The impact of cardiovascular disease and chronic kidney disease on life expectancy and direct medical cost in a 10-year diabetes cohort study

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Abstract

Objective

The relative effects of various cardiovascular diseases (CVD) and varying severity of chronic kidney disease (CKD) on mortality risk, direct medical cost and life expectancy in patients with diabetes mellitus (DM) are unclear. The aim of this study was to evaluate these associations.

Research Design and Methods

This was a retrospective cohort study that included 208,792 adults with diabetes stratified into 12 disease status groups with varying combinations of heart disease, stroke, moderate CKD (eGFR:30-59ml/min/1.73m^2) and severe CKD (eGFR: <30ml/min/1.73m^2) in 2008-2010. The effect of risk mortality, annual direct medical costs and life expectancy were assessed using Cox regression, Gamma generalized linear with log link function, and flexible parametric survival models.

Results

Over a median follow-up of 8.5 years (1.6 million patient-years), 50,154 deaths were recorded. Mortality risks for patients with only a single condition among heart disease, stroke and moderate CKD were similar. The mortality risks were 1.75 times, 2.63 times and 3.58 times greater for patients with one, two and all three conditions (consisting of stroke, heart disease and moderate CKD), compared with patients without these diseases, suggesting an independent and individually additive effect for any combination. A similar trend was observed in annual public healthcare costs with 2.91, 3.90 and 3.88 fold increased costs for patients with one, two and three conditions, respectively. Increases in the number of conditions reduced life expectancy greatly, particularly in younger patients. Reduction in life expectancy for a 40-year-

old with one, two and three conditions were 20, 25, 30 years for men and 25, 30, 35 years for women. A similar trend of greater magnitude was observed for severe CKD.

Conclusion

The effect of heart diseases, stroke, CKD and the combination of these conditions on all-cause mortality and direct medical costs are independent and cumulative. CKD, especially severe CKD, appears to have a particularly significant impact on life expectancy and direct medical costs in patients with diabetes. These finding supports the importance of preventing both CVD and CKD in patients with DM.

Keywords: Diabetes mellitus; CKD; CVD; mortality risk; direct medical cost; life expectancy

Manuscript Text

Introduction

Diabetes mellitus (DM) is a highly prevalent non-communicable disease, affecting 451 million people and causing 5 million deaths worldwide in 2017 (1). It is estimated that the number of patients with diabetes will rise to 693 million by 2045 (1). The annual global medical costs for patients with diabetes was estimated to be around USD612-USD1,099 billion in 2014 (2). The average medical cost spent on each DM patient was 2.3 times higher than those patients without diabetes (3). Cardiovascular diseases (CVD) and chronic kidney diseases (CKD) are two major causes of morbidity, affecting 20-40% of patients with DM (4-6). The number of CVD incidence had increased by over 25% during the period from 1990 to 2010 whereas that of CKD had been doubled in general population (7). Given that the increase in life expectancy, the prevalence of CVD and CKD among all DM patients will keep growing and thus, increasing economic burden as well as premature mortality.

Some studies have suggested that the mortality risks for CVD and CKD are similar in the general population (8; 9). Nevertheless, most studies conducted amongst patients with diabetes have assessed the mortality risk caused by either CVD or CKD alone (10-14). Moreover, the results to date have been inconsistent in that the relative mortality risks have ranged from 1.5 to 3.3 for CVD and from 0.94 to 5.0 for CKD (10-15). It is therefore hard to compare the differences between the burden of the CVD and CKD. The impact of the co-morbid CVD and CKD is also unclear, such as whether the effect on CVD and CKD is additive or multiplicative remains unknown. There is currently only limited evidence demonstrating the actual reduction

of life expectancy among these patients, which is more clinically meaningful and easy to understand. In addition, the medical cost for treating CVD and CKD among patients with DM has been inconsistent between studies (16; 17). The most appropriate method to evaluate these associations is to estimate the burden of CVD and CKD in the same cohort. Hence, the aim of this study was to evaluate the impact of CVD and CKD individually and jointly on mortality risks, life expectancy and direct medical costs based on a 10-year Hong Kong diabetes cohort. This will help facilitate the development of healthcare policies including resource allocation and treatment prioritization for the prevention of CVD and CKD for patients with DM.

