Diabetes with early kidney involvement may shorten life expectancy by 16 years

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This study aimed to identify the excess risks associated with diabetic patients with early kidney involvement (early diabetic kidney disease). The mortality risks of early diabetic kidney disease, defined as diabetes in early stages 1-3 chronic kidney disease (CKD), were assessed from a cohort of 512,700 adults in Taiwan participating in a health surveillance program from 1994-2008. Three related groups were identified and compared: diabetes without CKD, early diabetic kidney disease, and early CKD without diabetes. Deaths were ascertained through the National Death Registry. One-third of diabetics had early kidney disease, and approximately two-thirds of patients were classified with early CKD due to proteinuria. Patients with early diabetic kidney disease had more lifestyle risks such as inactivity or obesity, which characteristically amplified excess mortality by up to five times. The three-fold increase in all-cause mortality (hazard ratio 3.16) and a 16-year loss in life expectancy made early diabetic kidney disease a serious and yet often overlooked disease, with most patients unaware of their kidney involvement. Mortality for early diabetic kidney disease was nearly twice as high as that for early CKD (hazard ratio 2.01) or diabetes without CKD (hazard ratio 1.79). The 16-year life span loss is much worse than individually from early CKD (six years) or diabetes (ten years). Thus, identifying early proteinuria among diabetic patients and realizing the importance of reducing lifestyle risks like inactivity is a clinical challenge, but can save lives.

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Diabetes continues to be an important global health challenge despite increased public awareness, intensive monitoring, and aggressive management. The current number of more than 415 million people with diabetes estimated worldwide may increase to over 642 million by 2040.[1,2] Diabetes is associated with increased mortality and morbidity, particularly for cardiovascular disease, stroke, or renal failure, but also for several types of cancer.[3,4] Our knowledge and efforts in managing diabetes-related complications have brought about a substantial decline in their rate of occurrence in the past 2 decades,[5,6] but a large burden of disease still persists as diabetes prevalence continues to increase. The major challenge, however, is to make these patients aware of the seriousness of the condition so that early intervention is possible.

Diabetic kidney disease (DKD) is, by definition, diabetes with kidney involvement, presenting as albuminuria and/or an impaired glomerular filtration rate (GFR).[7–11] DKD, the most common cause of end-stage renal disease (ESRD), has increased by 34% in the US in the last 20 years, despite increasing use of medications that lower blood sugar or blood pressure.[10] Advanced cases of DKD are irreversible and beyond the opportunity for prevention. On the other hand, early DKD, defined as diabetes with CKD stages 1 to 3, clinically expressed as proteinuria and mild loss of kidney function, has a high chance of being medically controlled or even reversed to normal. For the medical community outside the nephrology specialty, however, there is limited vigilance to detect early DKD because its serious nature is not well-known.

With the availability of a large cohort of half a million individuals,[12] we analyzed the characteristics and mortality outcomes of early DKD. Life expectancy for individuals with DKD was then calculated and compared with that for those with "diabetes without CKD" or "CKD without diabetes." Analysis of CKD subjects from this same cohort has been reported previously.[13–15]

RESULTS

A total of 512,700 subjects were identified; among them, 27,455 (5.4%) had diabetes. One-third of those with diabetes (9067 or 33.3%) had early DKD, whereas two-thirds

Table 1 | Baseline demographics and clinical characteristics of participants by diabetes and chronic kidney disease

	Total participants	Reference population[a]	Diabetes without CKD	Early CKD[b] without diabetes	Early DKD[c]
N	512,700	434,268	18,388	50,977	9,067
Mean age (SD)	41.6 (14.0)	39.7 (12.8)	51.1 (11.8)	50.2 (16.5)	59.3 (11.7)
Age (%)					
20–39	53.1	58.3	12.9	32.4	6.9
40–59	33.2	32.5	52.8	30.9	38.5
≥60	13.8	9.2	34.3	36.7	54.6
Male (%)	49.8	49.3	52.2	52.3	54.1
Lower education level (middle school or below, %)	26.3	22.2	54.6	43.5	66.3
Chronic kidney disease (%)					
Stage 1	1.8	0	0	15.2	14.4
Stage 2	4.5	0	0	38.0	40.0
Stage 3	5.0	0	0	46.8	45.6
Total proteinuria	7.5	0	0	60.8	72.3
Trace (±)	5.6	0	0	48.2	41.1
1+	1.2	0	0	8.5	17.5
≥2+	0.8	0	0	4.1	13.8
Hypertension[d] (%)	18.0	13.7	45.5	35.5	64.6
High serum cholesterol[e] (%)	10.7	9.4	20.1	15.2	27.6
Lifestyle risk factors (anyone of the following, %)	61.8	61.9	62.6	60.5	62.6
Physical inactivity	53.5	53.9	48.5	52.1	50.8
Smoking	23.9	23.5	24.0	27.5	25.9
Drinking[f]	17.4	17.1	19.0	19.7	18.4
Obesity[g]	4.0	3.3	9.9	6.0	12.3
Unawareness of disease status	N/A	N/A	44.4	96.8	98.1

CKD, chronic kidney disease; DKD, diabetic kidney disease; N/A, not applicable.
[a]Participants with neither diabetes nor CKD.
[b]Stages 1 to 3.
[c]Diabetes with CKD stages 1 to 3.
[d]Defined as blood pressure ≥ 140/90 mm Hg, self-reported history of hypertension, or use of antihypertensive drugs.
[e]Defined as total cholesterol ≥ 240 mg/dl.
[f]Defined as regular drinking with ≥ 3 times/wk and 2 drinks/time.
[g]Defined as body mass index > 30.

