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Complete List of Authors:	Ou, Huang-tz; National Cheng Kung University College of Medicine, Institute of Clinical Pharmacy and Pharmaceutical Sciences ; National Cheng Kung University College of Medicine, Pharmacy Lee, Tsung-Ying ; National Cheng Kung University College of Medicine, Institute of Clinical Pharmacy and Pharmaceutical Sciences Li, Chung-Yi; National Cheng Kung University College of Medicine, Public Health; China Medical University, Public Health Wu, Jin Shang ; National Cheng Kung University College of Medicine, Family Medicine; National Cheng Kung University Hospital, Family Medicine Sun, Zih Jie ; National Cheng Kung University Hospital, Family Medicine; National Cheng Kung University Hospital Dou-Liou Branch, Family Medicine
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Incidence of diabetes-related complications in ethnic Chinese with newly diagnosed type 1 diabetes, 1999-2013

Huang-Tz Ou PhD[1,2,*], Tsung-Ying Lee MS[1], Chung-Yi Li PhD[3,4], Jin-Shang Wu MD[5,6], Zih-Jie Sun MD[6,7]

[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2]Department of Pharmacy, College of Medicine, National Cheng Kung University Tainan, Taiwan
[3]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[4]Department of Public Health, China Medical University, Taichung, Taiwan
[5]Department of Family Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[6]Department of Family Medicine, National Cheng Kung University Hospital, Tainan, Taiwan
[7]Department of Family Medicine, National Cheng Kung University Hospital, Dou-Liou Branch, Dou-Liou, Taiwan

Corresponding author
Huang-Tz Ou, PhD
Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University,
1 University Road, Tainan 7010, Taiwan
Phone: +886-6-2353535 ext.5685
Fax: +886-6-2373149
Email: huangtz@mail.ncku.edu.tw

Abstract

Objective: To estimate the incidence densities and cumulative incidence of diabetes-related complications in patients with type 1 diabetes for a maximum of 15-year follow-up. The estimations were further stratified by gender and age at diagnosis (i.e., early-onset: 0-12 years, late-onset: ≤ 13 years).

Design: A population-based longitudinal cohort study.

Setting: Taiwan's National Health Insurance medical claims.

Participants: 4,007 patients newly-diagnosed with type 1 diabetes were identified during 1999-2012.

Outcome measures: Acute complications included diabetic ketoacidosis (DKA) and hypoglycemia. Chronic complications were cardiovascular diseases (CVD), retinopathy, neuropathy, and nephropathy.

Results: The incidence density of retinopathy was greatest (97.74 per 1,000 person-years), followed by those of nephropathy (31.36), neuropathy (23.93), and CVD (4.39). Among acute complications, the incidence density of DKA was greatest (121.11 per 1,000 person-years). The cumulative incidences of acute complications after 12 years following diagnosis were estimated to be 52.1%, 36.1%, and 4.1% for DKA, mild hypoglycemia, and

hospitalized hypoglycemia, respectively. For chronic complications, the cumulative incidence of retinopathy after 12 years following diagnosis was greatest (65.2%), followed by those of nephropathy (30.2%), neuropathy (23.7%), and CVD (4.1%). Females with late-onset diabetes were greatly affected by advanced retinopathy (i.e., sight-threatening diabetic retinopathy) and hospitalized hypoglycemia, whereas those with early-onset diabetes were more vulnerable to DKA. Chronic complications were more commonly seen in late-onset diabetes, whereas early-onset diabetes were most affected by acute complications.

Conclusions: Ethnically Chinese patients with type 1 diabetes were greatly affected by DKA and retinopathy. Significant age-sex disparities in the incidence of diabetes-related complications affect such individuals.

Strengths and limitations of this study

- ✓ This is the largest longitudinal cohort study of ethnically Chinese patients with type 1 diabetes followed for a maximum of 15 years to provide up-to-date incidence estimates of acute and chronic complications.
- ✓ The analyses stratified by gender and age at diabetes-onset indicated significant age-gender disparities in the epidemiological data of diabetes-related complications in type 1 diabetes, which highlight importance for clinical attention and developing preventive strategies.
- ✓ The study limitations resulting from the use of medical reimbursement claims data, including potential misclassifications of diabetes-related complications and lack of clinical biomarkers such as blood glucose, may underestimate rather than overestimate the incidence rates of diabetes-related complications.
- ✓ The incidence estimates of diabetes-related complications may only be generalizable to ethnically Chinese population with type 1 diabetes.

Introduction

It has been estimated that the incidence of type 1 diabetes increases by about 3-5% per year worldwide.[1-3] The annual incidence rate of childhood (< 15 years) type 1 diabetes in Taiwan was 5.3 per 100,000 children in the period 2003-2008.[4] Type 1 diabetes accounts for only 5-10% of the diabetic population, but it remains a devastating chronic disorder with acute complications, including diabetic ketoacidosis (DKA) and hypoglycemia, and chronic complications, which can be divided into microvascular (i.e., retinopathy, neuropathy, nephropathy) and macrovascular complications (i.e., cardiovascular diseases; CVD). Although treatment and care for type 1 diabetes have improved,[5-7] diabetes-related complications are major obstacles to glycemic control for many patients and contribute to most of the increased morbidity and premature mortality in such individuals.[8] The toxicity effect of prolonged chronic hyperglycemia is a leading cause of microvascular and macrovascular diseases among type 1 diabetes patients, with hypertension and dyslipidemia being exacerbating factors.[9]

Assessing the epidemiology of diabetes-related complications is essential for developing preventive strategies and planning treatment protocols to minimize the impact of the complications. However, there is very little longitudinal data (e.g., Pittsburgh Epidemiology

of Childhood-Onset Diabetes Complications (EDC) Study,[10] EURODIAB IDDM Complications Study[11]) on the incidence of complications for type 1 diabetes, and previous estimates widely vary by country and follow-up period (e.g., 7 years,[12] 12 years,[13] 18 years,[14] 30 years[10]). In addition, a limited number of diabetes-related complications have been investigated (e.g., microalbuminuria[12, 14] and cardiovascular diseases; CVD[13]), with no previous study targeting an ethnic Chinese population with type 1 diabetes. Ethnic variations in diabetes-related complications have been recognized; Caucasian patients are greatly affected by CVD,[15, 16] while the prevalence of end-stage renal failure (ESRD)[17] and the odds of microalbuminuria and macroaluminuria[18] in Asian populations are much higher compared to those for Caucasian patients. Given the significance of rising life expectancy in recent years among ethnic Chinese patients with type 1 diabetes,[19] it is important to provide precise up-to-date estimates of incidence of its complications and compare them to those for other countries. We therefore utilized a longitudinal population-based cohort of newly diagnosed type 1 diabetes patients who were followed during the period 1999-2013 to evaluate the incidence densities and cumulative incidences of acute and chronic complications to provide contemporary estimates for an ethnic Chinese population. Efforts were also made to examine whether there were age and sex differences in the incidences of type-1-diabetes-related

complications.

Materials and Methods

The Institutional Review Board of National Cheng Kung University Hospital approved the study before commencement (A-ER-103-298).

Data source:

We utilized the Longitudinal Cohort of Diabetes Patients (LHDB) 1996-2013 data from the National Health Insurance Research Database (NHIRD). Taiwan's NHIRD is population-based and derived from the claims data of the National Health Insurance (NHI) program, a mandatory-enrollment, single-payment system that covers over 99% of Taiwan's population.[20] The LHDB is a valid national dataset that consists of a random sample of 120,000 de-identified diabetes incident cases from each calendar year, who were tracked back to 1996 and followed up to 2013 to establish a longitudinal cohort. The LHDB is representative of Taiwan's population with diabetes and provides research opportunity to evaluate long-term health outcomes of patients.

Cohort:

From the LHDB, we selected 4,677 patients with a diagnosis of type 1 diabetes

(International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM = 250.x1 or 250.x3) from outpatient files of the LHDB and having received a Catastrophic Illness Card (CIC) for type 1 diabetes (Figure 1) in the period 1999-2012. Because patients with a CIC are eligible for exemption from insurance premiums and co-payments, the approval of such a status is subject to evaluation and review by the Bureau of NHI of Taiwan. The CIC patient data are accurate and reliable with a positive predictive value of 98.3% for type 1 diabetes.[19] We further excluded 670 potential type 2 diabetes cases who consumed any oral antihypoglycemic agents (OHAs) after CIC was issued, including sulfonylureas, meglitinides, acarbose, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide-1 receptor agonists, and however, those who used metformin alone, thiazolidinediones alone, or both were retained. Patients who were prescribed metformin, thiazolidinediones, or both were retained because these OHAs are insulin-sensitizers that can be combined with insulin treatments for cases with insulin resistance,[21, 22] which is also seen in patients with type 1 diabetes in Taiwan based on our expert opinions. To estimate the incidence rates of diabetes-related complications, we further selected cases without a history of microvascular or macrovascular diseases before type 1 diabetes diagnosis (Table 1). Study patients were stratified by gender and age at first type 1 diabetes diagnosis (i.e., early-onset: 0-12 years,

late-onset: ≤ 13 years).

Diabetes-related complications:

The complications of interest included acute complications, namely DKA (confirmed by hospital admission or emergency room visit for DKA), mild hypoglycemia (confirmed by outpatient visit for hypoglycemia), and hospitalized hypoglycemia, and chronic complications, namely CVD, nephropathy, retinopathy, and neuropathy. A list of diabetes-related complications and the corresponding ICD-9-CM codes are provided in Supplementary Table 1; this list was confirmed by the expert panel before being applied.