Methods

Study Design

This population-based retrospective cohort study included patients aged 18 years or above with the diagnosis of DM and managed by the Hong Kong Hospital Authority over the period between 1 January 2008 and 31 December 2010. The Hong Kong Hospital Authority is the statutory body that manages all the public-sector hospitals and primary care clinics in Hong Kong. It is responsible for managing over 90% of patients with DM as the health services are heavily subsidised by the Hong Kong government (18). The ecology of Hong Kong health care system is comparable to the United States (US) and United Kingdom (UK). The monthly rates for outpatient care used in Hong Kong are higher compared to US and UK, but the use of hospital-based events including accident and emergency attendances and hospitalizations are similar (19). The International Classification of Primary Care-2 (ICPC-2) codes of ‘T89’ or ‘T90’ are used to define the clinical diagnoses of DM. Baseline was defined as the first attendance of a doctor consultation in a primary care outpatient clinic during the inclusion period.

Ethics approval for this study was received from the regional Institutional Review Boards in Hong Kong. Consent from individual subjects was not needed because all patient records were retrieved from the computerized administrative system of the Hospital Authority anonymously.

Disease status groups

Subjects were divided into 12 mutually exclusive disease and disease combination groups at the baseline: (1) heart diseases including coronary heart disease and heart failure; (2) stroke; (3) moderate CKD; (4) severe CKD; (5) heart diseases and stroke; (6) heart diseases and moderate CKD; (7) stroke and moderate CKD; (8) heart diseases and severe CKD; (9) stroke and severe CKD; (10) heart diseases, stroke and moderate CKD; (11) heart diseases, stroke and severe CKD; (12) none of these (reference group). The diagnoses of CVD and CKD were defined according to the diagnostic codes of the ICPC-2 or the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM). Moderate and severe CKD were defined as eGFR $\geq$ 30ml/min/1.73m^2 & eGFR < 60ml/min/1.73m^2 and eGFR < 30ml/min/1.73m^2, respectively (as described in the **supplementary table 1)**.

Outcome Measures

The primary outcome was all-cause mortality. Mortality data was obtained from the Hong Kong Death Registry, a population-based government official registry with the registered death records of all Hong Kong citizens. Meanwhile, secondary outcomes were the annual direct medical cost and life expectancy. The total medical cost per patient was calculated by the product of the frequency of attendance and the unit cost of attendance. It included the utilization of medical services, such as general and specialist out-patient clinic, allied health professional services (including clinical psychologists, dietitians, occupational therapists and

physiotherapists), accident and emergency services and hospital in-patient services. The frequency for health service utilizations was retrieved from the computerise administrative system of Hong Kong Hospital Authority. The unit cost of relevant health service utilization was based on the published costs as per the Government of the Hong Kong Special Administrative Region Gazette and Hospital Authority Ordinance (chapter 113) in 2013 (20). The unit cost is based on a cost recovery basis, and is the lump sum covering all medical services used during the visits including consultation, investigations, medications and other treatments used. The annual public direct medical costs referred to the total cost for each kind of health service attendance.

Baseline Covariates

The patients' socio-demographics, behaviour characteristics, clinical parameters, disease characteristics and treatment modalities are the baseline covariates. Socio-demographics parameters include gender and age. Behaviour characteristics includes the smoking status. Clinical parameters consist of systolic and diastolic blood pressure (SBP and DBP), low-density lipoprotein-cholesterol (LDL-C), hemoglobin A1c (HbA1c) and body mass index (BMI). Disease characteristic include self-reported duration of DM Medication treatment included the use of anti-hypertensive drugs including angiotensin converting enzyme inhibitor/angiotensin receptor blockers, β-blockers, calcium channel blockers, diuretics and other anti-hypertensive drugs, the use of anti-diabetes drugs and the use of lipid-lowering agents at baseline. All laboratory tests were conducted in Hospital Authority laboratories using the same protocol and accredited by the College of American Pathologists, the Hong Kong Accreditation Service or the National Association of Testing Authorities, Australia.