(18,388 or 66.7%) had no kidney involvement. Approximately 50,977 participants (9.9%) had early CKD without diabetes, and 434,268 participants (84.7%) constituted a reference group with neither diabetes nor CKD. Their baseline characteristics are summarized in Table 1. Early DKD patients were older (mean age: 59.3 years) and 54.1% were men. Two-thirds

Table 2 | Hazard ratios for all causes and cause-specific mortality by diabetes and chronic kidney disease status

	Reference[a] *N* = 434,268		Diabetes without CKD *N* = 18,388			Early CKD without diabetes[b] *N* = 50,977			Early DKD[c] *N* = 9067		
	365.5		616.4			606.2			1182.4		
Adjusted mortality rate[d]	Deaths (n)	HR[e]	Deaths (n)	HR[e]	(95% CI)	Deaths (n)	HR[e]	(95% CI)	Deaths (n)	HR[e]	(95% CI)
All causes	**9440**	**1**	**1600**	**1.76**[d]	**(1.6, 1.9)**	**5186**	**1.58**[d]	**(1.5, 1.7)**	**2037**	**3.16**[d]	**(3.0, 3.4)**
CVD	1645	1	284	1.40[d]	(1.2, 1.7)	1329	1.74[d]	(1.6, 1.9)	431	2.78[d]	(2.4, 3.2)
Stroke	717	1	123	1.26	(0.9, 1.7)	564	1.64[d]	(1.4, 1.9)	182	2.74[d]	(2.2, 3.4)
CHD	394	1	94	1.97[d]	(1.4, 2.7)	356	2.04[d]	(1.7, 2.5)	140	3.86[d]	(3.0, 5.0)
Diabetes	154	1	335	22.8[d]	(17.2, 30.3)	164	1.87[d]	(1.3, 2.7)	533	49.66[d]	(37.6, 65.6)
Kidney diseases	67	1	28	4.69[d]	(2.6, 8.6)	269	9.56[d]	(6.4, 14.4)	121	19.79[d]	(12.4, 31.5)
All cancer	**4292**	**1**	**535**	**1.42**[d]	**(1.3, 1.6)**	**1734**	**1.28**[d]	**(1.2, 1.4)**	**441**	**1.75**[d]	**(1.5, 2.0)**
Lung cancer	948	1	93	1.02	(0.8, 1.3)	365	1.04	(0.9, 1.2)	79	1.39[d]	(1.1, 1.8)
Liver cancer	873	1	148	2.19[d]	(1.7, 2.8)	375	1.74[d]	(1.5, 2.1)	123	3.18[d]	(2.5, 4.0)
Colorectal cancer	406	1	61	1.57[d]	(1.1, 2.2)	172	1.24[d]	(1.0, 1.6)	62	2.28[d]	(1.6, 3.2)
Bladder cancer	44	1	12	1.83	(0.6, 5.4)	50	2.54[d]	(1.3, 4.9)	6	2.55	(0.9, 7.0)
Respiratory system	600	1	69	1.28	(0.9, 1.8)	422	1.42[d]	(1.2, 1.7)	105	2.46[d]	(1.9, 3.2)
Infectious disease	135	1	26	1.58	(0.8, 3.1)	85	1.59[d]	(1.1, 2.4)	24	2.34[d]	(1.2, 4.5)

CI, confidence interval; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; HR, hazard ratio.
[a]Participants with neither diabetes nor CKD.
[b]CKD stages 1 to 3.
[c]Diabetes with CKD stages 1 to 3.
[d]Expressed as per 100,000 person-years, with sex and age standardized to the 2009 Taiwanese population.
[e]Adjusted by 11 variables: age, sex, body mass index, education level, systolic blood pressure, cholesterol, smoking, drinking, physical activity, Chinese herbal medicine use, and analgesic use.

(64.6%) had hypertension, and one-quarter (27.6%) had high serum cholesterol levels. Compared with early CKD, early DKD exhibited more proteinuria as a whole (72.3% vs. 60.8%), and twice as much advanced or serious proteinuria (17.5% vs. 8.5% for 1+ and 13.8% vs. 4.1% for ≥2+). An overwhelming majority (98%) of individuals with early DKD were unaware of their kidney involvement, because a large proportion of them came from less-educated groups. The lifestyle risks of DKD subjects were more substantial than those of other groups, with more than 50% physically inactive, 25% smoking, and 10% obese.

During an average follow-up period of 8 years, a total of 18,263 deaths occurred. Age-adjusted mortality rates for early DKD participants (1182/100,000) were 3 times higher than for the reference group (365.5/100,000) (Table 2). (The Kaplan-Meier survival curve is shown in Supplementary Figure S1.) After controlling for potential confounders, when compared with the reference group, early DKD patients had a 3-fold increase in all-cause mortality (hazard ratio [HR]: 3.16; 95% confidence interval [CI]: 3.0, 3.4) compared with participants with diabetes and no CKD (HR: 1.76; 95% CI: 1.6, 1.9) or participants with early CKD and no diabetes (HR: 1.58; 95% CI: 1.5, 1.7). The increased mortality was also found for cardiovascular disease mortality, with an HR of 1.74 (95% CI: 1.6, 1.9) for early CKD without diabetes, 1.40 (95% CI: 1.2, 1.7) for diabetes without CKD, and 2.78 (95% CI: 2.4, 3.2) for early DKD. In early DKD patients, mortality for all cancers (HR: 1.75; 95% CI: 1.5, 2.0), lung cancer (HR: 1.39; 95% CI: 1.1, 1.8), liver cancer (HR: 3.18; 95% CI: 2.5, 4.0), and colorectal cancer (HR: 2.28; 95% CI: 1.6, 3.2) were all significantly increased, with greater increases than for other groups. Additional causes of increased mortality were diabetes, kidney diseases, respiratory system disorders, and infectious diseases (Table 2).