Statistics:

The incidence density of diabetes-related complications was calculated by dividing the number of incident cases with individual complication events by the total person-years observed over 15 years of follow-up (1999-2013). The 95% confidence intervals (CIs) were calculated assuming a Poisson distribution of cases.[23] Because a cohort of newly diagnosed type 1 diabetes patients was utilized, we were able to provide visual illustrations about the cumulative incidences of diabetes-related complications by diabetes duration since diabetes onset. The cumulative incidence of diabetes-related complications was estimated by using the life table method (using the SAS LIFETEST procedure). Significant differences in incidence

density between age-sex subgroups were indicated by a 95% CI for the difference in incidence density between subgroups.[24] SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for the aforementioned analyses.

Results

The overall and age-sex specific incidence densities of diabetes-related complications are presented in Tables 1 and 2, respectively. The incidence rate of retinopathy (97.74 per 1,000 person-years) was greatest, followed by those of nephropathy (31.36), neuropathy (23.93), and CVD (4.39). Among acute complications, the incidence density of DKA was greatest (121.11 per 1,000 person-years). As shown in Table 2, the incidence densities of retinopathy, DKA, and hospitalized hypoglycemia in females were significantly higher than those in males. The incidence densities of DKA and mild hypoglycemia in the early-onset group (0-12 years) were significantly higher than those noted in the late-onset group (≤ 13 years), while those of advanced retinopathy (i.e., sight-threatening diabetic retinopathy; STDR), neuropathy, nephropathy, CVD, and hospitalized hypoglycemia in the late-onset group were significantly higher. Figures 2 and 3 show cumulative incidences for acute and chronic complications, respectively, along with diabetes duration. The cumulative incidences

at the 12th year after diagnosis were 52.1%, 36.1%, and 4.1% for DKA, mild hypoglycemia, and hospitalized hypoglycemia, respectively. For chronic complications, the 12-year cumulative incidence of retinopathy was greatest (65.2%), followed by those of nephropathy (30.2%), neuropathy (23.7%), and CVD (5.2%). At 5 years after diabetes diagnosis, around 45% of patients experienced hypoglycemia, while at 10 years after diagnosis, about half of patients had hypoglycemia. Age-sex specific cumulative incidences of diabetes-related complications are illustrated in Supplementary Figure 1.

Discussion

To the best of our knowledge, this is the largest cohort study of ethnically Chinese patients with newly diagnosed type 1 diabetes. We provided up-to-date estimates of the incidence of acute and chronic complications in type 1 diabetes patients followed for a maximum of 15 years. We observed age-gender disparities in the incidence of diabetes-related complications in type 1 diabetes. Although comparisons of the epidemiology of diabetes-related complications between studies are difficult, as potential determinants of the complications (e.g., age, gender, diabetes duration) differ, the estimates from different studies may reveal some racial or ethnic differences. In the following, we compare our results

for ethnically Chinese patients with those reported for other countries or ethnicities.

Acute diabetes-related complications in type 1 diabetes patients

Diabetic ketoacidosis

Among acute complications, hyperglycemic events, including DKA and hyperglycemic hyperosmolar syndrome (HHS), are leading causes of morbidity and mortality among individuals with diabetes,[25] and utilize significant healthcare resources.[26] DKA was the most common acute complication among the Taiwanese population with type 1 diabetes; the incidence density followed for 15 years was 121.11 per 1,000 person-years, and half of the study population (~52%) experienced DKA at 12 years after diabetes diagnosis. Consistent with previous studies from the United States,[27] Australia,[28] and Canada,[29] we found that the incidence of DKA in female patients, especially those with early-onset diabetes (i.e., 0-12 years), was higher than that in male patients. A cohort of 1,234 children with type 1 diabetes in the United States showed that female patients were greatly affected by DKA. A female preponderance of DKA was observed in a longitudinal study of childhood type 1 diabetes in Australia.[28] Similarly, a Canadian study of childhood type 1 diabetes showed that female sex was a significant predictor of DKA.[29] In fact, insulin omission or intentional insulin under-treatment due to fear of weight gain[30] and high prevalence of eating disorders[31] and

psychiatric disorders[27] among female type 1 diabetes patients have been recognized as precipitating causes of DKA. Hence, effective interventions such as health education and communication for type 1 diabetes females are needed to reduce the incidence of DKA.

Hypoglycemia

Increased hypoglycemic events have been recognized as a result of the undesired effects of intensive insulin therapy with strict glycemic control.[32] The present study showed that the incidence rates of hospitalized and mild hypoglycemia in the Taiwanese population with type 1 diabetes were 3.89 and 39.93 per 1,000 person-years, respectively, which are much lower than that reported in type 1 diabetes children (0-19 years) in the United States (incidence of severe hypoglycemia: 190 per 1,000 person-years).[27] Such discrepancies in international data may be explained by different definitions and assessment approaches for hypoglycemic events. We targeted hospital admissions for severe hypoglycemia based on ICD-9 CM codes, whereas the United States study used patients' reported survey data and classified severe hypoglycemia as acute episodes requiring the assistance of another person for treatment reported in the preceding 3 months.[33]

Moreover, we observed that early-onset patients were greatly affected by acute complications (i.e., DKA, hypoglycemia). It has been documented that among young children

with type 1 diabetes, inconsistent eating patterns and lesser ability to recognize and report acute symptoms make it difficult to achieve glycemic control, leading to glycemic fluctuations that cause multiple episodes of hyperglycemia (i.e., DKA) and hypoglycemia.[34] Frequent exposures to hyperglycemia and hypoglycemia in early-onset type 1 diabetes patients could lead to a range of neurocognitive dysfunctions and brain changes.[35] Also, structural brain changes in type 1 diabetes children may occur due to recurrent hypoglycemia.[36] Hence, given the high rates of acute complications and associated serious consequences, effective management protocols and identification and treatment of precipitating causes are needed.[37] In particular, regular glycemic monitoring and identification of risk factors in young type 1 diabetes patients are needed to reduce the frequency and severity of DKA and hypoglycemia.

Chronic diabetes-related complications in type 1 diabetes

Diabetic retinopathy

Diabetic retinopathy is the main cause of blindness in the adult population.[38] Almost all type 1 diabetes patients develop evident retinopathy in the first 20 years of diagnosis.[39] The present study showed that more than half (~69%) of type 1 diabetes patients experienced some form of diabetic retinopathy at 12 years after diagnosis. We observed that the incidence

density of diabetes retinopathy is greatest among chronic complications in Taiwanese type 1 diabetes patients (4.53 per 100 person-years over a period of 15 years of follow-up). As compared to the incident density of proliferative retinopathy (19.5 per 1,000 person-years) in the Pittsburgh EDC Study of type 1 diabetes patients with a mean age of 28 years and diabetes duration of 19 years at baseline examination,[10] our estimate (5.87 per 1,000 person-year) based on a cohort of newly diagnosed type 1 diabetes patients is lower. Such a difference between studies may be explained by diabetes duration and age at baseline of study examination. Moreover, comparing the prevalence of STDR in type 1 diabetes patients in this study (2.00 % for women and 1.66 % for men) with that previously observed in Taiwanese type 2 diabetes patients (2.75% for women and 2.87% for men)[40] reveals a slightly lower advanced diabetic retinopathy (i.e., STDR) in the type 1 diabetes versus type 2 diabetes patients. However, the lower rate of STDR in our study may be due to the other study's inclusion of prevalent type 2 diabetes cases with longer diabetes duration[40] as compared to incident type 1 diabetes targeted in this study.

Consistent with previous studies,[41, 42] the present study demonstrated a female preponderance in diabetic retinopathy. A large cohort of 8,114 type 1 diabetes patients and families assembled over 25 years from the United States showed that females had 1.7 fold

higher retinopathy risk ($p < 0.001$) as compared to that of males.[41] Also, a cross-sectional study of 247 Italian type 1 diabetes patients showed a significant relationship between diabetic retinopathy and female gender ($p = 0.01$).[42] Although exact hormone, genetic, lifestyle, or environmental factors are unclear, a differential effect of sex steroid hormones has been proposed to explain this gender discrepancy.[43] Also, age at diabetes onset has been shown to be associated with the development of diabetic retinopathy.[42, 44] An early age at onset (5-14 years) appears to modify the long-term risk of proliferative retinopathy.[44] Consistent with other studies, we observed lower incidence of diabetic retinopathy in early-onset patients as compared to that in late-onset patients. Nevertheless, given a high rate of diabetes retinopathy observed among Taiwanese type 1 diabetes patients, early detection using routine eye examination, control for risk factors of diabetic retinopathy (e,g., hypertension, hyperglycemia, hyperlipidemia),[9] as well as development of tailored intervention strategies for age-sex subgroups are important.