Data Analysis

Multiple imputation was used to handle all missing baseline covariates to minimize potential bias influenced by missing data (21). The chained equation method was used to impute all the missing data five times with all baseline covariates and mortality outcome. Pooled estimates and the corresponding 95% confidence intervals (CIs) were calculated based on the Rubin's rule (22). Descriptive statistics were used to summarize patients' characteristics for each disease status group. Cumulative incidences and incidence rates for all-cause mortality with 95% CIs were calculated. Incidence rates for outcome events were estimated based on the 95% confidence interval under Poisson distribution (23). In order to evaluate the associations between disease group status and primary outcome, multivariable Cox proportional hazards regression models were used with adjustments based on all baseline characteristics. Proportional hazards assumptions were also considered while fitting the Multivariable Cox proportional hazards regression models by using the scaled Schoenfeld residuals plots against time for the covariates. The variance inflation factor was used to determine the presence of multi-collinearity. Hazard ratios (HRs) with corresponding 95% CIs and p-values were reported accordingly. Three measurements including (i) the relative excess risk due to interaction (RERI), (ii) the attributable proportion due to interaction (AP) and (iii) the synergy index (SI) were used to examine the additive or multiplicative interaction between disease status groups based on the adjusted HRs from the Cox regression. RERI and AP equal 0 and SI equals 1 indicated the absence of an interaction effect (24), and suggested an additive interaction between disease status groups.

Subgroup analyses were used to determine if there were any relationships between different disease status groups and mortality. Stratification was by gender (men, women), age (<65years, ≥65years), smoking status (non-smoker, smoker), duration of DM (<5years; ≥5years), BMI (<27.5kg/m^2, ≥27.5kg/m^2), blood pressure (systolic blood pressure <130mmHg and diastolic

blood pressure < 80mmHg, systolic/ diastolic blood pressure ≥ 130/80mmHg), HbA1c (<7%, ≥7%), LDL-C (<2.6mmol/L, ≥2.6mmol/L), the use of anti-hypertension drugs (No, Yes), the use of anti-diabetes drugs (No, Yes) and the use of lowering lipid drugs (No, Yes) at baseline.

For secondary outcomes, the estimated direct medical cost incurred for each disease status group per year was calculated using the mean of the annual cost of health service attendances within 5-years after baseline. A generalized linear method with Gamma family, log link function and adjusting for baseline characteristics was used to evaluate the adjusted difference in annual cost of public health service utilization between disease status groups. This model could be used in the application of estimating the additive effect of complications on medical costs (25-27). Meanwhile, a flexible parametric survival model for relative survival was used to estimate the life expectancy losses within different disease status groups (28). This model could calculate the life expectancy (29-31) based on the measurement of loss in expectation of life by extrapolating the estimated linear trend at the end of follow-up period without consideration of any proportional hazards model assumption. Age and gender were considered as covariates with time dependent effects. Restricted cubic splines were used to model age continuously and non-linearly.

All significance tests were two-tailed and considered statistically significant if p-value were less than 0.05. Statistical analysis was performed with Stata Version 13.0.

Results

At total of 208,792 DM patients were identified and included for analysis in this cohort study. Of these, 11,922 (5.7%), 10,736 (5.1%), 11,367 (5.4%) and 1,114 (0.5%) had stroke, heart diseases, moderate CKD and severe CKD respectively. Among all patients with DM, 35,139

(16.8%) had 1 condition of either stroke, heart disease or CKD, 6,981 (3.3%) had 2 conditions, while 801 (0.4%) patients had 3 conditions. **Supplementary table 2** shows the data completion rates for each baseline covariate (with over 75% data completion on average.) Table 1 illustrates all the baseline characteristics of the cohort by disease group status. In general, the average age of the subjects was 65 years old (standard deviation [SD]: 12), where women accounted for 54% of the cohort.

After a median follow-up period of 8.5 years (1.6 million patient-years), there were 50,154 deaths. **Table 2** shows the incidence rate for mortality ranged from 2.11 to 40.95 per 100 patient years amongst the different disease status groups. The trend in the incidence rate increased from one, two and three conditions among stroke, heart and moderate CKD. In particular, the incidence rate for mortality in patients with severe CKD was higher than any combination of stroke, heart and moderate CKD. Similar pattern of HRs was observed after adjusting for other covariates as shown in **Table 2**. The mortality risk was higher for patients with more conditions among CKD, heart disease and stroke. Compared to those without a history of CKD and CVD, the adjusted HRs for subjects with one, two and three conditions among stroke, heart disease and moderate CKD was increased by 1.75 times, 2.63 times and 3.58 times respectively. The mortality risk for patients with severe CKD was much higher. **Supplementary table 3** demonstrates that REFI, AP and SI for stroke, heart disease, moderate/ severe CKD except for stroke and severe CKD absented the interaction effect, which suggests that it is more likely that there is an additive interaction between disease status groups. **Supplementary table 4** shows comparable patterns in different subgroups compared to the main analysis.