Comparison of mortality risks of early DKD with other groups

A direct comparison of mortality risks, with the use of a forest plot in Figure 1, between early DKD and early CKD without diabetes (left) or diabetes without CKD (right) yielded the following findings. All-cause mortality for early DKD was nearly twice as high compared with early CKD without diabetes (HR: 2.01) or diabetes without CKD (HR: 1.79).

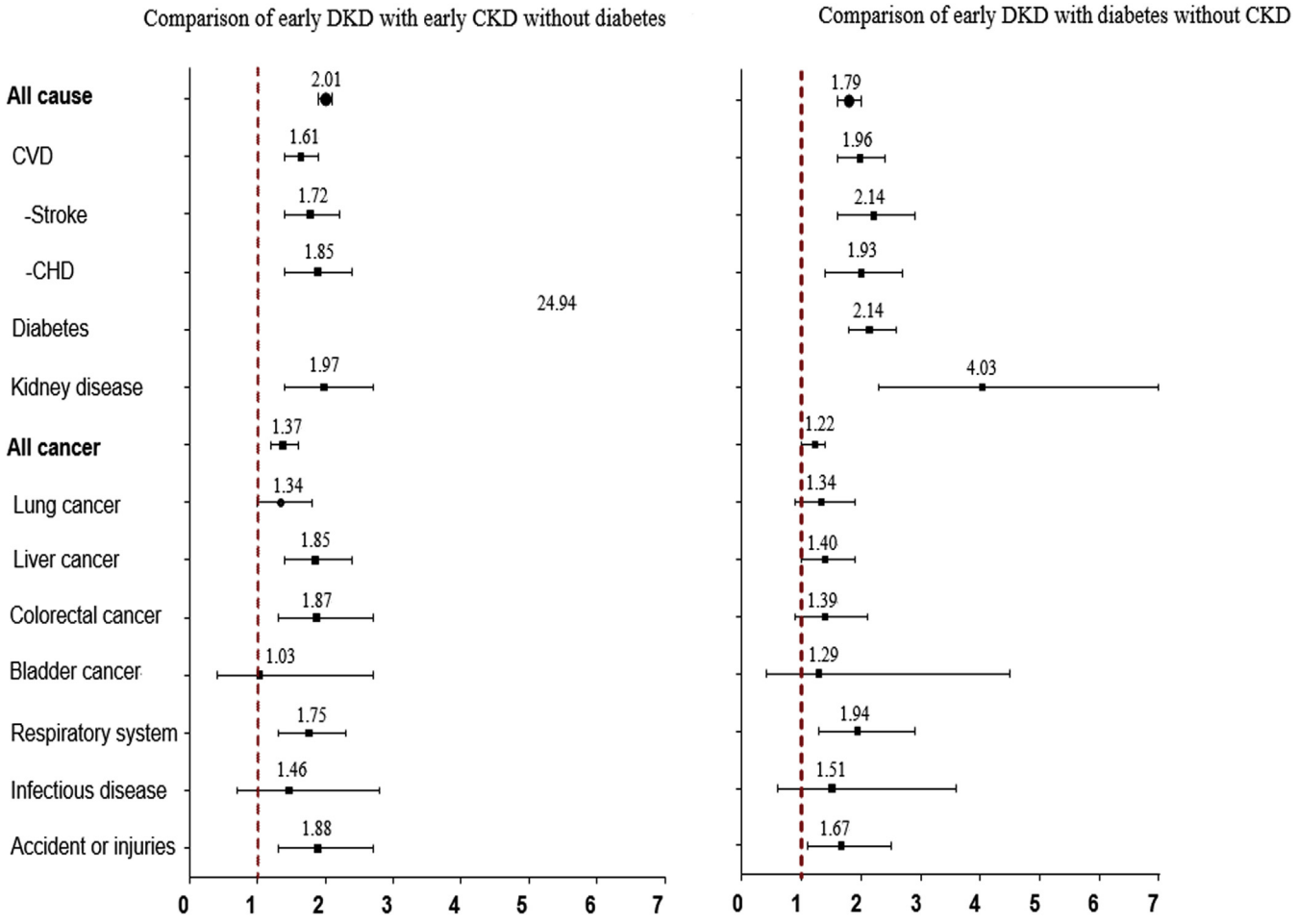


Figure 1 | Comparisons of early diabetic kidney disease (DKD) with early chronic kidney disease (CKD) without diabetes and diabetes without CKD in all-cause and cause-specific mortality risk. Hazard ratios were adjusted for 11 variables: age, sex, body mass index, education level, systolic blood pressure, cholesterol, smoking, drinking, physical activity, Chinese herbal medicine, and analgesic use. CHD, coronary heart disease; CVD, cardiovascular disease.

Cardiovascular disease mortality for early DKD was also higher (HR: 1.61 vs. 1.96), including stroke (HR: 1.72 vs. 2.14), coronary heart disease (HR: 1.85 vs. 1.93), and kidney disease (HR: 1.97 vs. 4.03). All-cancer mortality for early DKD was also significantly increased (HR: 1.37 vs. 1.22), including liver cancer (HR 1.85 vs. 1.40) and colorectal cancer (HR 1.87 vs. 1.39). These significant increases for early DKD compared with the other groups remained twice as high when DKD status was reassessed for those participants returning for second or third screenings (Supplementary Table S1).