Diabetic nephropathy

Our results show that diabetic nephropathy is the second most common microvascular complication among the Taiwanese population with type 1 diabetes. Without interventions, diabetes patients with microalbuminuria typically progress to proteinuria and overt diabetic

nephropathy.[45] Diabetic nephropathy is a leading cause of ESRD among patients with diabetes.[45] As estimated, individuals with type 1 diabetes face a 20-50% chance of developing ESDR that requires dialysis or renal transplantation.[46] The Pittsburgh EDC Study reported that the incidence density of renal failure (based on self-reported renal transplantation and dialysis) was 6.3 per 1,000 person-years over 12 years of follow-up,[10] while the present study based on ICD-9 codes of renal failure found that the incidence of renal failure was 1.31 per 1,000 person-years over 15 years of follow-up. Of note, the EDC study enrolled more advanced type 1 diabetes cases (i.e., mean age of 28 years and diabetes duration of 19 years at baseline examination[10]) than those in our study (i.e., newly diagnosed type 1 diabetes cases in 2000-2012), which may explain the higher rate of renal failure in the EDC study. A large inception cohort study of Danish patients newly diagnosed with type 1 diabetes followed for a median of 18 years reported that the cumulative incidences of persistent microalbuminuria and macroalbuminuria were 33.6% and 14.6%, respectively, while the present study found that overall cumulative incidence of any form of diabetic nephropathy was 30.2% at 12 years after diabetes diagnosis. Moreover, early-onset diabetes appears to be protective for developing diabetic nephropathy[12, 47-49] and may delay the time until microalbuminuria.[49] Consistently, we found that late-onset diabetes patients were more

affected by diabetic nephropathy than were early-onset patients. Nevertheless, given the fact that Taiwan has the highest number of patients undergoing renal dialysis in the world, where diabetes contributes to about 40 % of end-stage renal failure cases,[50] it is critical for routine annual screening of clinical signs of diabetic nephropathy (i.e., proteinuria, microalbuminuria), optimal control of glycemia and risk factors (e.g., retinopathy smoking, dyslipidemia, hypertension[14, 51, 52]), and early intervening medications for prevention (e.g., angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker for those with comorbid hypertension).[9]

Diabetic neuropathy

Diabetic neuropathy refers to the presence of symptoms, signs, or both of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.[53] Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies.[54] The epidemiological data of diabetic neuropathy is very limited. A study of 467 Italian type 1 diabetes patients showed that the prevalence rates of asymptomatic and symptomatic neuropathy were 7.2% and 21.3%, respectively.[55] The present study is the first study to provide epidemiology data on diabetic neuropathy among ethnically Chinese patients with type 1 diabetes from Asia. We found that

the incidence rate was 23.93 per 1,000 person-years over 15 years of follow-up, and that the cumulative incidence was 23.7% at 12 years after diabetes diagnosis. We also observed that the incidence of diabetic neuropathy in late-onset patients were much higher than that in early-onset patients. Similarly, the Italian study of type 1 diabetes showed that the prevalence of diabetic neuropathy was higher in patients at older ages.[55] Since diabetic neuropathy contributes to considerable disabilities and mortality, it is critical for clinicians to understand its manifestations, prevention, and treatment.[9] Early prevention strategies that control hypertension and hyperglycemia and identify patients with peripheral neuropathy or peripheral vascular disease and annual screening for these conditions are strongly recommended.[9]

Cardiovascular diseases

CVD is a leading cause of mortality in patients with type 1 diabetes[56, 57] and accounts for the greatest proportion of healthcare spending for patients with diabetes.[57, 58] As compared to patients without diabetes, type 1 diabetes increases the risk of CVD by ten fold,[56, 59] which contributes to two-thirds of mortality in patients with type 1 diabetes.[60, 61] The Pittsburgh EDC Study showed an incidence density of 3.6 per 1,000 person-years for coronary heart diseases (defined as coronary-artery-disease-related death, a history of myocardial infarction,

angiographic stenosis ≥ 50% including revascularization) over a period of 12 years,[10] while the present study found that the incidence density for a broader category of CVD (including myocardial infarction, ischemic heart diseases, heart failure, stroke, and arrhythmia, as shown in Supplementary Table 1) in the Taiwanese population with type 1 diabetes within 15 years of follow-up was 4.39 per 1,000 person-years. The cumulative incidences of CVD (including only stroke and coronary heart disease) at 12 years after diabetes was diagnosed was 1-2% among Finnish type 1 diabetes patients,[13] which is lower than that for the Taiwanese type 1 diabetes patients in the present study (~5.2%). Moreover, we found that late-onset patients were greatly affected by CVD. In fact, old age is recognized as a predictor of vascular diseases,[56] which may be explained by the calcification of extremity arteries and hypertension in older age patients, which are risk factors of macrovascular diseases.[62]

Methodological concerns

Some limitations of this study should be acknowledged. The classification of diabetes-related complications based on the ICD-9 CM codes in claims data may underestimate the occurrence of the complications. For example, patients experiencing clinical symptoms/signs of diabetes-related complications (e.g., hypoglycemia) may not see doctors if they can tolerate them. Also, the claims data do not capture clinical/minor

symptoms or signs of diabetes-related complications such as minor microalbuminuria. The glycemic biomarkers such as blood glucose were not available from the claims data so the identification of hyperglycemia or hypoglycemia was only based on the ICD-9 CM diagnosis codes. However, the claims records capture defined diabetes-related complications that are required for medical assistance or treatments, which lead to more conservative estimates and reveal important manifestations of diabetes-related complications for clinical attention. Lastly, the generalizability of our study results may be limited to ethnically Chinese populations. In addition, our results may represent only ethnically Chinese patients with type 1 diabetes in Taiwan.

Conclusions

Utilizing an incident cohort of type 1 diabetes patients diagnosed during the period 1999-2012 with a maximum of 15 years of follow-up, we found that most type 1 diabetes patients were affected by DKA and retinopathy, which highlight the critical need to identify precipitating causes and modifiable factors for developing preventive strategies and intervening treatment protocols to minimize the impact of these complications. Age and sex discrepancies appear in epidemiological data of diabetes-related complications; late-onset diabetes females were greatly affected by advanced retinopathy (i.e., STDR) and hospitalized

hypoglycemia, while early-onset females had a high incidence of DKA. Chronic diabetes-related complications were more common in late-onset type 1 diabetes patients, while early-onset individuals were most affected by acute complications. More attention should be given to identify potential risk factors and contributors to such age-sex differences in diabetes-related complications. Population-based data on the incidence of diabetes-related complications from this study are important for clinicians to recognize the need for diagnostic awareness and for policy-markers to develop effective treatments for patients with type 1 diabetes.

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Table 1: Overall incident number and incidence density of diabetes-related complications in patients with type 1 diabetes, 1999-2013

	Retinopathy	Proliferative retinopathy	STDR	Neuropathy	Nephropathy	Renal failure	CVD	DKA	Mild hypoglycemia	Hospitalized hypoglycemia
No. of cases*	3,359	3,970	3,983	3,742	3,634	4,003	3,916	2,205	3,934	3,987
No. of cases with event	1,532	157	90	558	688	36	117	996	913	105
Follow-up time (person-years)†	15,675	26,733	27,139	23,320	21,936	27,491	26,664	8,224	22,865	26,968
Incidence density (1,000 person-years) (95% CI)	97.74 (92.9-102.8)	5.87 (5.0-6.9)	3.32 (2.7-4.1)	23.93 (22.0-26.0)	31.36 (29.1-33.8)	1.31 (0.9-1.8)	4.39 (3.6-5.3)	121.11 (113.7-128.9)	39.93 (37.4-42.6)	3.89 (3.2-4.7)

* No. of cases refers to the number of patients who had no complication of interest in the baseline year (one year before diagnosis year).

† Cumulative follow-up time (person-years) was calculated as the sum of follow-up years during observation period.

Note: Patients with type 1 diabetes were retrieved from incidence cases from 2000 to 2012. Follow-up time started from the first diagnosis date to the time the event occurred, death, discontinued enrollment from Taiwan's National Health Insurance Program, or the end of 2013, whichever came first.

Abbreviations: STDR: sight-threatening diabetic retinopathy, CVD: cardiovascular disease, DKA: diabetic ketoacidosis, CI: confidence interval.

Table 2: Age-sex-specific incident number and incidence density of diabetes-related complications in patients with type 1 diabetes, 1999-2013

	Retinopathy	Proliferative retinopathy	STDR	Neuropathy	Nephropathy	Renal failure	CVD	DKA	Mild hypoglycemia	Hospitalized hypoglycemia
Male										
No. of cases*										
All male	1,618	1,886	1,892	1,778	1,695	1,901	1859	1,073	1,872	1,902
Early-onset (0-12 years)	654	719	719	714	700	719	712	396	718	719
Late-onset (≥13 years)	964	1,167	1,173	1,064	995	1,182	1,147	677	1,154	1,183
No. of cases with event										
All male	693	64	34	261	332	15	60	447	452	28
Early onset	305	14	1	37	86	1	7	239	202	11
Late onset	388	50	33	224	246	14	53	208	250	17
Follow-up time (person-years)†										
All male	7,813	12,908	13,102	11,345	10,403	13,248	12,798	4,322	11,025	13,115
Early-onset	3,333	5,290	5,368	5,180	4,817	5,358	5,280	1,317	4,277	5,297
Late-onset	4,480	7,618	7,734	6,165	5,586	7,891	7,518	3,005	6,749	7,818
Incidence density (1,000 person-years) (95% CI)										
All male	88.70	4.96	2.60	23.01	31.91	1.13	4.69	103.43	41.00	2.13
	(82.2-95.6)	(3.8-6.3)	(1.8-3.6)	(20.3-26.0)	(28.6-35.5)	(0.6-1.9)	(3.6-6.0)	(94.1-113.5)	(37.3-45.0)	(1.4-3.1)
Early-onset	91.52	2.65	0.19	7.14	17.85	0.19	1.33	181.53	47.23	2.08
	(81.5-102.4)	(1.4-4.4)	(0.0-1.0)	(5.0-9.8)	(14.3-22.0)	(0.0-1.0)	(0.5-2.7)	(159.2-206.1)	(40.9-54.2)	(1.0-3.7)
Late-onset	86.60	6.56	4.27	36.34	44.04	1.77	7.05	69.22	37.05	2.17
	(78.2-95.7)	(4.9-8.7)	(2.9-6.0)	(31.7-41.4)	(38.7-49.9)	(1.0-3.0)	(5.3-9.2)	(60.1-79.3)	(32.6-41.9)	(1.3-3.5)

