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Sex differences in risk of incident microvascular and macrovascular complications: a population-based data-linkage study among 25 713 people with diabetes

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ABSTRACT

Background The global prevalence of diabetes is similar in men and women; however, there is conflicting evidence regarding sex differences in diabetes-related complications. The aim of this study was to investigate sex differences in incident microvascular and macrovascular complications among adults with diabetes.

Methods This prospective cohort study linked data from the 45 and Up Study, Australia, to administrative health records. The study sample included 25 713 individuals (57% men), aged ≥45 years, with diabetes at baseline. Incident cardiovascular disease (CVD), eye, lower limb, and kidney complications were determined using hospitalisation data and claims for medical services. Multivariable Cox proportional hazards models were used to assess the association between sex and incident complications.

Results Age-adjusted incidence rates per 1000 person years for CVD, eye, lower limb, and kidney complications were 37, 52, 21, and 32, respectively. Men had a greater risk of CVD (adjusted hazard ratio (aHR) 1.51, 95% CI 1.43 to 1.59), lower limb (aHR 1.47, 95% CI 1.38 to 1.57), and kidney complications (aHR 1.55, 95% CI 1.47 to 1.64) than women, and a greater risk of diabetic retinopathy (aHR 1.14, 95% CI 1.03 to 1.26). Over 10 years, 44%, 57%, 25%, and 35% of men experienced a CVD, eye, lower limb, or kidney complication, respectively, compared with 31%, 61%, 18%, and 25% of women. Diabetes duration (<10 years vs ≥10 years) had no substantial effect on sex differences in complications.

Conclusions Men with diabetes are at greater risk of complications, irrespective of diabetes duration. High rates of complications in both sexes highlight the importance of targeted complication screening and prevention strategies from diagnosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The absolute risk of cardiovascular disease appears to be higher in men with diabetes compared with women with diabetes. However, the evidence for sex differences in microvascular complications is limited and conflicting.

⇒ Further, there is little understanding of the potential impact of diabetes duration on sex differences in micro- and macrovascular complications.

WHAT THIS STUDY ADDS

⇒ Compared with women, men were at greater risk of incident cardiovascular disease, lower limb and kidney complications, and diabetic retinopathy.

⇒ Sex differences in rate of complications were similar for those with diabetes duration <10 years and ≥10 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Given the high rates of complication in both sexes, this study highlights the importance of targeted complication screening and prevention strategies from the time of diagnosis.

INTRODUCTION

Diabetes leads to numerous microvascular and macrovascular complications such as loss of vision, amputation, kidney failure, myocardial infarction and stroke, placing an enormous burden on individuals and their families, healthcare systems and society in general. Globally, the prevalence of diabetes continues to escalate. An estimated 537 million people aged 20–79 years were living with diabetes in 2021, which is projected to rise to a staggering 783 million by 2045.[1] In Australia, the prevalence of diabetes has tripled over the past three decades, affecting an estimated 1.3 million (5.1%) Australians in 2018–2021.[2]

Although the prevalence of diabetes is similar in men and women (worldwide prevalence of 8.9% and 8.4%, respectively),[3] the incidence and progression of diabetes-related complications appears to be more sex-specific. It is well established that the absolute risk of cardiovascular disease (CVD) is higher in men with diabetes than women with diabetes.[4] However, the evidence for sex differences in microvascular complications such as retinopathy, neuropathy and nephropathy is limited and conflicting. For instance, in the UK Prospective Diabetes Study, the incidence of retinopathy

was similar in men and women; however, women had a lower relative risk of retinopathy progression (RR 0.54, 95% CI 0.37 to 0.80).[5] In the prospective DiaGene cohort study of diabetes complications, the incidence of microalbuminuria (a biomarker of nephropathy) was higher in men, and men were more likely to develop two or three microvascular complications compared with women (OR 2.42, 95% CI 1.69 to 3.45).[6]

Ample duration of follow-up is required to assess long-term diabetes-related complications. Multiple studies have provided strong evidence that individuals with longer diabetes duration are at greater risk of complications[7 8]; however, there is little understanding of the potential impact of diabetes duration on sex differences in diabetes-related complications. The aim of this study was to investigate sex differences in incident micro- and macrovascular complications among a large population-based sample of people with diabetes. We also investigated whether sex differences were modified by duration of diabetes.

