)	<0.0001	2.25 (1.92–2.63)	<0.0001
Age (years)								
18–39	1.00		1.00		1.00		1.00	
40–49	5.17 (4.92–5.43)	<0.0001	4.59 (4.03–5.22)	<0.0001	5.63 (5.31–5.97)	<0.0001	4.28 (3.82–4.80)	<0.0001
50–59	12.46 (11.87–13.08)	<0.0001	10.35 (9.11–11.76)	<0.0001	13.96 (13.17–14.79)	<0.0001	10.12 (9.05–11.31)	<0.0001
60–69	21.78 (20.73–22.88)	<0.0001	15.33 (13.45–17.48)	<0.0001	25.11 (23.68–26.62)	<0.0001	17.97 (16.05–20.12)	<0.0001
70–79	29.73 (28.23–31.31)	<0.0001	19.04 (16.63–21.80)	<0.0001	32.55 (30.61–34.61)	<0.0001	28.51 (25.36–32.04)	<0.0001
≥80	29.08 (27.31–30.96)	<0.0001	17.28 (14.69–20.32)	<0.0001	27.29 (25.31–29.43)	<0.0001	36.03 (31.75–40.89)	<0.0001
Sex								
Male	1.39 (1.36–1.42)	<0.0001	2.21 (2.08–2.34)	<0.0001	1.38 (1.35–1.42)	<0.0001	1.05 (1.00–1.09)	0.043
Female	1.00		1.00		1.00		1.00	
Comorbidities								
Liver disease	0.78 (0.75–0.80)	<0.0001	0.64 (0.58–0.70)	<0.0001	0.78 (0.74–0.81)	<0.0001	0.90 (0.85–0.96)	0.0009
Hypertension	1.28 (1.25–1.32)	<0.0001	1.29 (1.20–1.38)	<0.0001	1.39 (1.35–1.44)	<0.0001	1.02 (0.97–1.07)	0.47
Anemia	0.91 (0.87–0.94)	<0.0001	0.86 (0.79–0.94)	<0.0001	0.88 (0.84–0.92)	<0.0001	0.99 (0.94–1.05)	0.81
Hyperlipidemia	0.85 (0.83–0.87)	<0.0001	1.19 (1.12–1.27)	<0.0001	0.77 (0.75–0.80)	<0.0001	0.89 (0.85–0.94)	<0.0001
Coronary artery disease	1.21 (1.18–1.25)	<0.0001	1.54 (1.44–1.65)	<0.0001	0.96 (0.92–0.998)	0.038	1.85 (1.75–1.95)	<0.0001
Chronic obstructive pulmonary disease	0.82 (0.80–0.84)	<0.0001	0.80 (0.75–0.86)	<0.0001	0.69 (0.67–0.71)	<0.0001	1.31 (1.24–1.37)	<0.0001
Gastrointestinal bleeding	0.75 (0.73–0.77)	<0.0001	0.73 (0.68–0.78)	<0.0001	0.73 (0.71–0.75)	<0.0001	0.88 (0.84–0.93)	<0.0001
Peripheral vascular disease	0.87 (0.83–0.90)	<0.0001	0.87 (0.79–0.96)	0.0041	0.79 (0.75–0.83)	<0.0001	1.08 (1.01–1.16)	0.017
Cancer	0.38 (0.36–0.40)	<0.0001	0.38 (0.34–0.44)	<0.0001	0.34 (0.32–0.37)	<0.0001	0.52 (0.47–0.56)	<0.0001