95% CI of incidence density difference for male, early vs. late-onset	**-8.5 to 18.3**	**-6.4 to -1.4‡**	**-5.9 to -2.3‡**	**-34.8 to -23.6‡**	**-33.1 to -19.3‡**	**-2.8 to -0.4‡**	**-8.1 to -3.3‡**	**91.5 to 133.1‡**	**2.4 to 17.9‡**	**-1.7 to 1.5**
Female										
No. of cases*										
All female	1,741	2,084	2,091	1,964	1,939	2,102	2,057	1,132	2,062	2,085
Early-onset	721	777	777	772	764	777	773	413	774	774
Late-onset	1,020	1,307	1,314	1,192	1,175	1,325	1,284	719	1,288	1,311
No. of cases with event										
All female	839	93	56	297	356	21	57	549	461	77
Early-onset	358	18	6	50	109	1	11	277	229	21
Late-onset	481	75	50	247	247	20	46	272	232	56
Follow-up time (person-years)†										
All female	7,862	13,825	14,037	11,976	11,533	14,243	13,866	3,902	11,840	13,853
Early-onset	3,616	5,848	5,910	5,610	5,283	5,927	5,871	1,183	4,642	5,777
Late-onset	4,246	7,977	8,127	6,365	6,250	8,317	7,995	2,719	7,199	8,076
Incidence density (1,000 person-years) (95% CI)										
All female	106.72	6.73	3.99	24.80	30.87	1.47	4.11	140.69	38.94	5.56
	(99.6-114.2)	(5.4-8.2)	(3.0-5.2)	(22.1-27.8)	(27.7-34.2)	(0.9-2.3)	(3.1-5.3)	(129.2-153.0)	(35.5-42.7)	(4.4-6.9)
Early-onset	99.01	3.08	1.02	8.91	20.63	0.17	1.87	234.05	49.34	3.63
	(89.0-109.8)	(1.8-4.9)	(0.4-2.2)	(6.6-11.8)	(16.9-24.9)	(0.0-0.9)	(0.9-3.4)	(207.3-263.3)	(43.1-56.2)	(2.3-5.6)
Late-onset	113.29	9.40	6.15	38.80	39.52	2.40	5.75	100.05	32.23	6.93
	(103.4-123.9)	(7.4-11.8)	(4.6-8.1)	(34.1-44.0)	(34.7-44.8)	(1.5-3.7)	(4.2-7.7)	(88.5-112.7)	(28.2-36.7)	(5.2-9.0)

95% CI of incidence density difference for female, early vs. late-onset	**-28.8 to 0.2**	**-9.1 to -3.6‡**	**-7.3 to -3.0‡**	**-35.5 to -24.2‡**	**-25.3 to -12.5‡**	**-3.5 to -1.0‡**	**-6.0 to -1.7‡**	**108.4 to 159.6‡**	**9.8 to 24.4‡**	**-5.8 to -0.8‡**
95% CI of incidence density difference for male vs. female	**-27.8 to -8.2‡**	**-3.6 to 0.1**	**-2.8 to -0.02‡**	**-5.8 to 2.2**	**-3.6 to 5.7**	**-1.2 to 0.5**	**-1.0 to 2.2**	**-52.3 to -22.2‡**	**-3.1 to 7.2**	**-4.9 to -1.9‡**

* No. of cases refers to the number of patients who had no complication of interest in the baseline year (one year before diagnosis year).

† Cumulative follow-up time (person-years) was calculated as the sum of follow-up years during observation period.

Note: Patients with type 1 diabetes were retrieved from incidence cases from 2000 to 2012. Follow-up time started from the first diagnosis date to the time the event occurred, death, discontinued enrollment from Taiwan's National Health Insurance Program, or the end of 2013, whichever came first.

Abbreviations: STDR: sight-threatening diabetic retinopathy, CVD: cardiovascular disease, DKA: diabetic ketoacidosis, CI: confidence interval. ‡ $p < 0.05$