METHODS

Study population and data sources

We used data from The Sax Institute's 45 and Up Study, a large prospective cohort of 267 357 men and women aged over 45 years residing in the state of New South Wales (NSW), Australia. This cohort represents approximately 11% of the NSW population aged over 45. The cohort profile and research protocol have been published in detail previously.[9] Briefly, participants of the 45 and Up Study were randomly sampled from Services Australia Medicare enrolment database, between 2005 and 2009. Participants were invited by mail and agreed to participate by completing a sex-specific self-administered questionnaire and providing written consent for linkage of their survey responses to administrative health data collections. The estimated response rate was 19%. The full baseline survey questionnaires are available at https://www.saxinstitute.org.au/our-work/45-up-study/questionnaires/.

For this study we used data from participants' baseline questionnaires that were linked to their corresponding medical services claims (Medicare Benefits Schedule, MBS), prescription medication (Pharmaceutical Benefits Scheme, PBS), hospital admission (Admitted Patient Data Collection, APDC) and death registry data collections (Registry of Births Deaths and Marriages). Detailed information about the datasets and linkage process is provided in the online supplemental file 1. The 45 and Up Study was approved by the University of NSW Human Research Ethics Committee, and use of linked data for this study was approved by the NSW Population and Health Services Research Ethics Committee (Cancer Institute NSW reference: 2017/HRE0206).

Study sample

The present study includes all participants in the 45 and Up Study identified with diabetes at baseline. The online supplemental file 1 provides a detailed overview of diabetes case ascertainment. In brief, we used a combination of self-report and the multiple linked administrative data sources (MBS, PBS, APDC) to ascertain diabetes status.

Study exposures

The main exposures of interest were sex and diabetes duration at baseline. Diabetes duration at baseline was calculated using the age at first diabetes diagnosis identified from the baseline survey and categorised into <10 years or ≥10 years.

Study outcomes

Study outcomes were determined following literature review and consultation with clinical experts and defined as incident hospitalisation or treatment for the following four major groups and subgroups of diabetes-related micro- and macrovascular complications[10]:

1. Cardiovascular complications: ischaemic heart disease, transient ischaemic attack (TIA), stroke, heart failure, diabetic cardiomyopathy
2. Eye complications: diabetes with 'any ophthalmic complication', cataract, diabetic retinopathy
3. Lower limb complications: peripheral neuropathy, ulcers, cellulitis, Charcot foot, osteomyelitis, peripheral vascular disease, and minor or major amputation
4. Kidney complications: 'diabetes with kidney complication', acute kidney failure, chronic kidney disease, unspecified kidney failure, dialysis, and kidney transplant.

Diabetes-related complications were primarily ascertained from hospital admission records (APDC) using principal and additional International Statistical Classification of Diseases and Related Health Problems, Australian Modification (ICD-10-AM) diagnosis or Australian Classification of Healthcare Interventions (ACHI) procedure codes. As not all diabetes-related complications included in this analysis require hospital admission, we also included out-of-hospital treatment for complications such as home dialysis for chronic kidney disease, or retinal laser. This was identified using relevant MBS treatment items. A complete list of outcomes and associated diagnosis, procedure and treatment codes are presented in online supplemental table 1.

Covariates

Self-reported sociodemographic, lifestyle and health characteristics were identified from the baseline survey. All questions, response options and categories are provided in online supplemental table 2. Sociodemographic characteristics included age group, socioeconomic background (Index of Relative Socioeconomic Disadvantage (IRSD) quintile), household income, highest level of education, language other than English spoken at home, country of birth, and private health insurance. The IRSD is derived from income, education, unemployment, and other census data.[11]

Lifestyle and health factors included body mass index (BMI), smoking status, physical activity, fruit and vegetable consumption, family history of diabetes, and previous history of CVD (including heart disease and stroke), history of high blood pressure and blood pressure treatment, and treatment for high cholesterol. Of note, previous history of CVD was not included in the CVD complications analysis, as individuals with a prior history were excluded from this analysis.

Statistical analysis

Contingency tables were used to describe the baseline characteristics of participants, grouped by sex. For all major groups and subgroups of diabetes complications, we calculated age-adjusted incidence rates of complications per 1000 person-years, based on the subpopulation at risk (time to first event, death or end of follow-up time). We used Kaplan-Meier estimators to compare age-standardised cumulative complication rates for major outcome groups stratified by sex and duration of diabetes.