CONCLUSIONS

This study shows that the occurrence of diabetes and the occurrence of ESRD synergistically contribute to the increased incidence of CV events, especially for AMI and stroke, in an approximately multiplicative magnitude. For example, when the incidence rates in males aged between 50 and 59 years are considered, diabetes alone and ESRD alone elicit 1.98- and 4.24-fold increased risks of AMI, while the presence of both together is associated with an 11.52-fold increased risk (Table 2). Such a magnitude for increased risks of AMI and stroke are nearly more than a multiplicative effect, while that of CHF is slightly less than that. Since we only included newly diagnosed cases of diabetes/ESRD and stratified all the results by age, sex, and presence of diabetes and/or ESRD, these factors cannot be potential confounders to our findings. When we summarized all CV events (AMI, stroke, and CHF) together, the same trend appears to be consistently present (Supplementary Table 5). Furthermore, a monotonic increment of CV risk pattern could also be observed with the presence of diabetes, ESRD, or both even after adjustment for multiple confounding factors, including mortality, in the Cox model (Table 3). Similarly, nearly multiplicative effects of diabetes and ESRD for AMI and stroke, but not for CHF, were again found. As we included new ESRD patients with prevalent diabetes and excluded those who developed diabetes after ESRD, we might have overestimated the synergistic effect of diabetes/ESRD. We thus conducted the same estimation of incidence rates and aHRs of CV events using only ESRD patients with de novo development of diabetes. After adjustment for competing risk of death, we still detected synergistic effects for AMI and stroke, although the magnitudes were slightly lower than a multiplicative effect (Table 3). Therefore, we tentatively conclude that diabetes and ESRD work synergistically in the occurrence of CV events, while a nearly multiplicative effect could also be revealed for risks of AMI and stroke. Moreover, since the 20-year risk of a composite CV event ranged from 0.73 to 0.87 in men and 0.57 to 0.86 in women of the diabetes/ESRD or de novo diabetes/ESRD group, these numbers would be easily explained to patients in order to convince them to take preventive measures more proactively.

Diabetes is known to increase CV risks in ESRD patients (23). However, few studies have explored the effect of de novo diabetes on CV risks in ESRD patients, and our study results highlighted the heavy burden of CV events in this population (Tables 2–3 and Supplementary Table 5). The incidence rates and 20-year risks at various age intervals of all CV outcomes except CHF were similar between the diabetes/ESRD and de novo diabetes/ESRD groups, whose risks in both populations were substantially higher than those in the nondiabetes/ESRD population. Only modest reduced risk of CHF was noted in patients in the de novo diabetes/ESRD group compared with that in the diabetes/ESRD group. The slightly reduced hazard ratios in the de novo diabetes/ESRD group compared with the diabetes/ESRD group could be partially explained by the higher mortality rates in the de novo diabetes/ESRD group (data not shown). We thus propose proactive regular screening of the presence of de novo diabetes after dialysis for early glycemic control and prevention and elimination of multiple risk factors related to CV events.

From a pathophysiological point of view, diabetes and ESRD patients share many CV risk factors leading to atherosclerosis, including hypertension, hyperlipidemia, endothelial dysfunction, oxidative stress, and insulin resistance (23–25). However, some CV risk factors are unique and probably mechanistically independent in diabetic or ESRD patients, which may work synergistically to accelerate the occurrence of CV events. For example, patients with diabetes would have hyperinsulinemia and hyperglycemia, which may play a central role in the activation of local inflammatory signaling of the vasculature and subsequent atherosclerosis (26). The imbalanced calcium and phosphate metabolism in ESRD patients may induce vascular calcification and arterial stiffness, which may lead to elevated blood pressure and risk of CV events (27). Indoxyl sulfate, one of the many uremic toxins, can induce oxidative stress, impair endothelial healing ability, and associate with increased CV-related mortality (28). Hypervolemia and positive sodium balance may aggravate the development of CHF in dialysis patients (29). Furthermore, even the hemodialysis procedure itself, which can induce a repeated inflammatory response, likely predisposes dialysis patients to coronary artery disease and stroke (30). Long-term exposure to high-glucose dialysate in peritoneal dialysis patients might result in insulin resistance, obesity, and an atherogenic lipid profile, which contribute to further development of CV events (31). Therefore, the synergistic effects of these two major factors are pathophysiologically plausible and deserve further studies for prevention.

We found that young females without diabetes or ESRD are less likely to develop CV events compared with males of the same age in Taiwanese (Table 2 and Supplementary Table 5), which corroborates previous reports from Western countries (32–34). While this trend of developing CV events, especially AMI and stroke, persists for women with either diabetes or ESRD alone, strikingly, this advantage for younger women almost totally disappears for those with the combination of both illnesses (Table 2). This indicates that the possible effect of intrinsic cardioprotective factors in young females might be diminished by the combined effect of diabetes and ESRD, and more studies should be carried out to test different hypotheses related to the hormonal balance between estrogens and androgens (35–37).