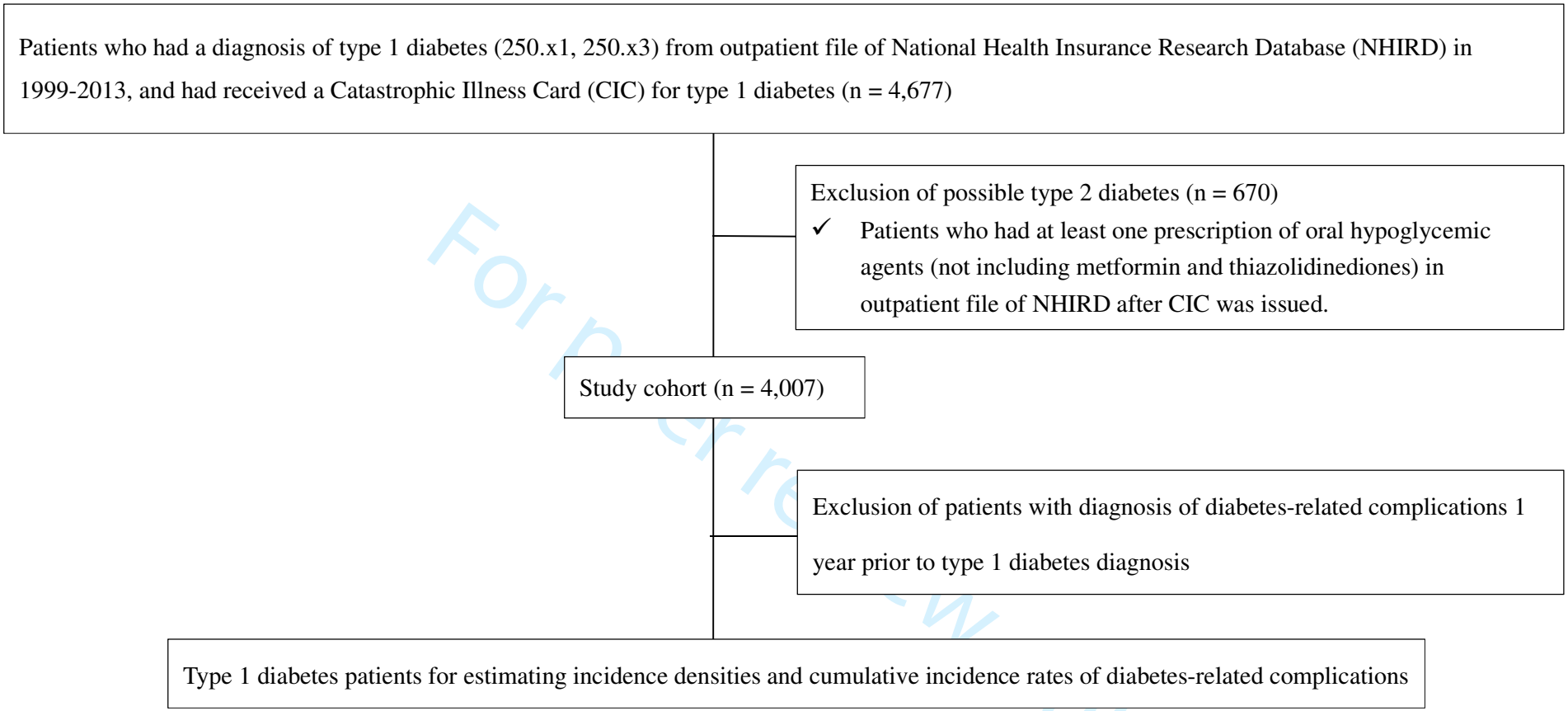


Figure 1. Flowchart of study cohort selection

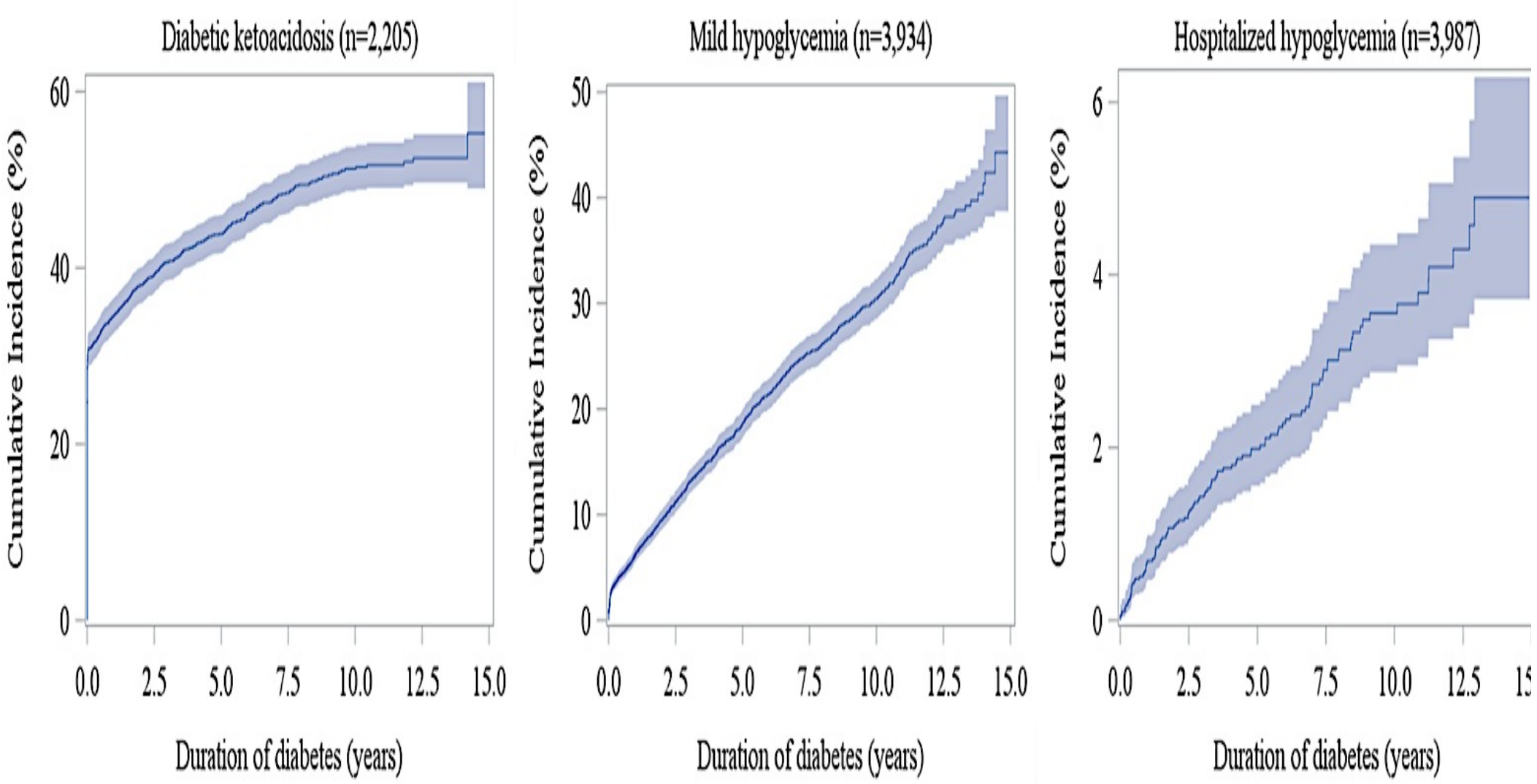


Figure 2: Cumulative incidences of diabetic ketoacidosis, mild hypoglycemia according to the duration of diabetes in patients with type 1 diabetes

Note: Shadow area indicates 95 % confidence interval.

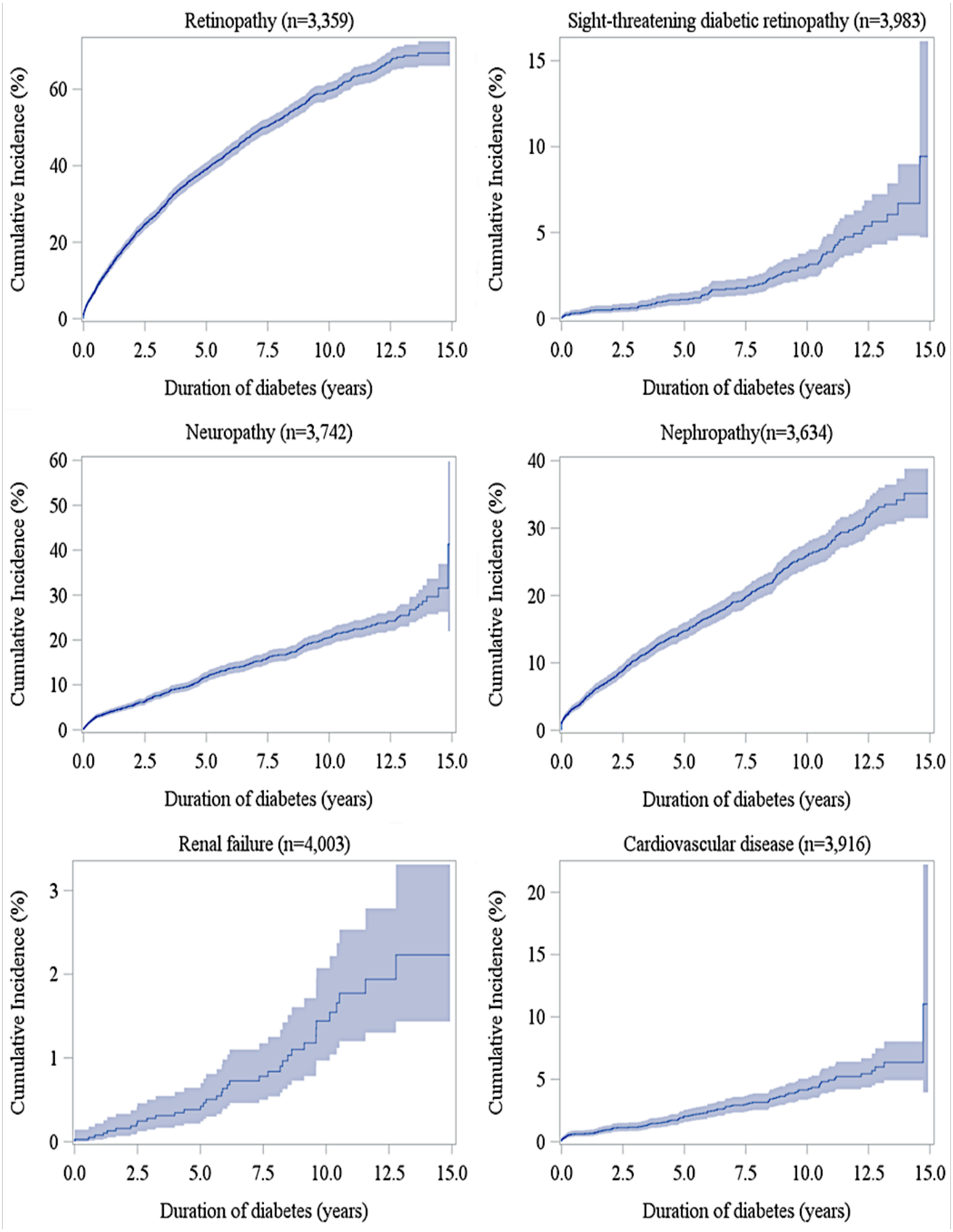


Figure 3: Cumulative incidences of retinopathy, sight-threatening diabetic retinopathy, neuropathy, nephropathy, renal failure, and cardiovascular diseases according to the duration of diabetes in patients with type 1 diabetes.

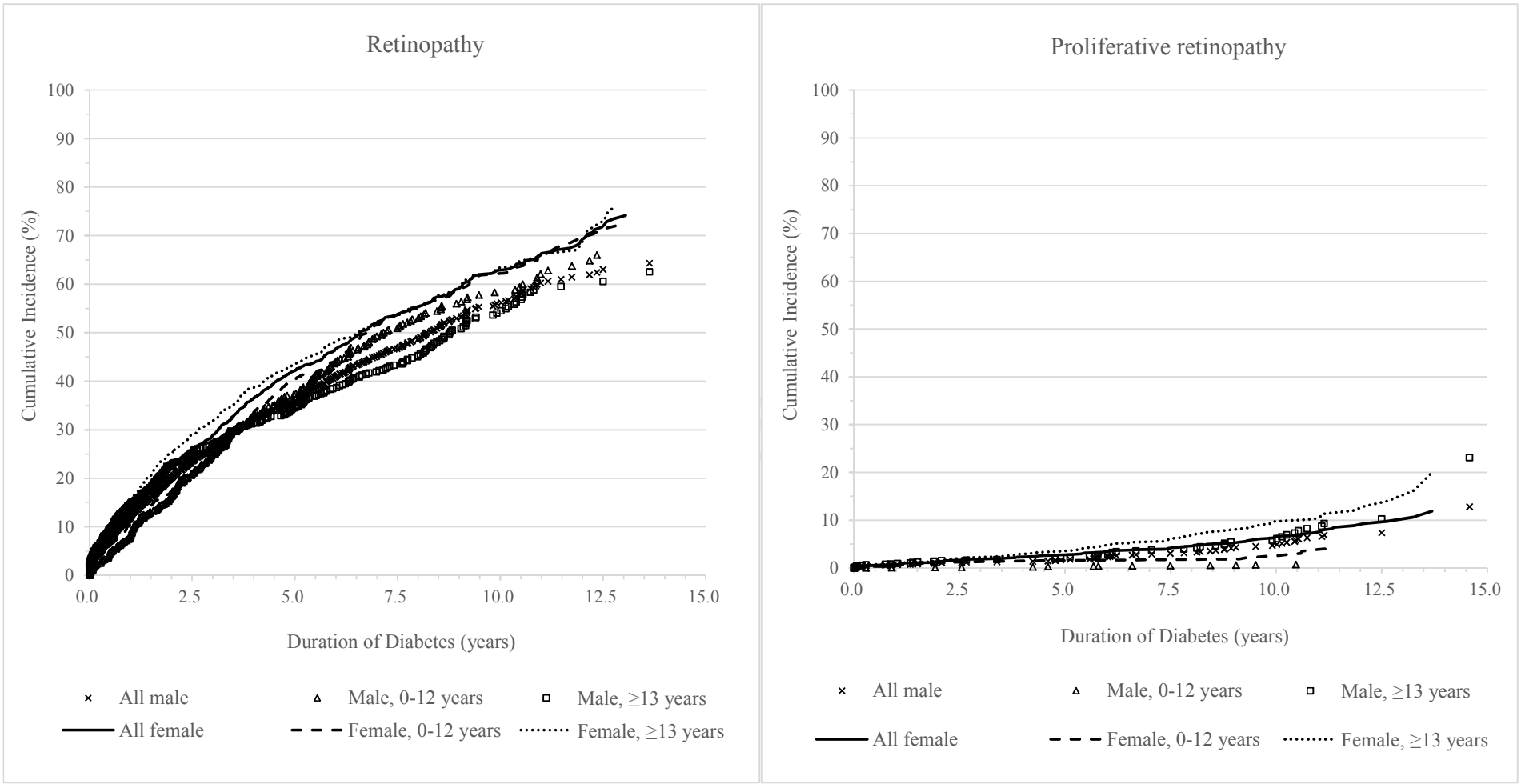
Note: Shadow area indicates 95 % confidence interval.