Cox proportional hazards models were used to estimate crude and adjusted hazard ratios (aHR) to assess associations between sex and incident CVD, lower limb, eye, and kidney complications. For analysing each group of complications (ie, CVD, lower

limb, eye, and kidney), we excluded those with a prior history of that group of complications (ie, between January 2001 and their baseline survey date). The models for each outcome were conducted adjusting for other factors in a sequential process: (1) unadjusted, (2) adjusted for age and sex, (3) adjusted for age, sex, sociodemographics, and lifestyle, and (4) adjusted for all sociodemographic, lifestyle, and health-related factors. Person-years were calculated from the date of recruitment until incident treatment or hospitalisation, death, or end of follow-up (ie, December 2019). All models account for the competing risk of death before complication. Proportionality assumptions were verified based on the methods of Lin *et al*.[12]

Multiple imputation was performed using full conditional specification and incorporating sociodemographic, lifestyle and health factors described above. Thirty imputations were conducted and estimates from the imputed datasets were combined by calculating the mean of the parameter of interest and standard errors adjusted for the uncertainty produced by the imputation process. The missing at random (MAR) assumption required for imputation was considered reasonable based on the missingness patterns in the data (table 1) and the large number of variables included in the imputation process.[13] All analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Sample characteristics

The full baseline 45 and Up sample included 267 357 participants. There were 266 471 active participants available for this analysis. We excluded participants if they did not have diabetes at baseline (n=232 535), their diabetes status was uncertain (n=8166), or there were inconsistencies in their age, death, or baseline data (n=57). Our final sample included 25 713 participants (online supplemental figure 1).

Table 1 presents the baseline characteristics of the cohort by sex, with almost half of the cohort aged 60–74 years and a slightly higher proportion of females aged 45–59 years with diabetes. A higher proportion of men were overweight (38.7% in men vs 27.8% in women), had higher educational attainment, held private health insurance, and had a history of heart disease. In terms of smoking status, although a similar proportion of men and women were current smokers, a higher proportion of men were ex-smokers (51% compared with only 29% women). Of the 19 277 (75%) people with diabetes who had an age of diagnosis, 58% had a duration of diabetes <10 years and 42% had a duration of diabetes ≥10 years at baseline. There were no meaningful differences in baseline characteristics between those with and without an age of diagnosis (online supplemental table 3).

Incident CVD complications

During 177 851 person-years of follow-up, the overall incidence rate of CVD complications was 37 per 1000 person-years, which was higher among men than women (43 vs 30 per 1000) (figure 1A). After adjustment of covariates, compared with women, the aHR for any incident CVD complication in men was 1.51 (95% CI 1.43 to 1.59) (figure 1B). Among the CVD complication subgroups, associations were similar to the overall result for heart failure and stroke and stronger for myocardial infarction and other coronary heart disease (online supplemental figure 2). These associations are reflected in the cumulative hazard curves which show that at 10 years' follow-up, 44.4% (95% CI 43.0% to 45.9%) of men and 30.9% (95% CI 29.7% to 32.2%) of women with diabetes experienced a CVD complication (p<0.001) (figure 2A). The sex difference in rate of CVD complications at 10 years was similar, although slightly greater, for those with diabetes <10 years compared with ≥10 years' duration (online supplemental figure 6, online supplemental table 4).

Incident eye complications

The incidence rate of eye complications was 52 per 1000 person years and was similar for men and women (52 vs 53 per 1000) (figure 1A). Compared with women, men had a lower risk of any eye complication (aHR 0.94, 95% CI 0.89 to 0.98) (figure 1B), with results largely influenced by the lower risk of cataract surgery among men (aHR 0.90, 95% CI 0.86 to 0.95) (online supplemental figure 3). In contrast, men had a slightly greater rate and risk of diabetic retinopathy (10 vs 9 per 1000 person years; aHR 1.14, 95% CI 1.03 to 1.26) (online supplemental figure 3). At 10 years' follow-up, the cumulative incidence of eye complications was 57.0% (95% CI 55.3% to 58.8%) in men and 60.9% (95% CI 58.9% to 62.9%) in women (p<0.001) (figure 2B); for diabetic retinopathy these rates were 9.8% (95% CI 9.2% to 10.4%) in men and 8.9% (95% CI 8.2% to 9.5%) in women. When stratified by duration of diabetes, there was no statistical sex difference in risk of diabetic retinopathy for those with diabetes <10 years (aHR 1.12, 95% CI 0.95 to 1.31) at baseline and ≥10 years' duration (aHR 1.16, 95% CI 0.99 to 1.36) at baseline (online supplemental figure 6, online supplemental table 4).