Comparison of mortality risks on levels of estimated GFR, proteinuria, fasting glucose, and blood pressure for early DKD and other groups

For early DKD, all-cause mortality risks were significantly higher across all levels of estimated GFR (eGFR; Figure 2a), proteinuria (Figure 2b), fasting glucose (Figure 2c), and blood pressure (Figure 2d) when compared with other groups. This significantly higher mortality persisted even when levels of eGFR, proteinuria, fasting glucose, and systolic blood pressure were at normal values.

Comparison of life expectancy for early DKD and other groups

At age 30 years, the life expectancy of participants with early DKD was 14.8 years shorter for men and 16.9 years shorter for women compared with the reference group. At age 50 years, the life expectancy of participants with early DKD was 11.5 and 14.1 years shorter for men and women, respectively, compared with the reference group. In comparison, at age 30 years life expectancy was 10.2 years (men) and 11.7 years (women) shorter for the diabetes without CKD group, and 5.7 years (men) and 6.7 years (women) shorter for the CKD without diabetes group (Figure 3, Supplementary Table S2).

Interaction of early DKD with lifestyle risks

Four lifestyle risk factors—physical inactivity, smoking, drinking and obesity—were more prevalent among

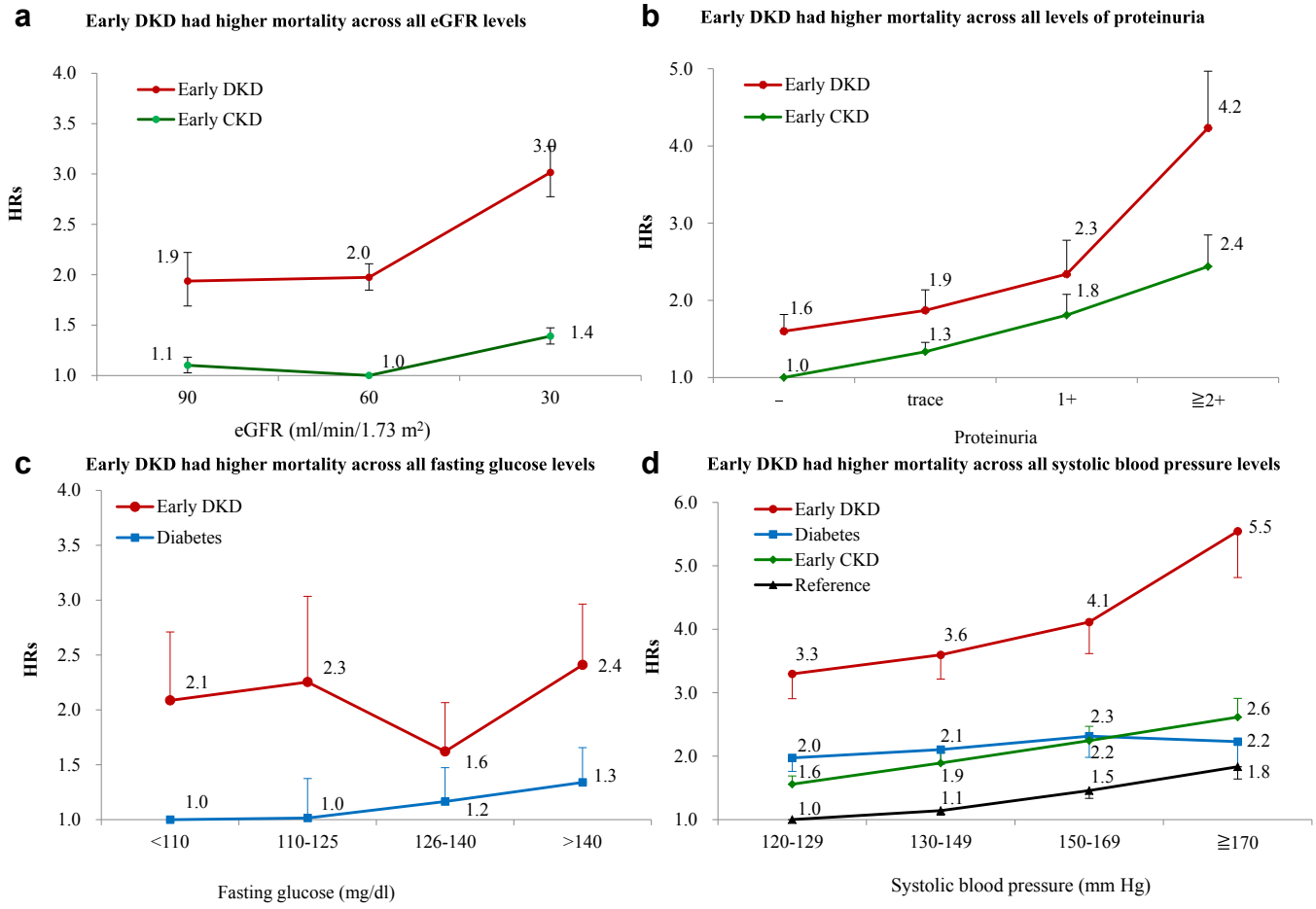


Figure 2 | Hazard ratios (HRs) of early diabetic kidney disease (DKD) for all-cause mortality by (a) estimated glomerular filtration rate (eGFR) levels, (b) proteinuria levels, (c) fasting glucose levels, and (d) systolic blood pressure levels. The reference group consisted of participants with neither diabetes nor chronic kidney disease (CKD). Early CKD was defined as CKD stages 1 to 3 without diabetes. Diabetes was defined as diabetes without CKD. Early DKD was defined as diabetes with early CKD stages 1 to 3. HRs were adjusted for 11 variables: age, sex, body mass index, education level, systolic blood pressure, cholesterol, smoking, drinking, physical activity, Chinese herbal medicine use, and analgesic use.