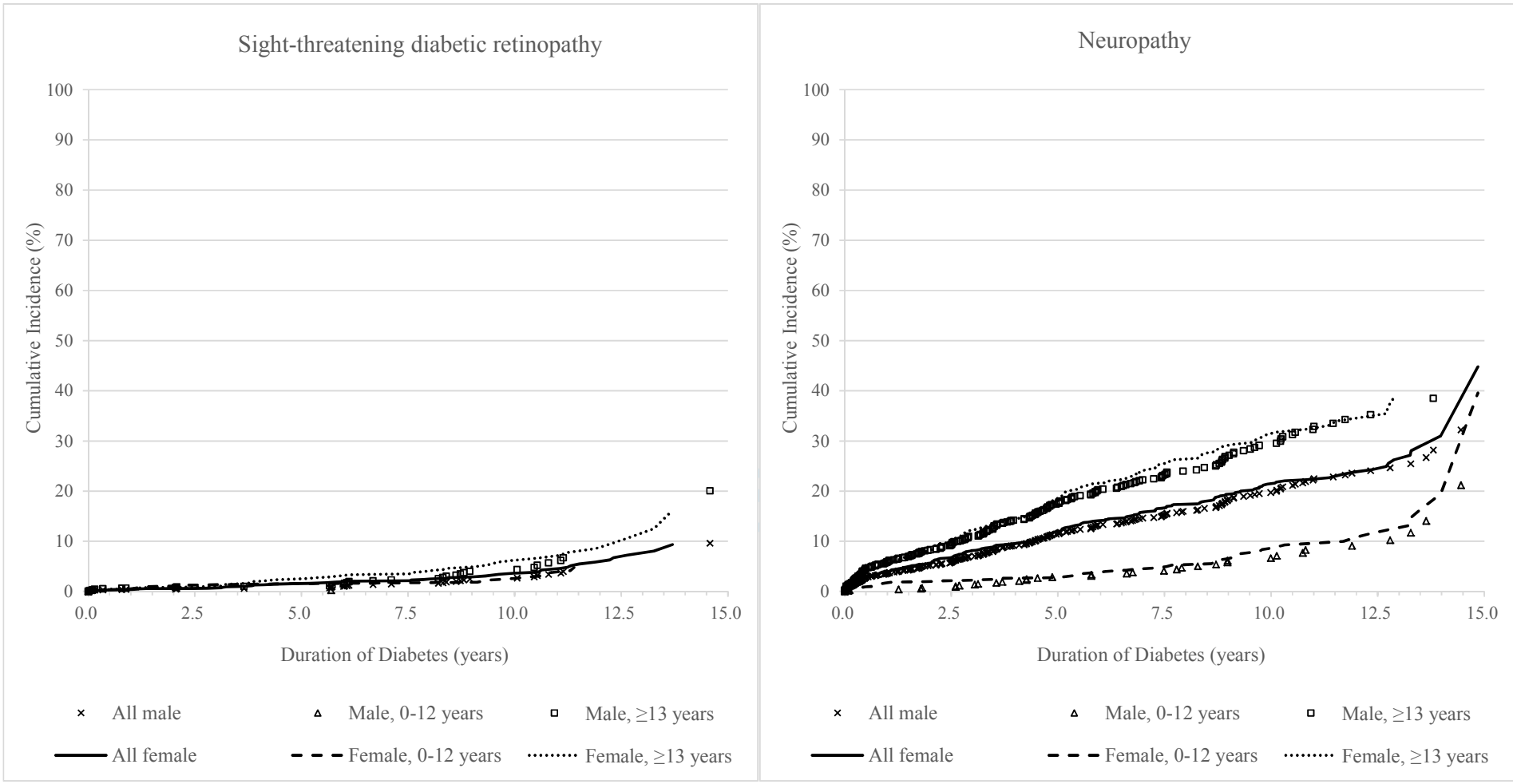
Supplementary Table 1: Diabetes-related acute and chronic complications

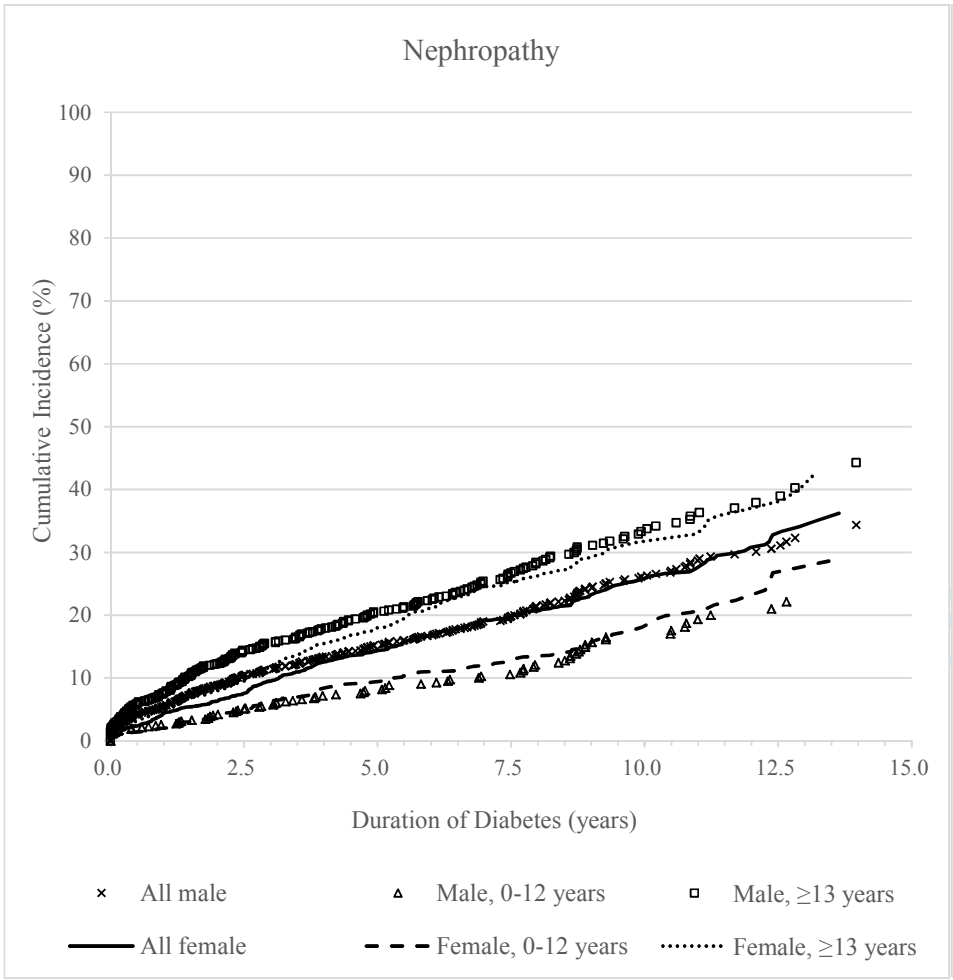
Complications	ICD-9-CM disease codes	ICD-9-CM procedure codes	NHI procedure codes
CVD (cardiovascular disease and cerebrovascular disease)[a,b]			
Acute myocardial infarction	410, 412*	---	---
Ischemic heart disease	411, 413, 414, V45.81, V45.82	00.66, 36.0, 36.1, 36.2, 36.3, 36.9, 88.9	---
Heart failure	428		---
Stroke	430-437, 438*, V12.54	00.61, 00.63, 38.11, 38.12	---
Cardiogenic shock	785.51	---	---
Sudden cardiac arrest	V12.53	---	---
Arteriosclerotic cardiovascular disease	429.2	---	---
Arrhythmia	426, 427	---	---
Microvascular complications[a,c]			
Nephropathy	250.4, 403, 404, 580, 581, 582, 583, 584, 585, 586, 587, 588, 593, 791.0, V13.03, V42.0, V45.1, V56	38.95, 39.27, 39.42, 39.95, 54.98, 55.4, 55.5, 55.6	---
Renal failure (dialysis or transplantation)[d]	V45.1, V56	39.95, 54.98 55.6	---
Retinopathy	250.5, 361, 362, 364, 365, 366, 368, 369, 377, 379.2	12.41, 12.73, 14.23, 14.24, 14.25, 14.33, 14.34, 14.35, 14.53, 14.54, 14.55, 16.92, 16.99	86206B, 86207B, 60001C, 60002C*, 60003C, 60004C*
Proliferative retinopathy[d]	362.02	---	60001C, 60002C*, 60003C, 60004C*
Sight-threatening diabetic retinopathy[e]	---	---	86206B, 86207B, 60001C, 60002C*, 60003C, 60004C*
Neuropathy	250.6, 302.72, 337.1, 354, 355, 357.2, 358.1, 607.84, 713.5, 729.2	---	---
Metabolic complications			
Diabetic ketoacidosis[a]	250.1	---	---
Hypoglycemia[a,f]	251.0, 251.1, 251.2, 270.3, 775.0, 775.6	---	---