Incident lower limb complications

The incidence rate of lower limb complications was 21 per 1000 person years and was higher among men than women (25 vs 18 per 1000) (figure 1A). The risk of any lower limb complication was 1.5 times higher in men than women (aHR 1.47, 95% CI 1.38 to 1.57) (figure 1B), and the risks of peripheral neuropathy, ulcer and cellulitis were similar. The difference was stronger for peripheral vascular disease, with the risk of complications over two times higher for men. While the incidence was low, the risk of osteomyelitis and amputation was over 2.5-fold higher in men than in women (online supplemental figure 4). The cumulative incidence of lower limb complications at 10 years was higher among men at 24.6% (95% CI 23.7% to 25.5%) versus 17.8% (95% CI 16.9% to 18.7%) in women (figure 2C), and this pattern was relatively similar irrespective of diabetes duration (online supplemental figure 6, online supplemental table 4).

Incident kidney complications

The incidence rate of kidney complications was 32 per 1000 person years and was higher among men than women (36 vs 26 per 1000) (figure 1A). The risk of any kidney complication was 1.6 times higher in men than in women (aHR 1.55, 95% CI 1.47 to 1.64) (figure 1B), with similar risk estimates for specific subgroups, including kidney failure, chronic kidney disease and dialysis (online supplemental figure 5). This pattern of a higher risk of kidney complications in men is reflected in the cumulative incidence at 10 years, which was higher among men at 35.2% (95% CI 34.0% to 36.3%) versus 25.3% (95% CI 24.3% to 26.3%) in women (figure 2D). The sex difference in rate of kidney complications at 10 years was similar, although slightly greater, for those with diabetes ≥10 years compared with <10 years' duration (online supplemental figure 6, online supplemental table 4).

DISCUSSION

Our study demonstrates that men with diabetes have a higher rate and greater risk of most diabetes-related complications

Table 1 Baseline sociodemographic, lifestyle and health characteristics of the cohort of participants with diabetes by sex (n=25 713).