Table 3 displays the estimated public direct medical costs per annum ranging from USD 4,065 to USD 35,362 across the different disease status groups. A similar trend was observed to the

mortality rates with an incremental increase in medical costs with a cumulative increase in number of conditions. The annual public medical cost for DM patients with one, two and three conditions among stroke, heart disease and moderate CKD increased by 1.91 times, 2.90 times and 3.88 times when compared to those without a history of CKD and CVD respectively. The medical costs for patients with severe CKD alone or in a combination of stroke and heart disease was much higher. More detailed findings are shown in **Table 3**.

Figure 1 shows the estimated loss of life expectancy for different disease status groups (with comparison group). The estimated life expectancy loss for men (women) aged 40 years old with stroke, heart diseases and moderate CKD was nearly 21.1 (95% C.I.: 15.5-26.6) (female: 26.2 (95% C.I.: 20.6-31.9))years, 16.6 (95% C.I.: 9.6-23.7)((female: 21.7 (95% C.I.: 14.0-29.5)) years, 23.2 (95% C.I.: 18.6-27.7) ((female: 28.3 (95% C.I.: 23.7-32.9)) years and 31.5 (95% C.I.: 30.2-32.7) ((female: 36.3 (95% C.I.: 35.0-37.7)) years respectively. In addition, the estimated life expectancy loss for men (women) with severe CKD or in a combination of any 2 or 3 conditions was even more prominent with the results shown in **Figure 1**. The life expectancy loss for patients of younger age was much larger than that of older patients, but the reduction in life expectancy for elderly was still high. For instance, the years of life lost for 40-year-old men (women) with DM with both stroke, heart disease and severe CKD was 18.9 (95% C.I.: 18.2-19.6) (female: 22.6 (95% C.I.: 21.9-23.4)).

Discussion

This large cohort study involved over 50,000 incident deaths across 1.59 million patient-years at risk and contributes to the evidence for estimating mortality risk, direct medical costs and life expectancy loss due to various combinations of CVD and CKD for patients with DM. The findings demonstrated similar mortality risks associated with stroke, heart diseases and

moderate CKD. This supports the recommendation from the National Kidney Foundation and the American College of Cardiology/American Heart Association that CKD should be treated as a CHD risk equivalent (32; 33). Our analyses also found the effect of stroke, heart diseases and moderate CKD on mortality risk were individually additive and non-overlapping for any combination. The mortality risk associated with severe CKD is larger than the combined effects of stroke, heart diseases and moderate CKD. Similar patterns were observed for direct medical costs. Additionally, increases in the number of conditions reduced life expectancy greatly, particularly amongst younger patients.

No previous study has yet evaluated the individual and combined effect of CVD and CKD on mortality risk and direct medical cost among DM patients. A few studies conducted in the general population have found that patients with stroke, heart diseases and CKD had similar mortality risks and direct medical costs (34; 35). Our study confirmed this finding and extended the impact of these combination of diseases on mortality risks and direct medical cost in patients with DM. In this cohort of DM patients, the risks were observed to be additive and non-overlapping . The increase in the number of conditions including stroke, heart disease and CKD corresponded to the rise in mortality risks and direct medical costs. Our findings provide further evidence for the importance of CVD prevention among patients with CKD, and the prevention of CKD among patients with CVD (32; 36; 37) and suggests that prevention of CVD and CKD might play equally important roles in decreasing the disease burden in patients with DM. A previous study conducted in the Canadian general population demonstrated similar mortality risks for patients with CHD and those with moderate to severe CKD (9). Our results partially confirmed this finding because of the substantially higher mortality risk associated with severe CKD compared to CHD among patients with DM. We recommend that the effect

of severe CKD and moderate CKD should be considered independently when evaluating mortality risks and prevention of severe CKD be prioritized.