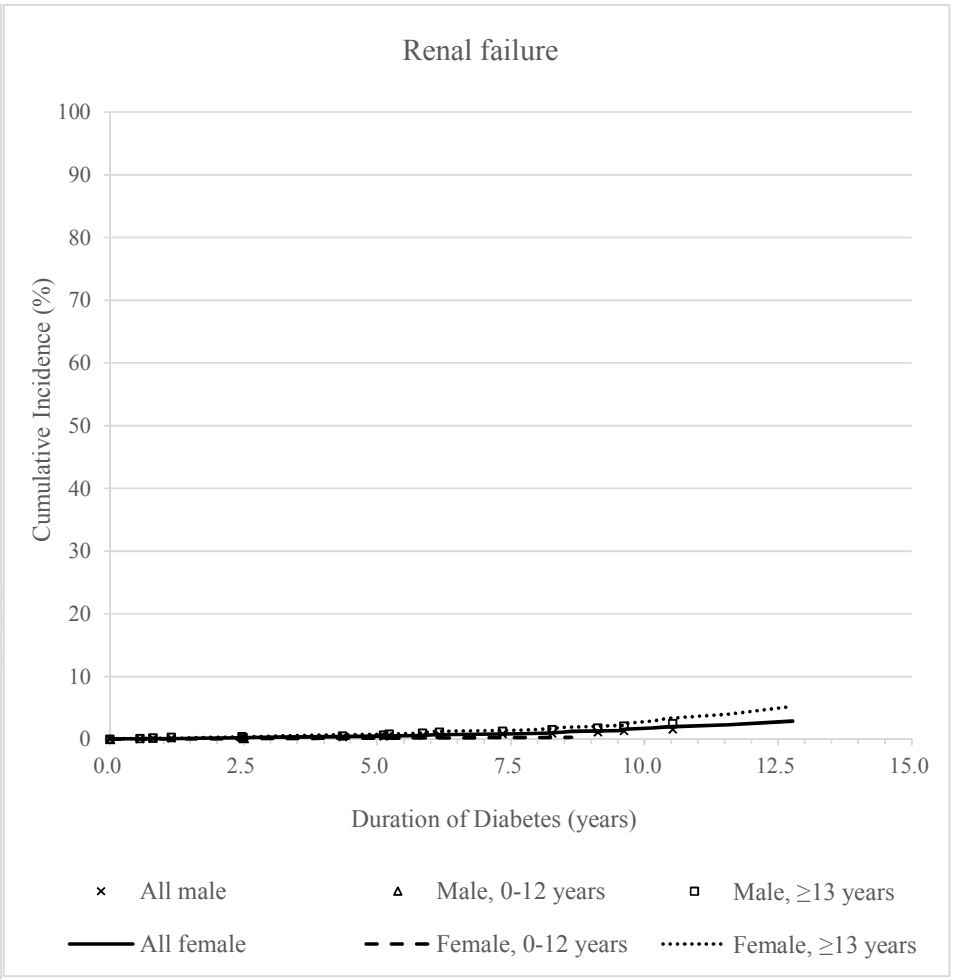
*For identifying prevalent cases only. a: Nutr Metab Cardiovasc Dis. 2014;24(1):10-7. b: Pharmacoepidemiol Drug Saf. 2009;18(6):497-503. c: Diabetes Care. 2008;31(3):596-615. d: Diabetes. 2006;55(5):1463-9. e: JAMA Ophthalmol. 2014;132(8):922-928. f: BMC Endocr Disord. 2008;8:4. Abbreviations: ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification, NHI: Taiwan National Health Insurance.

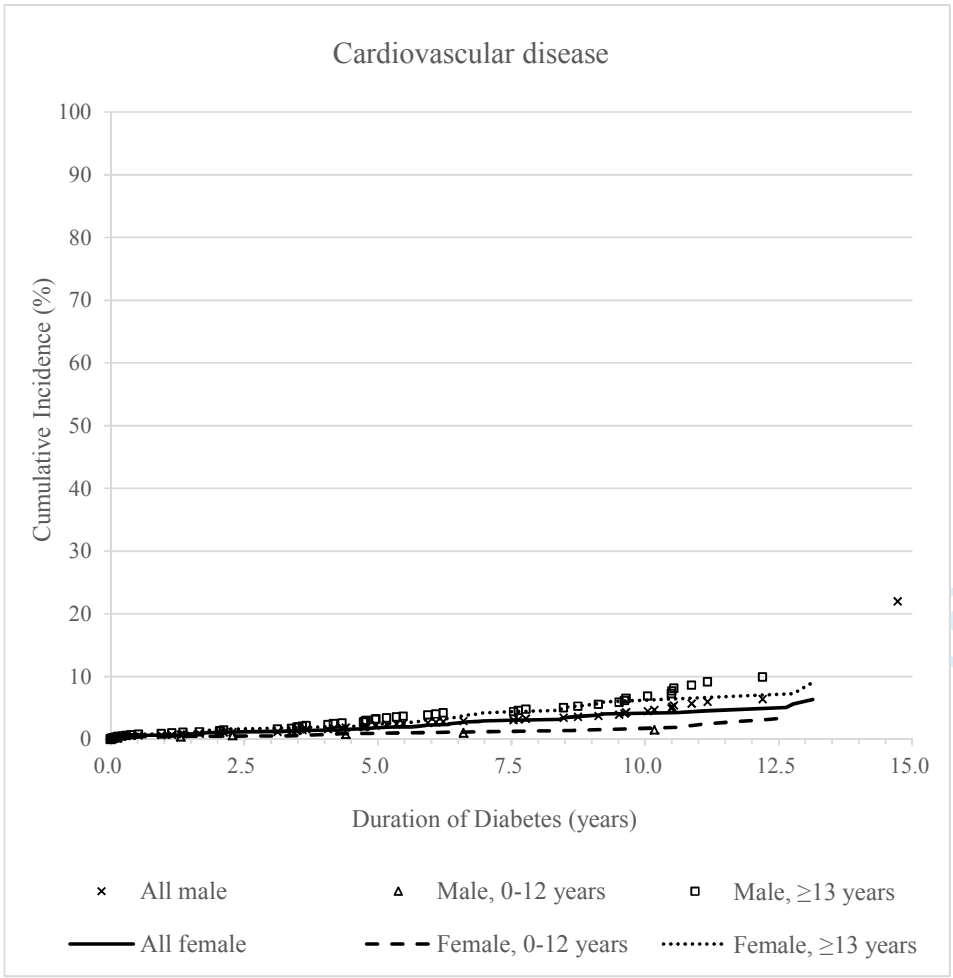
Supplementary Figure 1: Age-sex-specific cumulative incidences of diabetes complications according to duration of diabetes in patients with type 1 diabetes (early-onset: 0-12 years, late-onset: ≥13 years)