		Males (n=14 697)	Females (n=11 016)	Total (n=25 713)	P value
Sociodemographics					
Age group (years)	45–59	3373 (23)	3055 (27.7)	6428 (25)	<0.001
	60–74	7223 (49.1)	5011 (45.5)	12 234 (47.6)	
	75+	4101 (27.9)	2950 (26.8)	7051 (27.4)	
Duration of diabetes (years)	<10	6360 (43.3)	4851 (44.0)	11 211 (43.6)	0.001
	≥10	4898 (33.3)	3168 (28.8)	8066 (31.43)	
	Missing	3439 (23.3)	2997 (27.2)	6463 (25.1)	
Index of socioeconomic disadvantage, quintile	1st quintile (most disadvantaged)	3903 (26.6)	3403 (30.9)	7306 (28.4)	<0.001
	2nd quintile	3369 (22.9)	2605 (23.6)	5974 (23.2)	
	3rd quintile	2674 (18.2)	1930 (17.5)	4604 (17.9)	
	4th quintile	2143 (14.6)	1486 (13.5)	3629 (14.1)	
	5th quintile	2263 (15.4)	1355 (12.3)	3618 (14.1)	
	Missing	345 (2.3)	237 (2.2)	582 (2.3)	
Household income per year (AU$)	<30 000	6355 (43.2)	4946 (44.9)	11 301 (44)	<0.001
	30 000 to <70 000	3326 (22.6)	1724 (15.6)	5050 (19.6)	
	70 000+	2064 (14)	850 (7.7)	2914 (11.3)	
	Missing	2952 (20.1)	3496 (31.7)	6448 (25.1)	
Highest education	Up to school or intermediate certificate	5082 (34.6)	6010 (54.6)	11 092 (43.1)	<0.001
	Higher school to diploma	6700 (45.6)	3407 (30.9)	10 107 (39.3)	
	Degree or higher	2530 (17.2)	1288 (11.7)	3818 (14.8)	
	Missing	385 (2.6)	311 (2.8)	696 (2.7)	
Language other than English spoken at home	No	12 642 (86)	9598 (87.1)	22 240 (86.5)	0.01
	Yes	2055 (14)	1418 (12.9)	3473 (13.5)	
Country of birth	Australia	10 252 (69.8)	8074 (73.3)	18 326 (71.3)	<0.001
	Asia/MidEast/South Europe/North Africa	1396 (9.5)	869 (7.9)	2265 (8.8)	
	Other	2887 (19.6)	1958 (17.8)	4845 (18.8)	
	Missing	162 (1.1)	115 (1)	277 (1.1)	
Private health insurance	No	5983 (40.7)	5111 (46.4)	11 094 (43.1)	<0.001
	Yes	8324 (56.6)	5563 (50.5)	13 887 (54)	
	Missing	390 (2.7)	342 (3.1)	732 (2.8)	
Lifestyle					
Body weight (BMI, kg/m^2)	Underweight/normal (<25)	2760 (18.8)	2157 (19.6)	4917 (19.1)	<0.001
	Overweight (25 to <30)	5686 (38.7)	3063 (27.8)	8749 (34)	
	Obese (30+)	5351 (36.4)	4722 (42.9)	10 073 (39.2)	
	Missing	900 (6.1)	1074 (9.7)	1974 (7.7)	
Smoking status	Current regular smoker	1029 (7.0)	705 (6.4)	1734 (6.7)	<0.001
	Past regular smoker	7466 (50.8)	3184 (28.9)	10 650 (41.4)	
	Never smoked	6202 (42.2)	7127 (64.7)	13 329 (51.8)	
Moderate to vigorous physical activity (minutes/week)	0–149	4027 (27.4)	3118 (28.3)	7145 (27.8)	0.001
	≥150	10 038 (68.3)	7149 (64.9)	17 187 (66.8)	
	Missing	632 (4.3)	749 (6.8)	1381 (5.4)	
Health					
Family history of diabetes	No	8556 (58.2)	5734 (52.1)	14 290 (55.6)	<0.001
	Yes	6141 (41.8)	5282 (47.9)	11 423 (44.4)	
Ever told by a doctor you have high blood pressure	No	6067 (41.3)	4303 (39.1)	10 370 (40.3)	<0.001
	Yes	8630 (58.7)	6713 (60.9)	15 343 (59.7)	
Takes blood pressure medication	No	7130 (48.5)	5491 (49.8)	12 621 (49.1)	0.034
	Yes	7567 (51.5)	5525 (50.2)	13 092 (50.9)	
Treated for high cholesterol in last month	No	10 349 (70.4)	7345 (66.7)	17 694 (68.8)	<0.001
	Yes	4348 (29.6)	3671 (33.3)	8019 (31.2)	
Ever told by a doctor you have heart disease	No	10 514 (71.5)	9025 (81.9)	19 539 (76)	<0.001
	Yes	4183 (28.5)	1991 (18.1)	6174 (24)	
Ever told by a doctor you have had a stroke	No	13 582 (92.4)	10 303 (93.5)	23 885 (92.9)	<0.001
	Yes	1115 (7.6)	713 (6.5)	1828 (7.1)	

BMI, body mass index.