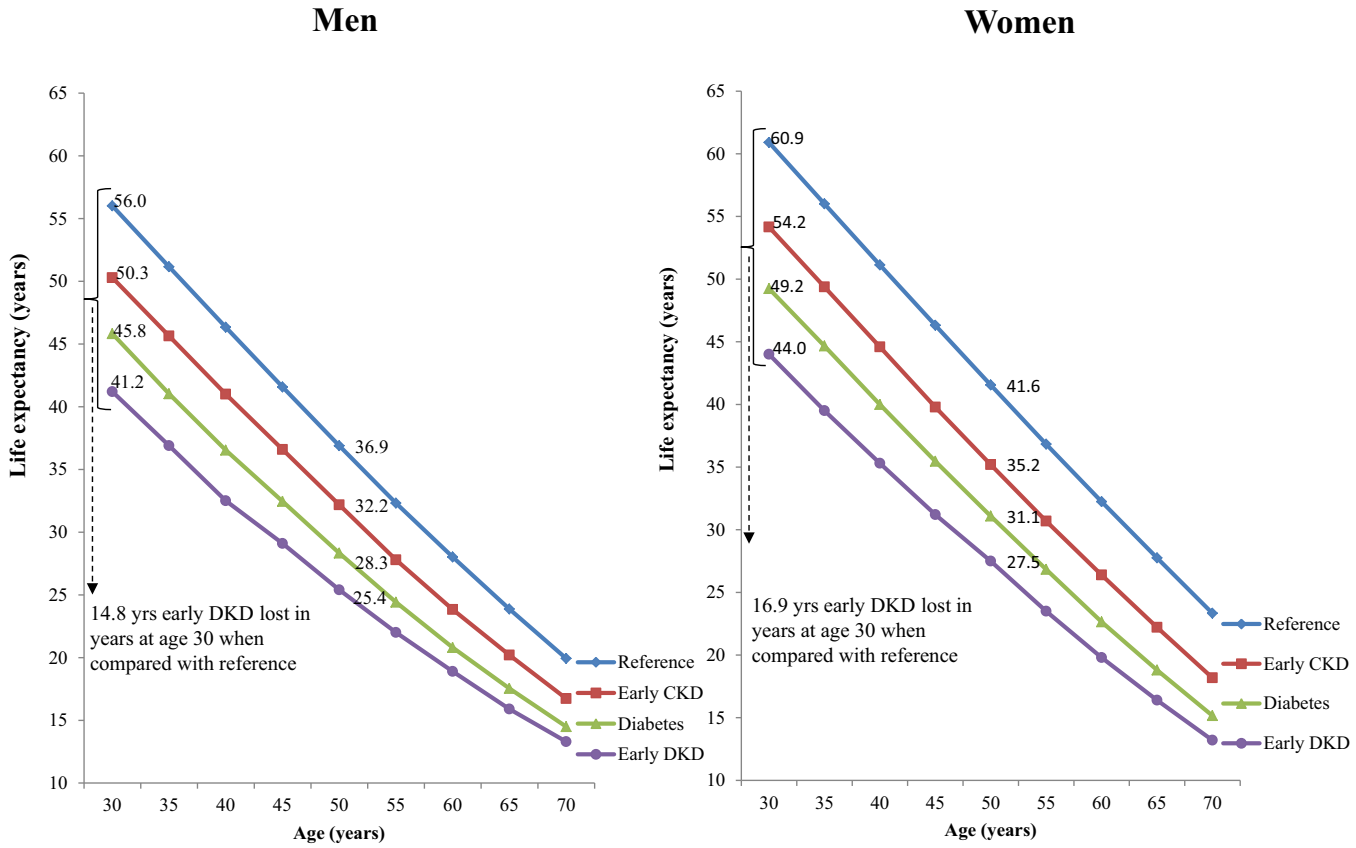


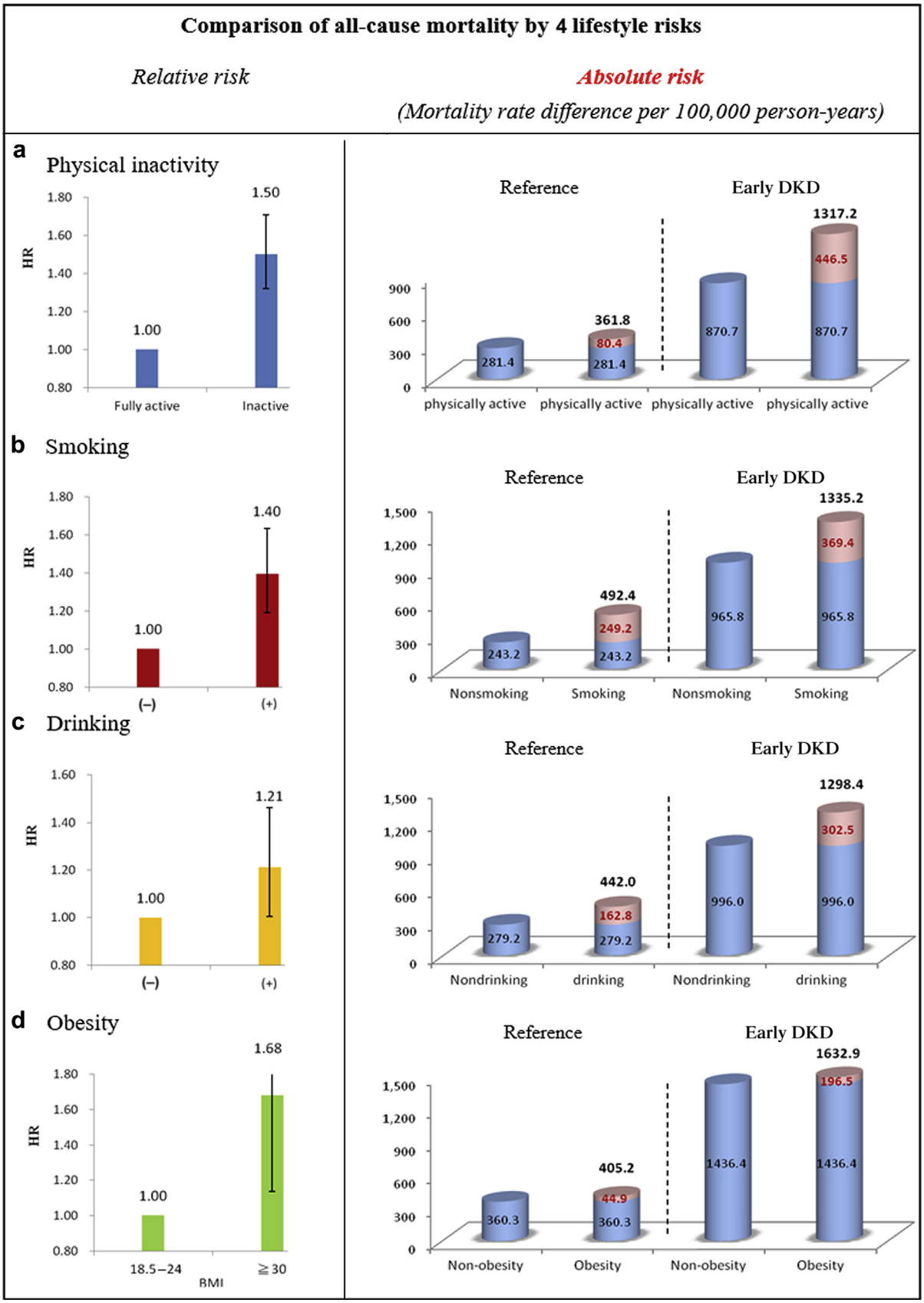
Figure 3 | Shortened life expectancy for early diabetic kidney disease (DKD) and in comparison with early chronic kidney disease (CKD) without diabetes and diabetes without CKD. The reference group consisted of participants with neither diabetes nor CKD. Early CKD was defined as CKD stages 1 to 3 without diabetes. Diabetes was defined as diabetes without CKD. Early DKD was defined as diabetes with early CKD stages 1 to 3.

participants with early DKD compared with the reference population. Two-thirds of participants with early DKD had at least 1 of the 4 risk factors. Each was associated with increased mortality among the reference group (Figure 4 and Supplementary Figure S2), but amplified such risks among those with early DKD. For example, the excess mortality risk of physical inactivity in the reference group was 80.4/100,000, the difference between mortality risk for inactive (361.8) versus active (281.4) lifestyles. This excess mortality risk was 5 times higher for physical inactivity among participants with early DKD, 446.5/100,000 (difference between inactive [1317.2/100,000] and active [870.7/100,000]). Similar observations were seen for obesity, smoking, and drinking, with 5-fold, 50%, and 2-fold amplified mortality risk differences, respectively, for participants with early DKD.

DISCUSSION

In this study, we found that life expectancy for patients with diabetes complicated by early CKD was shortened by an average of 16 years. Mortality risks for this population were doubled compared with those for diabetic patients without CKD or early CKD patients without diabetes, and tripled compared with those for the reference population. Notably, however, an overwhelming majority of participants with early DKD (98%) were not aware of having such a serious condition.

Several characteristics of early DKD were noteworthy when compared with the other 3 groups, diabetes without CKD, early CKD without diabetes, and the reference group. First, up to three-quarters of early DKD patients had proteinuria, a condition more prevalent and more serious than early CKD, and early detection of proteinuria is a cornerstone of early DKD management.[9,16] Checking GFR alone may be inadequate for detecting most early DKD cases. Diabetes patients often focused on checking urine for sugar levels but not regularly checking it for protein levels, a process easily achieved with the urine dipstick method. Second, given the same level of proteinuria, early DKD had more ominous outcomes and higher mortality than early CKD (Figure 2b). Furthermore, heavier proteinuria was found 2 to 3 times more in early DKD and had made DKD outcome even worse. Third, given the same fasting blood glucose level, the mortality outcome was consistently worse for early DKD than for the other groups (Figure 2c). This suggests that good glycemic