Ethnicity may affect the distinct distribution and burdens of CV diseases. According to the 2012 annual report from the American Heart Association, the incidence and lifetime risk for AMI are higher than those of stroke and CHF in the general population (34). In contrast, we demonstrated that the incidence and 20-year risk of stroke are higher than those of AMI and CHF in all stratified populations (Table 3). Among these, our findings in diabetic patients are consistent with those of previous

studies that examined other ethnic Chinese populations (38). However, as 9 or 10 modifiable risk factors may contribute to ~90% of the risk of AMI and strokes (39,40), the different patterns of CV events could be more easily explained by the prevalence of different risk factors in different ethnic groups, and the prevention strategy should focus on reducing the risk factors that the local population faces, in addition to reactive control of comorbidities (Table 1).

In our study, the available results did not seem to support the multiplicative effect of diabetes and ESRD on the risk of developing CHF. Since many risk factors contribute to the occurrence of CHF, including infection, fluid overload, high salt intake, valvular heart diseases, smoking, overweight, coronary artery disease, medications used, etc., such a complex network between these factors cannot simply be explained by diabetes and ESRD and finally revealed the attenuated effect of diabetes and ESRD in synergy for the risk of developing CHF.

This study has the following limitations. First, since the NHI Research Database did not contain any information related to the usual risk factors for CV events, such as BMI and smoking, we were unable to control for them in our data analysis. However, as patients with diagnosis of either diabetes or ESRD are commonly advised to quit smoking and maintain their ideal body weight, the magnitude of potential confounding effects might not be sufficiently large to account for the multiplicative effect of these two conditions. Second, we were unable to include individuals who died of CV disease before reaching any hospital, which might result in an underestimation of the incidence of CV events. However, as the hospitalization of those with CV events into the emergency department or ward usually did not depend on presence of diabetes/ESRD, the bias would not be a differential one and would only lead toward the null effect. Third, based on the representative national cohorts for the study, we identified that there were only 0.22% (120 of 53,342 subjects) with type 1 diabetes in our diabetes/non-ESRD group, while there were 0.38% (437 of 115,201) subjects with type 1 diabetes in the other incident ESRD cohort registered in the catastrophic illness during 1998–2009. Thus, our findings related to diabetes should be limited to type 2 diabetes.

In conclusion, the occurrence of diabetes and the occurrence of ESRD synergistically associate with increased risks of CV events and have a nearly multiplicative effect on risks of AMI and stroke. Twenty-year risks for any CV events are ~13–50% in the diabetic population and 30–87% in ESRD patients. De novo diabetes carries CV-related 20-year risks similar to those of prevalent diabetes in ESRD patients, while the risks were attenuated after accounting for the effect of death. Thus, the ongoing efforts to reduce the traditional or unique CV risk factors in diabetes and/or ESRD populations should never be overemphasized. Moreover, we recommend regular proactive screening of diabetes in ESRD patients for early intervention.

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References

1. World Health Organization. *Preventing Chronic Diseases: a Vital Investment*. Geneva, World Health Organization, 2005
2. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005; 365:331–340
3. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med 2003; 139:137–147
4. Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives - a position statement from Kidney Disease Improving Global Outcomes. Kidney Int 2007;72:247–259
5. US Renal Data System. USRDS 2011. Annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States [internet], 2011. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. Available from http://www.usrds.org/adr.htm. Accessed 2 May 2012
6. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234
7. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16: 434–444
8. Longenecker JC, Coresh J, Powe NR, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am Soc Nephrol 2002;13:1918–1927
9. Xue JL, Frazier ET, Herzog CA, Collins AJ. Association of heart disease with diabetes and hypertension in patients with ESRD. Am J Kidney Dis 2005;45:316–323
10. Fox CS, Coady S, Sorlie PD, et al. Trends in cardiovascular complications of diabetes. JAMA 2004;292:2495–2499
11. Roberts MA, Polkinghorne KR, McDonald SP, Ierino FL. Secular trends in cardiovascular mortality rates of patients receiving dialysis compared with the general population. Am J Kidney Dis 2011; 58:64–72
12. Sarnak MJ. Cardiovascular complications in chronic kidney disease. Am J Kidney Dis 2003;41(Suppl.):11–17
13. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32(Suppl. 3):S112–S119
14. Perneger TV, Klag MJ, Whelton PK. Cause of death in patients with end-stage renal disease: death certificates vs registry reports. Am J Public Health 1993;83:1735–1738