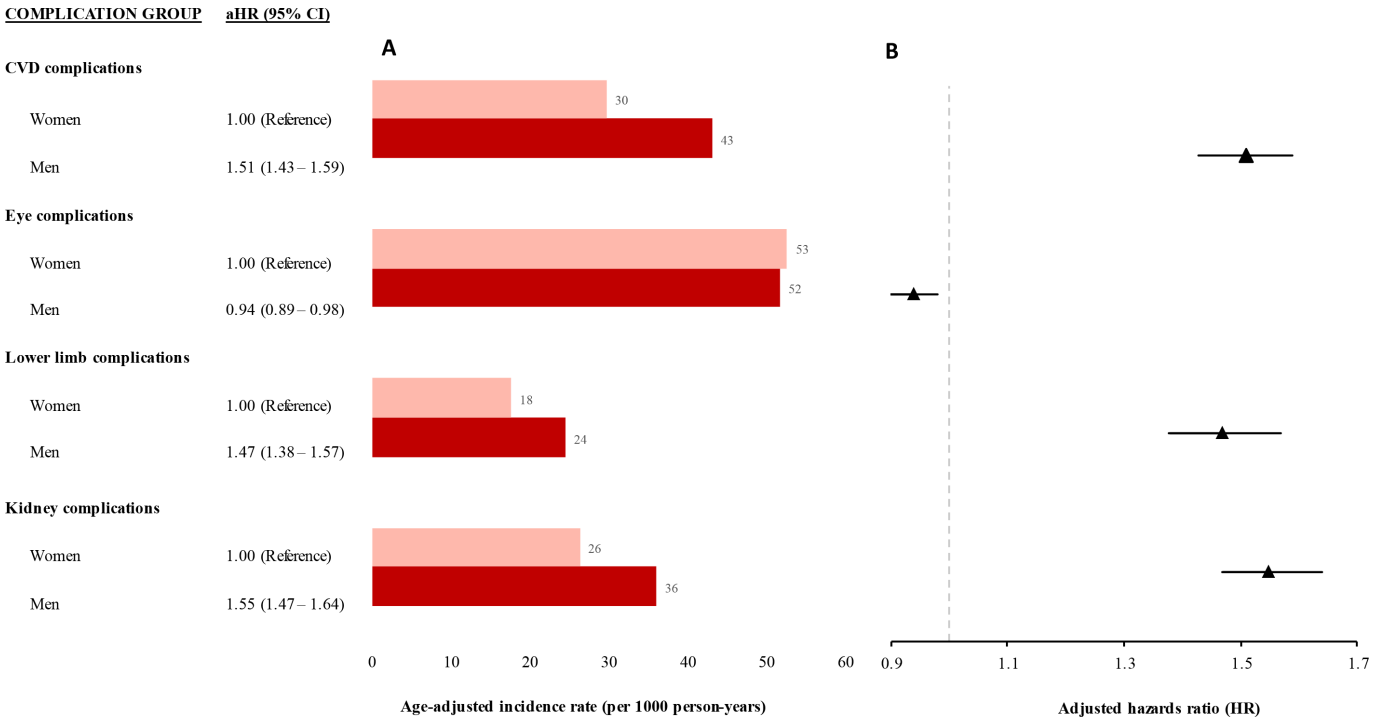

Figure 1 (A) Age-adjusted incidence rates per 1000 person-years of incident diabetes-related complications by sex and (B) adjusted hazards ratio (aHR) (95% CI) for association between sex and incident diabetes-related complications. Hazards ratios are calculated from Cox proportional hazard models based on multiple imputed data adjusted for age, sociodemographics (education, SEIFA, income, language, country of birth, private insurance), lifestyle (BMI, smoking, diet and physical activity) and health history (family history of diabetes, cardiovascular disease, blood pressure and treatment for high cholesterol). BMI, body mass index; SEIFA, Socio-Economic Indexes for Areas.

compared with women, and this difference remained consistent irrespective of the duration of diabetes. For every 1000 people with diabetes, our findings suggest that an average of 37, 52, 21, and 32 people will develop CVD, eye, lower limb, and kidney complications every year. Men had a 1.5-fold increased risk of CVD, lower limb, and kidney complications, and risk of diabetic retinopathy was 14% greater in men than in women. These findings are reflected in the ~1.4 times higher 10-year rates for CVD, lower limb, and kidney complications in men compared with women.

The greater risk of CVD complications observed for men in our study is consistent with other large population-based studies in France[14] and Denmark.[15] These studies reported a higher incidence of major adverse cardiovascular events including heart failure in men with diabetes compared with women with diabetes (incidence rate (IR) 96 vs 66/1000 person-years,[14] and IR 24.9 vs 19.9/1000 person-years[15]). Men, irrespective of diabetes status, have been shown to have a greater CVD risk factor burden than women.[16–18] A recent study using nationally representative survey data from Australians aged 45–74 years showed men had a higher average BMI, waist circumference, systolic and diastolic blood pressure, total: high density lipoprotein (HDL) cholesterol ratio, triglycerides and glycated haemoglobin (HbA1c) compared with women, and a higher proportion of men were also current or ex-smokers.[17] Our study observed similar differences in baseline characteristics, with men more likely to be overweight, have a history of heart disease or stroke, and be previous smokers. Men may also be less likely to adopt primary prevention strategies, such as healthy lifestyle change and medication use,[16 19] and to engage in health seeking behaviours, such as preventative health checks.[20 21] Further, women are known to be at lower risk of CVD complications compared with men due to the protective effects of reproductive factors such as breastfeeding and the use of hormone replacement therapy within 10 years of menopause.[22] There are important age-specific sex differences in CVD complications. Women have an older age of CVD onset compared with men,[23] and experience lower rates of CVD up until the age of 80 years.[18] It is possible that the sex differences in CVD complications observed in our study may resolve if the cohort were to be followed for a longer time.