Comparison of all-cause mortality by 4 lifestyle risks
Relative risk
Absolute risk
(Mortality rate difference per 100,000 person-years)
a
Physical inactivity
HR
1.80
1.60
1.40
1.20
1.00
0.80
1.50
1.00
Fully active
Inactive
Reference
Early DKD
1317.2
446.5
900
600
300
0
361.8
80.4
281.4
281.4
870.7
870.7
physically active
physically active
physically active
physically active
b
Smoking
HR
1.80
1.60
1.40
1.20
1.00
0.80
1.40
1.00
(–)
(+)
Reference
Early DKD
1335.2
369.4
1,500
1,200
900
600
300
0
492.4
249.2
243.2
243.2
965.8
965.8
Nonsmoking
Smoking
Nonsmoking
Smoking
c
Drinking
HR
1.60
1.40
1.20
1.00
0.80
1.21
1.00
(–)
(+)
Reference
Early DKD
1298.4
302.5
1,500
1,200
900
600
300
0
442.0
162.8
279.2
279.2
996.0
996.0
Nondrinking
drinking
Nondrinking
drinking
d
Obesity
HR
1.80
1.60
1.40
1.20
1.00
0.80
1.68
1.00
18.5–24
≧ 30
BMI
Reference
Early DKD
1632.9
196.5
1,500
1,200
900
600
300
0
405.2
44.9
360.3
360.3
1436.4
1436.4
Non-obesity
Obesity
Non-obesity
Obesity

control alone, reducing fasting glucose level as low as possible among early DKD patients, was inadequate for best survival outcomes. This is in line with the observation in clinical trials that intensive lowering of blood glucose levels among patients with diabetes did not result in significant mortality reduction.[17,18] Similarly, controlling systolic blood pressure in hypertension *per se* was inadequate for the best mortality results in early DKD patients (Figure 2d). The inadequacy of treating early DKD with 1 risk factor at a time marks DKD as a unique disease.

The important role of lifestyle risks in early DKD has not been fully appreciated. First, lifestyle risks are ubiquitous in early DKD, with two-thirds of patients having at least 1 of the 4 lifestyle risks (i.e., physical inactivity, smoking, alcohol drinking, and obesity). Each of these risks would amplify the mortality risk of early DKD beyond its impact on the general public. For example, the excess mortality risk of physical inactivity was 5 times greater in early DKD than in the non-DKD group, as shown in Figure 4. Similar observations, but with less impact on absolute mortality, were seen for obesity, smoking, and drinking, where early DKD amplified mortality risk differences (Supplementary Figure S2). Through these amplifications, the role of lifestyle risks became particularly important in early DKD. At the same time, the degree of benefit that could be gained through regular exercise was 5-times greater in those with early DKD compared with an average individual. Such a gain has been shown among fully active DKD participants in this cohort.[19] Because more than one-half of participants with early DKD were physically inactive, engaging in regular exercise should be emphasized as a clinical routine. Incidentally, exercise has been reported to demonstrate the added benefit of reducing proteinuria in diabetes.[20] Similar to physical inactivity, smoking was reported in a sizable portion of participants with early DKD, and quitting smoking should also have been a clinical priority. However, in reality, the majority of participants with early DKD were unaware of it, and the few who were aware of their diabetes status were preoccupied with blood sugar control or blood pressure control, with little attention paid to the importance of modifying their lifestyle risks.

Thus, reducing lifestyle risks should become a centerpiece of treatment for every early DKD case discovered in the primary care setting. Reducing lifestyle risks will also help lower the cancer risk increase found in early DKD. Early DKD demonstrated significantly increased cancer risks (1.75) compared with diabetes (1.42) and early CKD (1.28). To our knowledge, this is the first study highlighting the large life-shortening effect and strong cancer relationship with DKD.

Viewing early DKD as a unique and serious condition on its own will facilitate its detection and management. In summary, early DKD is, in this study, characterized by 3 distinct observations: highly prevalent proteinuria with 16-year loss of life, larger-than-average benefits if lifestyle changes are made, and unsatisfactory survival outcome when the treatment is targeted at 1 risk at a time, lowering blood sugar or lowering blood pressure.

There are important limitations in this study. First, proteinuria was determined by a single urine sample measurement, not meeting the requirement of persistent albuminuria in the Kidney Disease Outcomes Quality Initiative definition of kidney damage.[21] Therefore, DKD prevalence in our study population might have been overestimated. However, up to 75% of proteinuria was reported to persist.[10] The estimated hazard ratios for early DKD, however, would probably be biased toward the null hypothesis due to nondifferential misclassification when we applied the same criteria to the reference group. Second, the classification of early DKD was based on the blood and urine tests at the initial examination and ignored the temporal changes in subsequent time periods. However, major results for early DKD persisted when second or third returning examinations were considered, as shown in Supplementary Table S1. Third, urinary albumin-creatinine ratio (ACR), the gold standard for measuring albuminuria, is preferred by most nephrologists in establishing the diagnosis of DKD. However, the higher cost and time-consuming nature of ACR testing, and the low prevalence of proteinuria in the general public (7%),[22,23] made ACR impractical for screening healthy subjects in general practice.[24] Instead, we used the machine-read dipstick method to detect proteinuria. The comparability of the dipstick method and ACR for determining albuminuria has been well-reported.[23,25] Finally, the serious outcome of early DKD may be a health disparity or inequality issue, with more DKD found among the less-educated population. Our cohort comprised fee-paying participants for medical screening, with higher socioeconomic status and health consciousness, and therefore a lower rate of early DKD. Thus, due to possible selection bias, the public health implications of early DKD in Taiwan may be much more serious.