The data from the 1950-1980s Framingham Heart Study with 9,033 participants demonstrated that men and women aged 50 years with DM and CVD had 7.1 years and 6.8 years reduction in life expectancy respectively, compared to those without CVD. (38) The results were lower than our expectation. One potential explanation could be the rapid increase in global life expectancy between 1950s and 2010s (39). Although ethnic differences and the historical characteristics of the Framingham Heart Study discourage extrapolation of those findings to the current context, our sample size was much larger and more detailed analytical techniques used which can provide more reliable results. Meanwhile, two large general population cohort studies demonstrated a reduction of life expectancy for Taiwanese people aged 60 with moderate and severe CKD was around 4 to 13 years, whereas 4 to 9 years amongst Canadian subjects (34). These years of life loss results were less than those observed in our current study because our study population was limited to patients with DM. DM patients have an average of around 8 to 10 years life expectancy loss compared to those without DM (14; 38). Hence, our findings would likely be similar to the previous studies if diabetes was taken into account. The average life expectancy loss for men and women with stroke, heart diseases and severe CKD within the age group of 40 to 60 (decrease by 37 years and 21 years, respectively) were surprising in that they were larger than the 10-year loss for lifelong smokers and 11-year loss for those with HIV infection.(40-42).

Our findings demonstrated that around 20% of our cohort of patients with DM had at least one complication among CKD, stroke and heart diseases. Limited symptoms could be observed at the earlier stages of CKD because of the difficulty in discovering the symptoms related to

uremia until the latest stage with severe CKD. (43) Therefore, the early stages of CKD could gradually progress to severe CKD asymptomatically. Previous studies in Taiwan showed an under-diagnosis, under-treatment and lack of awareness for CKD. (44). A review suggested that early treatments including an education program and pharmacologic therapies might help to reverse the early stages of CKD (45). In addition, most treatment guidelines currently to focus primarily on CVD risk screening with care plans stratified by risk. Even though various common risk factors are recognized for both CKD and CVD, proper screening for early identification and management for CKD could potentially slow down or even prevent CKD deterioration. While many clinicians focus on the importance in controlling and preventing CVD, the severity and prevention of CKD may be easily neglected. Our findings highlights the importance of CKD management for patients with DM directed at preventing and delaying CKD deterioration.

One major strength of this cohort study was the large sample size of DM patients followed up in primary care. All missing data handling was conducted using multiple imputation and multiple adjustment with some confounding variables included to show the comparison of burdens between CKD and CVD. Using data extracted from the Hong Kong Hospital Authority's administrative database ensured that the patient data was accurate and reliable.

There are also several potential limitations. Only patients with DM in Hong Kong were included in our study. Mortality risks, direct medical cost and health policies vary with time and, thus our findings might be inappropriate to extend to the general population and patients with diabetes living in other countries or regions. Researchers should be cautious if extrapolating our study findings to other settings. There were some potential confounding variables which were not considered in this study, such as drug compliance and usage and

socioeconomic characteristics. Duration of diabetes was self-reported and liable to self-report biases. However, our data analysis included the main clinical parameters and different medications. Approximately 1% of the patients included in this cohort had a diagnosis of type 1 DM. Due to the small sample size, our analyses were not able to be stratified by DM type. Hence, the results in study is largely only generalizable to patients with type 2 diabetes. The ICPC-2 codes were used to identify patients with DM as ICD-9CM codes for DM was unavailable in our dataset, and thus our cohort will miss patients which have not been coded with an ICPC-2 DM code. Our multiple imputation model did not include the medical costs for all missing predictors. Lastly, further studies with longer follow-up periods are required to make an accurate estimation of the projection of life expectancy.

Conclusion

This cohort study found high mortality risks and large annual public direct medical cost associated with the burden of with severe CKD among patients with DM. Our findings demonstrated similar burdens were incurred by those with a history of moderate CKD, stroke and heart diseases, which were closely additive and non-overlapping for different disease combinations. The estimated life expectancy of patients with DM with CKD and CVD drops gradually as disease severity deteriorates. Our findings highlight the importance of long term CKD and CVD management and prevention in patients with DM.

Consent for publication

Ethics approval was received from the Institutional Review Boards (IRB) of the Hong Kong Hospital Authority (Ref: UW 15-259). No consent was needed because the data was analyzed anonymously.

Availability of data and materials

Due to the confidentiality of the data used for this study and strict privacy policy from the data holder that the data can be kept among the designated research personnel only, the data cannot be provided to others, whether or not the data are made anonymous.