Evidence for sex differences in microvascular diabetes complications is less conclusive than for macrovascular complications. A meta-analysis of 10 studies (nine cohort) reported an elevated, but non-significant, increase in incident chronic kidney disease among women compared with men (adjusted women-to-men relative risk ratio (WMR) 1.14, 95% CI 0.97 to 1.34), with risk particularly higher for end stage renal disease (adjusted WMR 1.38, 95% CI 1.22 to 1.55).[24] In contrast, studies from the Netherlands and UK found a higher baseline prevalence and risk of incident microalbuminuria in men.[6 25] Although no studies have examined overall lower limb complications, the risk of amputation has been shown to be greater in men than in women.[26 27] Similarly, a meta-analysis of 20 studies found that men with diabetic foot have an approximate 50% increased amputation risk compared with women.[28] In contrast to the results for CVD, kidney and lower limb complications, our study found that women with diabetes were at greater risk of eye complications. This appeared to be largely driven by the inclusion of cataracts as a sub-group, which are more prevalent in women compared with men.[29 30] Considering diabetic retinopathy specifically, our results indicate a 14% greater risk of incident retinopathy in men which is consistent with a study from Italy which showed the incidence of diabetic retinopathy to be associated with the male sex (HR 1.31, 95% CI 1.05 to 1.63).[31] The mechanisms for