In conclusion, the higher mortality and shorter life expectancy associated with early DKD are worse than those commonly perceived for overall diabetes. Due to the more serious outcome of DKD even at its early stage, we propose

Figure 4 | Relative risk (hazard ratio [HR]) and absolute risk (mortality rate) increased in early diabetic kidney disease (DKD) compared with participants with neither diabetes nor chronic kidney disease (CKD) by different lifestyle risk factors, including (a) physical inactivity, (b) smoking, (c) drinking, and (d) obesity status. Age-adjusted mortality rates for early DKD participants (1182 per 100,000 person-years) were 3 times higher than for the reference group (365.5 per 100,000 person-years). The reference group consisted of participants with neither diabetes nor CKD. Early CKD was defined as CKD stages 1 to 3 without diabetes. Diabetes was defined as diabetes without CKD. Early DKD was defined as diabetes with early CKD stages 1 to 3. HRs were adjusted for 11 variables: age, sex, body mass index, education level, systolic blood pressure, cholesterol, smoking, drinking, physical activity, Chinese herbal medicine use, and analgesic use.

that early DKD be considered a disease in its own right to attract public attention. Special efforts are needed for prevention, early identification, and proper management of early DKD.

METHODS

Study population

This prospective cohort study consisted of 543,412 adults who participated in a self-paying comprehensive health surveillance program offered by a private firm (MJ Health Management Institution, Taiwan) between 1994 and 2008. Data including blood test or urine sample such as serum creatinine, eGFR, and urine protein test were nearly 95% complete for 513,926 individuals. The majority of participants returned for repeated examinations in subsequent years, but only results from the initial tests were used in our analysis. Those who returned for second and third screening evaluations were included in a sensitivity analysis to validate the results. A detailed description of the study has been documented elsewhere.[12,26]

The protocol was approved by the institutional review board of the National Health Research Institutes. Consent was obtained from all participants. Data related to individual identification were removed, and participants remained anonymous for the entire study period.

Data collection

In addition to a self-administered questionnaire for medical history, each participant underwent a standard panel of medical tests including blood tests, urine tests, body measurements, functional tests, and physical examinations. Overnight fasting blood and first morning voided urine samples were collected and analyzed.

Definition of diabetes, CKD, and early DKD

Diabetes was defined as fasting plasma glucose level $\geq$ 126 mg/dl (7 mmol/l), self-reported history of diabetes, or use of any anti-diabetes medication.

CKD was defined based on the Kidney Disease Outcomes Quality Initiative definition,[21] with eGFR estimated by the CKD-EPI Study equation,[27] and/or albuminuria determined by dipstick method and reported as negative, trace (+/–), 1 (+), and $\geq$ 2 (+), equivalent to ACR <10, 10 to 29, 30 to 299, and $\geq$ 300 mg/ml, respectively.[25] Early CKD was defined as CKD stages 1 to 3 without diabetes. Early DKD was defined as diabetes with CKD stages 1 to 3. CKD stage 1 was defined as eGFR $\geq$ 90 ml/min per 1.73 m^2 with positive urinary protein, and stage 2 was defined as eGFR $\geq$ 60 ml/min per 1.73 m^2 with positive urinary protein. Stage 3 was defined as eGFR 30 to 59 ml/min per 1.73 m^2.

Participants were classified into the following 4 groups: diabetes without CKD, early CKD without diabetes, diabetes with early CKD (early DKD), and a reference group with neither CKD nor diabetes. Individuals with CKD stage 4 ($n = 817$) and 5 ($n = 409$), either with or without diabetes, were excluded from the analysis. All the classifications were based on one-off measurements.

We assessed the early CKD status and associated mortality for those who returned in 1 or 2 years for repeated screening. One of 3 (34%) had 2 tests, and 1 of 5 (18%) had 3 tests.

Definition of awareness

Questions regarding awareness of nephritis or kidney disease and awareness of diabetes or currently taking diabetes medication were used to assess CKD and diabetes awareness, respectively.

Outcomes

National death file or National Cancer Registry file were matched with this cohort for mortality and cancer incidence statistics. Participants were monitored from the date of baseline measurement until 31 December 2008 or death.

Statistical analyses

A Cox proportional hazards model was used for HRs with 11 variables adjusted, including age, sex, body mass index, education level, systolic blood pressure, cholesterol, smoking, drinking, physical activity, Chinese herbal medicine use, and analgesic use. The proportional hazard assumption was examined and met by plotting the log-minus-log survival curves and survival times against cumulative survival. The age-standardized mortality rate was adjusted for the 2009 Taiwanese general population. The life table method was used to estimate remaining years in life or life expectancy.[28,29]

DISCLOSURE

All the authors declared no competing interests.

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CPW, CHC, MKT, and XW conceptualized and designed the study. MKT, JHL, PJL, and CPW analyzed and interpreted the data. CPW and CHC drafted the article and submitted it for publication. CPW, CHC, SPT, CW, CHC, CWK, and XW critically revised the article for important intellectual content. SPT, MKT, JHL, and PJL provided administrative, technical, and logistical support. CKT was responsible for collection and assembly of the data. All authors had final approval of the article.

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SUPPLEMENTARY MATERIAL

Table S1. Hazard ratios for all-cause mortality among study participants who obtained second and third screening tests.

Table S2. Shortened life expectancy for early diabetic kidney disease and comparisons with the reference, early chronic kidney disease without diabetes, and diabetes without chronic kidney disease groups by gender.

Figure S1. Kaplan-Meir survival curve for early diabetic kidney disease (DKD) and comparisons with the reference, early chronic kidney disease (CKD) without diabetes, and diabetes without CKD groups.

Figure S2. Relative risk (hazard ratios) increased in early diabetic kidney disease (DKD) compared with participants with neither diabetes nor chronic kidney disease (CKD) by different lifestyle risk factors.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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