15. National Health Research Institutes. National Health Insurance Research Database [internet]. Available from http://www.nhri.org.tw/nhird/date_01.html#_edn1
16. *2001 National Health Insurance Annual Statistical Report*. Taipei, Taiwan, Bureau of National Health Insurance, 2002
17. Lai MN, Wang SM, Chen PC, Chen YY, Wang JD. Population-based case-control study of Chinese herbal products containing aristolochic acid and urinary tract cancer risk. J Natl Cancer Inst 2010;102:179–186
18. Wu CY, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JT. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. Gastroenterology 2009;137:1641–1648.e1–e2
19. Tsan YT, Lee CH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. J Clin Oncol 2012;30:623–630
20. Wang JD. *Basic Principles and Practical Applications in Epidemiological Research*. Singapore, World Scientific, 2002, p. 135–137
21. Davis W. *Cancer Registration and Its Techniques*. Lyon, International Agency for Research on Cancer, 1978, p. 162–163
22. Yang WC, Hwang SJ; Taiwan Society of Nephrology. Incidence, prevalence and mortality trends of dialysis end-stage renal disease in Taiwan from 1990 to 2001: the impact of national health insurance. Nephrol Dial Transplant 2008;23:3977–3982
23. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. Am J Kidney Dis 2000;35(Suppl. 1):S117–S131
24. Tripepi G, Mattace Raso F, Sijbrands E, et al. Inflammation and asymmetric dimethylarginine for predicting death and cardiovascular events in ESRD patients. Clin J Am Soc Nephrol 2011;6:1714–1721
25. Krzyzanowska K, Mittermayer F, Wolzt M, Schernthaner G. Asymmetric dimethylarginine predicts cardiovascular events in patients with type 2 diabetes. Diabetes Care 2007;30:1834–1839
26. Hayden JM, Reaven PD. Cardiovascular disease in diabetes mellitus type 2: a potential role for novel cardiovascular risk factors. Curr Opin Lipidol 2000;11:519–528
27. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999;99:2434–2439
28. Barreto FC, Barreto DV, Liabeuf S, et al.; European Uremic Toxin Work Group (EUTox). Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. Clin J Am Soc Nephrol 2009;4:1551–1558
29. Ritz E, Dikow R, Adamzcak M, Zeier M. Congestive heart failure due to systolic dysfunction: the Cinderella of cardiovascular management in dialysis patients. Semin Dial 2002;15:135–140
30. Cheung AK, Sarnak MJ, Yan G, et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int 2000;58:353–362
31. Prinsen BH, Rabelink TJ, Romijn JA, et al. A broad-based metabolic approach to study VLDL apoB100 metabolism in patients with ESRD and patients treated with peritoneal dialysis. Kidney Int 2004;65:1064–1075
32. Anand SS, Islam S, Rosengren A, et al.; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J 2008;29:932–940
33. Kappert K, Böhm M, Schmieder R, et al.; ONTARGET/TRANSCEND Investigators. Impact of sex on cardiovascular outcome in patients at high cardiovascular risk: analysis of the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease (TRANSCEND) and the Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET). Circulation 2012;126:934–941
34. Roger VL, Go AS, Lloyd-Jones DM, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125:188–197
35. Lam CS, Little WC. Sex and cardiovascular risk: are women advantaged or men disadvantaged? Circulation 2012;126:913–915
36. Sutton-Tyrrell K, Wildman RP, Matthews KA, et al.; SWAN Investigators. Sex-hormone-binding globulin and the free androgen index are related to cardiovascular risk factors in multiethnic premenopausal and perimenopausal women enrolled in the Study of Women Across the Nation (SWAN). Circulation 2005;111:1242–1249
37. Karakitsos D, Patrianakos AP, De Groot E, et al. Androgen deficiency and endothelial dysfunction in men with end-stage kidney disease receiving maintenance hemodialysis. Am J Nephrol 2006;26:536–543
38. Khan NA, Wang H, Anand S, et al. Ethnicity and sex affect diabetes incidence and outcomes. Diabetes Care 2011;34:96–101
39. O'Donnell MJ, Xavier D, Liu L, et al.; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112–123
40. Yusuf S, Hawken S, Ounpuu S, et al.; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–952