Conflict of interest

I.C.K.W. received funding from Pfizer, Bayer and Novartis to evaluate real world evidence on pharmacological treatments of cardiovascular diseases but not related to current study. E.W.Y.C. received research grants from Bayer, Bristol-Myers Squibb, Janssen, a Division of Johnson and Johnson, Pfizer, and Takeda to evaluate real world evidence on pharmacological treatments of cardiovascular diseases but not related to current study. Other authors declare that they have no competing interests.

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Author Contributions

E.Y.F.W., and C.L.K.L. contributed to the study design and acquisition of data, researched the data, contributed to the statistical analysis and interpretation of the results, and wrote the manuscript. W.Y.C wrote the manuscript, contributed to the statistical analysis and

interpretation of the results, reviewed and edited the manuscript. All authors contributed to the interpretation of the results, reviewed and edited the manuscript. E.Y.F.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Baseline characteristics of patients by disease status after multiple imputation

Demographic	Total (N = 210,271)	(1) (N = 165,871)	(2) (N = 11,922)	(3) (N = 10,736)	(4) (N = 11,367)	(5) (N = 1,906)	(6) (N = 1,898)	(7) (N = 2,413)	(8) (N = 2,091)	(9) (N = 424)	(10) (N = 710)	(11) (N = 714)	(12) (N = 219)
Gender													
Women	53.6%	53.4%	48.6%	49.2%	62.1%	59.2%	51.1%	61.7%	53.5%	55.9%	67.2%	59.4%	58.0%
Men	46.4%	46.6%	51.4%	50.8%	37.9%	40.8%	48.9%	38.3%	46.5%	44.1%	32.8%	40.6%	42.0%
Age, year	65.4 (12.2)	63.1 (13.2)	72.1 (10.1)	71.5 (10.4)	75.2 (9.5)	73.6 (11.1)	76.1 (9.2)	78.6 (8.4)	77.7 (8.3)	76.0 (9.2)	77.8 (10.0)	79.7 (7.7)	78.4 (8.4)
Smoking Status													
Non-Smoker	89.3%	88.7%	90.0%	90.8%	92.9%	91.9%	93.5%	93.5%	92.6%	92.0%	95.4%	93.1%	93.1%
Smoker	10.7%	11.3%	10.0%	9.2%	7.1%	8.1%	6.5%	6.5%	7.4%	8.0%	4.6%	6.9%	6.9%
Duration of diabetes	7.7 (8.6)	7.0 (8.0)	8.8 (7.8)	9.5 (9.3)	11.0 (10.7)	12.8 (11.9)	10.7 (11.3)	12.9 (10.5)	11.9 (17.8)	11.9 (12.1)	15.2 (21.5)	13.8 (11.1)	12.4 (16.6)
SBP, mmHg	137.2 (18.9)	136.5 (20.3)	139.5 (19.9)	137.9 (20.3)	140.6 (20.5)	143.3 (24.1)	138.5 (21.5)	140.2 (21.8)	140.6 (22.6)	144.1 (26.2)	144.2 (24.4)	141.5 (24.0)	145.1 (25.9)
DBP, mmHg	74.7 (10.9)	75.5 (11.8)	73.3 (11.2)	72.5 (11.3)	71.0 (11.3)	70.8 (12.4)	71.3 (12.3)	69.6 (12.0)	70.5 (11.8)	70.8 (12.5)	68.7 (13.0)	70.3 (11.6)	69.5 (12.8)
HbA1c, %	7.5 (1.6)	7.5 (1.8)	7.2 (1.5)	7.3 (1.4)	7.3 (1.6)	7.2 (1.7)	7.1 (1.5)	7.4 (1.7)	7.2 (1.6)	7.0 (1.5)	7.2 (1.7)	7.2 (1.6)	6.9 (1.8)
HbA1c, mmol/mol	58.0 (17.5)	58.5 (19.8)	55.0 (16.3)	56.7 (15.7)	56.4 (17.1)	55.0 (19.0)	54.2 (16.6)	57.5 (18.1)	55.5 (17.4)	53.1 (16.1)	55.4 (18.8)	55.6 (17.2)	52.1 (19.4)
LDL-C, mmol/L	3.1 (1.0)	3.1 (1.0)	2.9 (0.9)	2.8 (1.0)	3.1 (1.0)	3.0 (1.1)	2.7 (1.0)	2.7 (1.1)	2.9 (1.1)	2.8 (1.1)	2.7 (1.2)	2.6 (1.0)	2.7 (1.2)
BMI, kg/m^2	25.4 (4.2)	25.5 (4.9)	25.1 (4.4)	25.8 (4.6)	25.1 (4.3)	24.9 (6.6)	25.4 (6.9)	25.3 (4.6)	25.0 (6.9)	25.2 (6.9)	25.4 (6.8)	24.9 (3.9)	24.3 (5.8)
Use of anti-hypertensive drugs	70.2%	66.1%	81.9%	85.9%	87.6%	86.8%	87.0%	89.0%	88.6%	89.9%	88.9%	90.1%	90.9%
Use of anti-diabetes drugs	79.6%	79.7%	77.5%	78.6%	83.5%	78.6%	73.9%	79.8%	79.8%	76.2%	75.8%	77.2%	67.1%
Use of lipid-lowering agents	12.6%	9.1%	26.3%	34.8%	11.7%	16.4%	37.9%	34.4%	24.6%	29.2%	33.8%	36.8%	41.1%