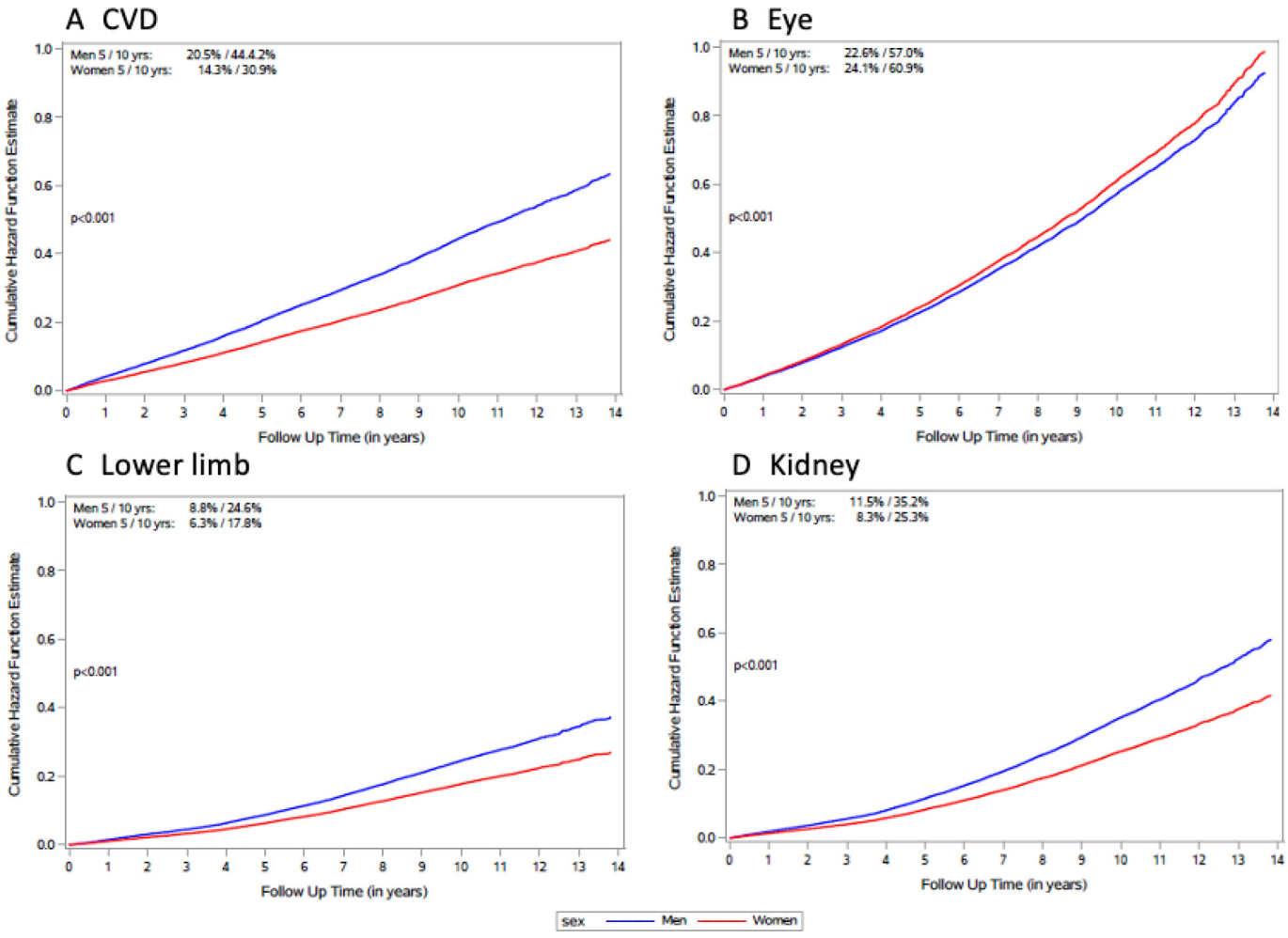

Figure 2 Cumulative incidence of macrovascular and microvascular complications by sex: (A) CVD complications; (B) eye complications; (C) lower limb complications; (D) kidney complications. Hazard function survival curves using Kaplan-Meier methods. P values in the figures represent the results for the log-rank test. CVD, cardiovascular disease.

sex differences in microvascular complications remains under-researched,[32] but possible factors include worse glycaemic and blood pressure control and treatment,[18] and an underutilisation of medical care for microvascular complications[28] in men compared with women. Large-scale studies examining sex differences in adherence to guideline-recommended processes of care, including medication adherence and healthy lifestyle behaviours, are needed to understand these findings better.

It is well understood that individuals with longer diabetes duration are at greater risk of complications. The UK Biobank study showed that with each 5 year increase in diabetes duration, there was a 20% increase in excess risk of CVD complications for both men and women.[7] Despite the greater complication-risk with longer disease duration, we observed a similar sex difference in risk of complications for those with diabetes duration <10 years compared with those with diabetes duration ≥10 years. Few studies have examined the effect of diabetes duration on sex differences in risk of complications; however, Duarte *et al* found that the magnitude of the association between duration of diabetes and glycaemic control was stronger for women compared with men.[33] Only individuals with age of diagnosis reported in the baseline survey could be included in our analysis stratified by disease duration (approximately two-thirds of the full sample), which may have influenced our findings.

The strengths of this study include the large population-based sample, the long follow-up time, and use of objective linked data to identify incident diabetes-related complications, avoiding issues of loss to follow-up and self-report. The data in our study did not include diabetes complications not requiring hospitalisation, with the exception of diabetic retinopathy and home dialysis. While our analyses took into account competing risk of CVD-related death before hospitalisation, these numbers were small (n=163), with no meaningful sex differences that might have had an impact on our results (online supplemental table 5). Given that diabetic kidney disease is frequently asymptomatic, unknown to patients,[34] and requires laboratory testing for detection, it is likely that the incidence of early-stage chronic kidney disease was underestimated in our study. On the other hand, as we excluded those with a prior history of complications to capture incident complications, this may have not allowed enough time for the development of end stage complications, such as limb amputations or requirement for kidney replacement therapy with dialysis or transplantation. As such, the absolute rates of complications should be interpreted with caution. The 45 and Up Study provides detailed information on sociodemographic, health and lifestyle covariates which we were able to adjust for in the analysis. However, we did not take into account all potential confounding/effect-modifying factors including

glycaemic, lipid and blood pressure control, medication use[35] and adherence which may have impacted the strength of the association between sex and risk of complications. We were also not able to differentiate between type 1 and type 2 diabetes in our study, precluding an analysis by type of diabetes. Although the 45 and Up cohort are broadly representative of the Australian population aged ≥45 years, the sample does overrepresent higher income earners, people aged 80 and over, and residents of rural and remote areas,[36] which may limit the generalisability of the results. Although men have a higher absolute risk of CVD complications, studies in patients with diabetes compared to those without diabetes have shown that the relative CVD risk conferred by diabetes is greater in women.[37–39] Sex differences in relative risk of diabetes complications was not assessed in our study.

In conclusion, although men with diabetes are at greater risk of developing complications, in particular CVD, kidney and lower-limb complications, the rates of complications are high in both sexes. The similar sex difference for those with shorter compared with longer diabetes duration highlights the need for targeted complication screening and prevention strategies from the time of diabetes diagnosis. Further investigation into the underlying mechanisms for the observed sex differences in diabetes complications are needed to inform targeted interventions.

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