(1) = None of cardiovascular disease or Moderate/Severe chronic kidney disease (CKD); (2) = Stroke only; (3) = Heart diseases only; (4) = Moderate CKD only; (5) = Severe CKD ease only; (6) = Stroke and Heart diseases; (7) = Heart diseases and Moderate CKD; (8) = Stroke and Moderate CKD; (9) = Stroke and severe CKD; (10) = Heart diseases and Severe CKD; (11) = Stroke, Heart diseases and Moderate CKD; (12) = Stroke, Heart diseases and Severe CKD. SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HbA1c = Hemoglobin A1c Test; LDL-C = Low Density Lipoprotein - Cholesterol; BMI = Body Mass Index

The values are presented as mean (SD) or %, as appropriate.

Table 2. Incidence rate and adjusted hazard ratios of all-cause mortality by disease status at baseline

Disease Status at Baseline	No. of Participants	No. of Deaths	Person-years	Incidence Rate (Cases/100 Person Years)	Hazard Ratio (95% CI)			
					Age and Sex	Age, Sex, and Smoking	Age, Sex, Smoking, Duration of diabetes and intermediate risk factors†	Age, Sex, Smoking, Duration of diabetes and intermediate risk factors† and medication‡
(1) None of CVD or Moderate/Severe CKD	165,871	27,748	1,313,958	2.11	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
(2) Stroke	11,922	5,388	80,829	6.67	1.83 (1.78,1.89)	1.82 (1.77,1.88)	1.83 (1.78,1.89)	1.85 (1.79,1.90)
(3) Heart diseases	10,736	4,168	76,696	5.43	1.50 (1.46,1.56)	1.49 (1.45,1.54)	1.50 (1.45,1.55)	1.52 (1.47,1.57)
(4) Moderate CKD	11,367	6,145	74,510	8.25	1.93 (1.87,1.98)	1.88 (1.83,1.93)	1.88 (1.83,1.93)	1.87 (1.82,1.93)
(5) Severe CKD	1,906	1,497	8,452	17.71	5.06 (4.80,5.33)	4.89 (4.63,5.16)	4.83 (4.58,5.09)	4.83 (4.58,5.09)
(6) Stroke and Heart diseases	1,898	1,220	10,790	11.31	2.49 (2.35,2.64)	2.46 (2.33,2.61)	2.49 (2.35,2.64)	2.53 (2.39,2.69)
(7) Heart diseases and Moderate CKD	2,413	1,780	12,865	13.84	2.67 (2.54,2.81)	2.55 (2.43,2.68)	2.55 (2.42,2.67)	2.58 (2.45,2.71)
(8) Stroke and Moderate CKD	2,091	1,579	11,162	14.15	2.87 (2.73,3.02)	2.79 (2.65,2.94)	2.79 (2.65,2.94)	2.81 (2.67,2.96)
(9) Stroke and Severe CKD	424	380	1,355	28.04	6.95 (6.27,7.69)	6.78 (6.11,7.53)	6.78 (6.11,7.52)	6.82 (6.15,7.56)
(10) Heart diseases and Severe CKD	710	639	2,358	27.10	5.96 (5.51,6.45)	5.65 (5.20,6.14)	5.66 (5.20,6.15)	5.76 (5.29,6.26)
(11) Stroke, Heart diseases and Moderate CKD	714	603	3,124	19.30	3.71 (3.42,4.02)	3.54 (3.26,3.84)	3.52 (3.25,3.82)	3.58 (3.30,3.89)
(12) Stroke, Heart diseases and Severe CKD	219	213	489	43.56	9.22 (8.05,10.55)	8.95 (7.81,10.26)	8.77 (7.64,10.06)	8.91 (7.76,10.22)

CVD = Cardiovascular disease; CKD = Chronic Kidney Disease; CI = Confidence Interval;

Notes:

Age was treated as continuous variable

* Significant at 0.05 level by multivariable Cox proportional hazard regression

† Intermediate risk factors include systolic blood pressure, diastolic blood pressure, hemoglobin A1c, low density lipoprotein - cholesterol and body mass index

‡ Diagnosis of diabetes and medication include the use of anti-hypertensive drugs, use of anti-diabetes drugs and use of lipid-lowering agents.

Table 3. Estimation of annual public direct medical cost by disease status at baseline

Disease Status at Baseline	Annual public direct medical cost (US$ (SD))	Multiplier (95% CI)			
		Age and Sex	Age, Sex, and Smoking	Age, Sex, Smoking, Duration of diabetes and intermediate risk factors†	Age, Sex, Smoking, Duration of diabetes and intermediate risk factors† and medication‡
(1) None of CVD or Moderate/Severe CKD	4,065 (12,041)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
(2) Stroke	11,037 (24,423)	2.01 (1.90,2.13)	2.02 (1.91,2.14)	2.01 (1.90,2.13)	2.06 (1.95,2.18)
(3) Heart diseases	9,115 (19,043)	1.67 (1.58,1.77)	1.68 (1.58,1.77)	1.61 (1.52,1.71)	1.66 (1.56,1.76)
(4) Moderate CKD	11,246 (21,111)	2.04 (1.93,2.16)	2.04 (1.93,2.16)	1.98 (1.87,2.10)	1.99 (1.88,2.11)
(5) Severe CKD	24,254 (34,849)	4.89 (4.29,5.58)	4.89 (4.29,5.59)	4.69 (4.10,5.37)	4.75 (4.16,5.44)
(6) Stroke and Heart diseases	17,596 (30,430)	2.83 (2.48,3.23)	2.86 (2.50,3.26)	2.81 (2.45,3.21)	2.92 (2.55,3.34)
(7) Heart diseases and Moderate CKD	20,023 (32,258)	3.15 (2.80,3.55)	3.14 (2.79,3.53)	2.89 (2.57,3.26)	3.00 (2.66,3.39)
(8) Stroke and Moderate CKD	17,433 (29,289)	2.83 (2.49,3.21)	2.82 (2.49,3.21)	2.72 (2.39,3.09)	2.77 (2.44,3.15)
(9) Stroke and Severe CKD	33,399 (42,417)	5.90 (4.47,7.81)	5.92 (4.48,7.83)	5.71 (4.31,7.56)	5.93 (4.48,7.86)
(10) Heart diseases and Severe CKD	37,405 (46,073)	6.50 (5.24,8.07)	6.54 (5.27,8.11)	5.90 (4.74,7.35)	6.15 (4.94,7.66)
(11) Stroke, Heart diseases and Moderate CKD	26,586 (36,157)	4.01 (3.23,4.97)	4.00 (3.23,4.96)	3.70 (2.97,4.60)	3.84 (3.08,4.77)
(12) Stroke, Heart diseases and Severe CKD	44,617 (48,421)	7.37 (5.00,10.87)	7.39 (5.01,10.89)	7.28 (4.92,10.77)	7.69 (5.20,11.37)

CVD = Cardiovascular disease; CKD = Chronic Kidney Disease; CI = Confidence Interval;

Notes:

Age was treated as continuous variable

The p-values for all multiplier were <0.001 by generalized linear model with Gamma family and log link function.

† Intermediate risk factors include systolic blood pressure, diastolic blood pressure, hemoglobin A1c, low density lipoprotein - cholesterol and body mass index

‡ Diagnosis of diabetes and medication include the use of anti-hypertensive drugs, use of anti-diabetes drugs and use of lipid-lowering agents at baseline.

Figure Legends

Figure 1a. Years of life lost by disease status for women at baseline compared with those with neither stroke, heart disease nor moderate/severe Chronic kidney disease (CKD).

Figure 1b. Years of life lost by disease status for men at baseline compared with those with neither stroke, heart disease nor moderate/severe Chronic kidney disease (CKD)