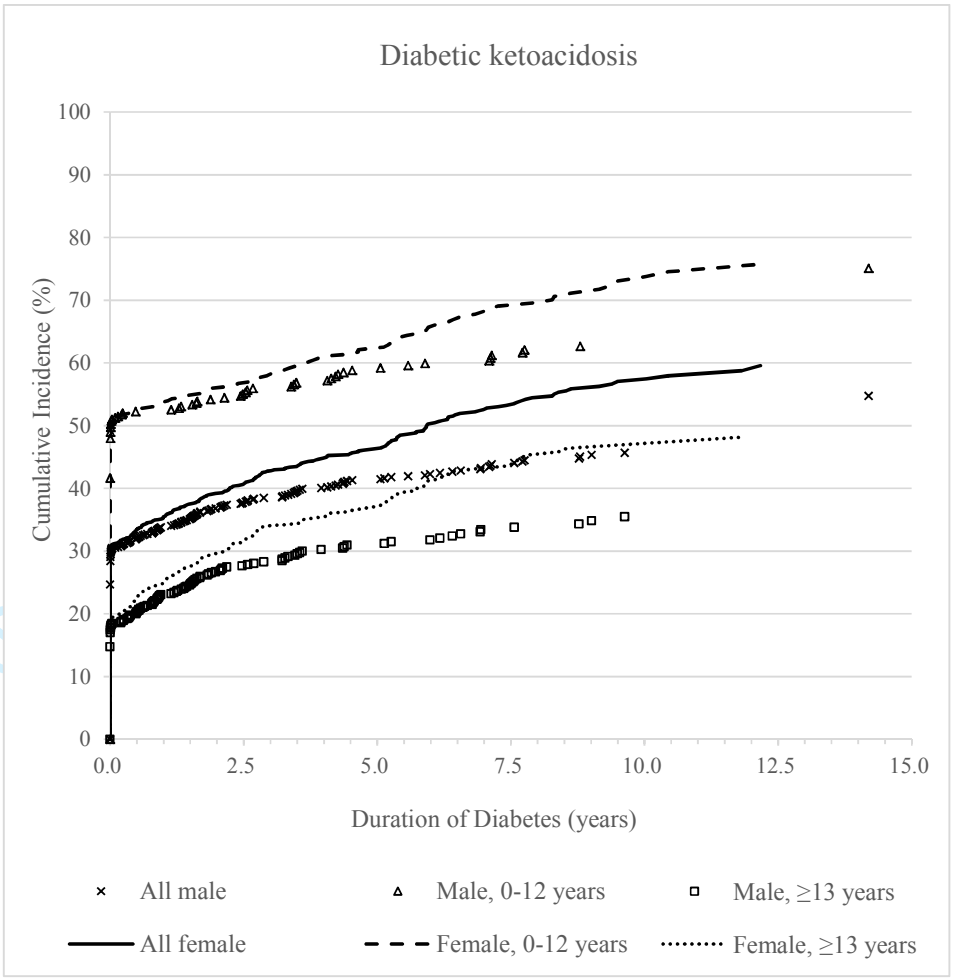


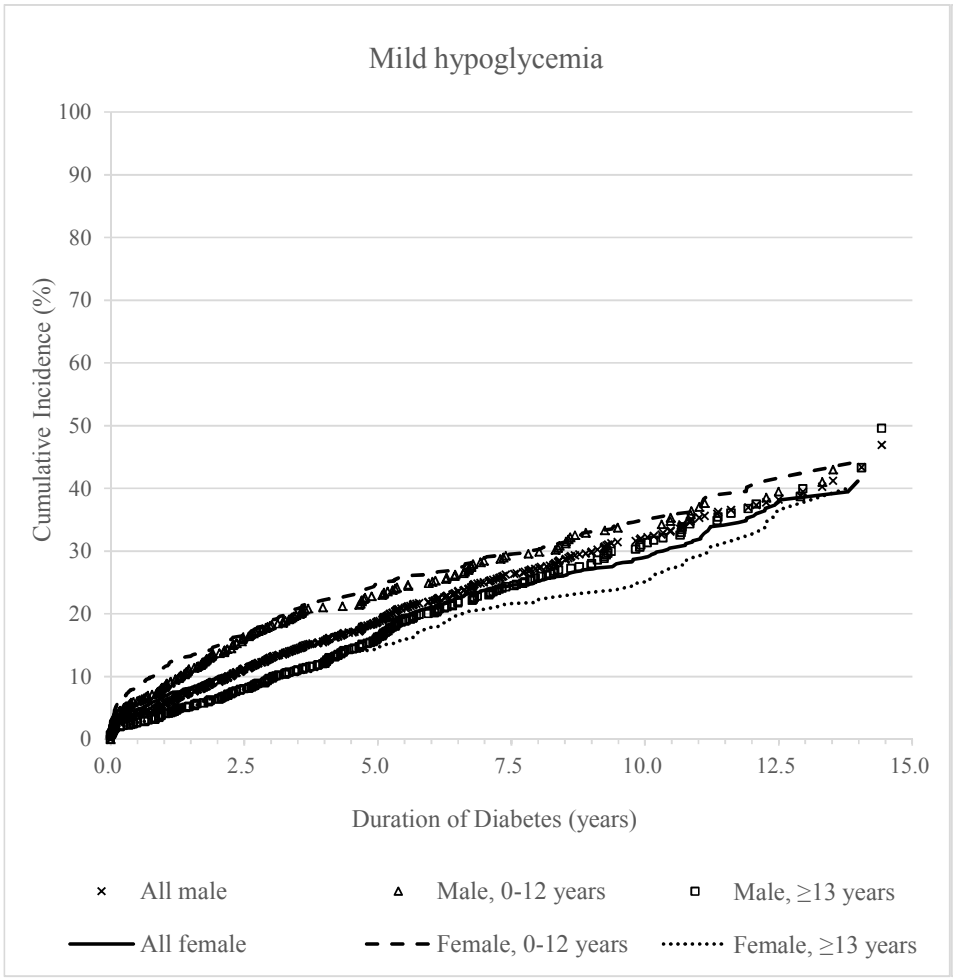

Sight-threatening diabetic retinopathy
Cumulative Incidence (%)
100
90
80
70
60
50
40
30
20
10
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years
Neuropathy
Cumulative Incidence (%)
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years

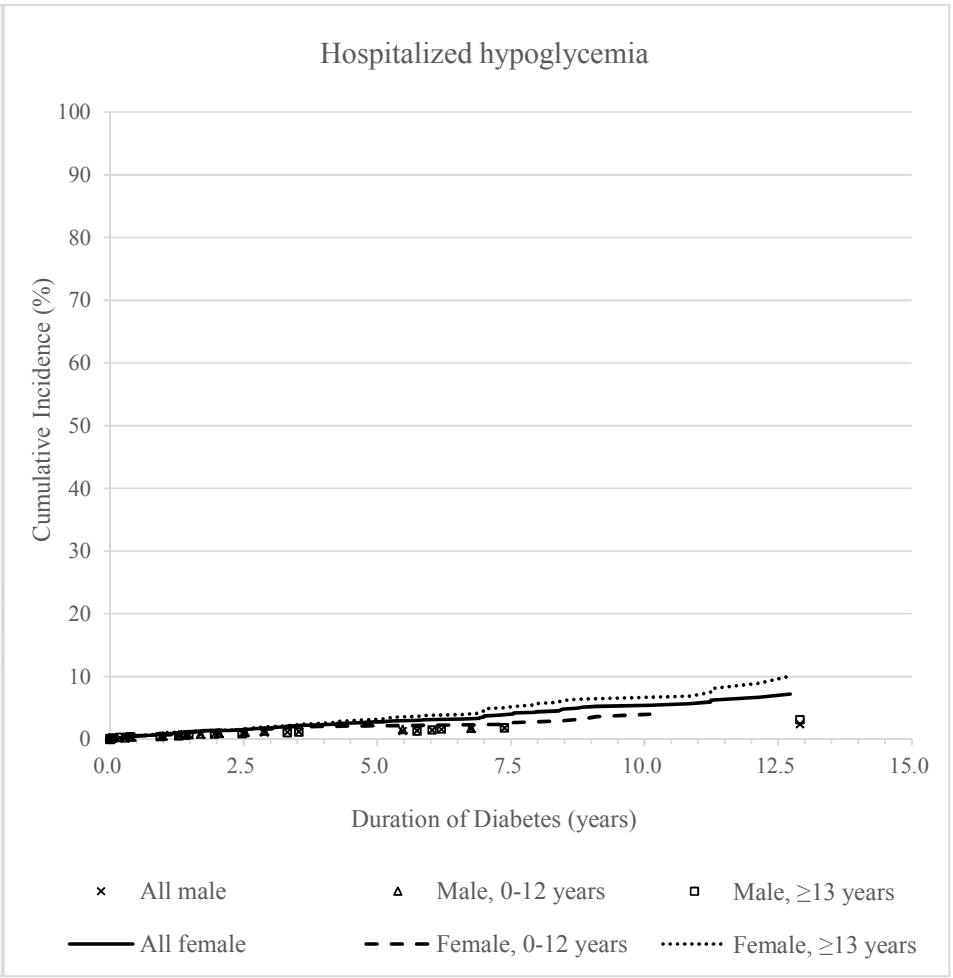

Nephropathy
Cumulative Incidence (%)
100
90
80
70
60
50
40
30
20
10
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Renal failure
Cumulative Incidence (%)
100
90
80
70
60
50
40
30
20
10
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Cardiovascular disease
Cumulative Incidence (%)
100
90
80
70
60
50
40
30
20
10
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Diabetic ketoacidosis
Cumulative Incidence (%)
100
90
80
70
60
50
40
30
20
10
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Mild hypoglycemia
Cumulative Incidence (%)
100
90
80
70
60
50
40
30
20
10
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Hospitalized hypoglycemia
Cumulative Incidence (%)
100
90
80
70
60
50
40
30
20
10
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7, 8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7, 8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	9, 10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9, 10

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11
		(*b*) Report category boundaries when continuous variables were categorized	10, 11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Incidence of diabetes-related complications in ethnic Chinese with newly diagnosed type 1 diabetes: A claim-based cohort of diabetes from 1999 to 2013

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Incidence of diabetes-related complications in ethnic Chinese with newly diagnosed type 1 diabetes: A claim-based cohort of diabetes from 1999 to 2013

Huang-Tz Ou PhD[1,2,*], Tsung-Ying Lee MS[1], Chung-Yi Li PhD[3,4], Jin-Shang Wu MD[5,6], Zih-Jie Sun MD[6,7]

[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2]Department of Pharmacy, College of Medicine, National Cheng Kung University Tainan, Taiwan
[3]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[4]Department of Public Health, China Medical University, Taichung, Taiwan
[5]Department of Family Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[6]Department of Family Medicine, National Cheng Kung University Hospital, Tainan, Taiwan
[7]Department of Family Medicine, National Cheng Kung University Hospital, Dou-Liou Branch, Dou-Liou, Taiwan

Corresponding author
Huang-Tz Ou, PhD
Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University,
1 University Road, Tainan 7010, Taiwan
Phone: +886-6-2353535 ext.5685
Fax: +886-6-2373149
Email: huangtz@mail.ncku.edu.tw

Abstract

Objective: To estimate the incidence densities and cumulative incidence of diabetes-related complications in patients with type 1 diabetes for a maximum of 15-year follow-up. The estimations were further stratified by gender and age at diagnosis (i.e., early-onset: 0-12 years, late-onset: ≥13 years).

Design: A population-based longitudinal cohort study.

Setting: Taiwan's National Health Insurance medical claims.

Participants: 4,007 patients newly-diagnosed with type 1 diabetes were identified during 1999-2012.

Outcome measures: Acute complications included diabetic ketoacidosis (DKA) and hypoglycemia. Chronic complications were cardiovascular diseases (CVD), retinopathy, neuropathy, and nephropathy.

Results: The incidence density of retinopathy was greatest (97.74 per 1,000 person-years), followed by those of nephropathy (31.36), neuropathy (23.93), and CVD (4.39). Among acute complications, the incidence density of DKA was greatest (121.11 per 1,000 person-years). The cumulative incidences of acute complications after 12 years following diagnosis were estimated to be 52.1%, 36.1%, and 4.1% for DKA, outpatient hypoglycemia,

and hospitalized hypoglycemia, respectively. For chronic complications, the cumulative incidence of retinopathy after 12 years following diagnosis was greatest (65.2%), followed by those of nephropathy (30.2%), neuropathy (23.7%), and CVD (4.1%). Females with late-onset diabetes were greatly affected by advanced retinopathy (i.e., sight-threatening diabetic retinopathy) and hospitalized hypoglycemia, whereas those with early-onset diabetes were more vulnerable to DKA. Chronic complications were more commonly seen in late-onset diabetes, whereas early-onset diabetes were most affected by acute complications.

Conclusions: Ethnically Chinese patients with type 1 diabetes were greatly affected by DKA and retinopathy. The incidence of diabetes-related complications after diagnosis differed by age and sex.

Strengths and limitations of this study

- ✓ This is the largest longitudinal cohort study of ethnically Chinese patients with type 1 diabetes followed for a maximum of 15 years to provide up-to-date incidence estimates of acute and chronic complications.
- ✓ The analyses stratified by gender and age at diabetes-onset indicated significant age-gender disparities in the epidemiological data of diabetes-related complications in type 1 diabetes, which highlight importance for clinical attention and developing preventive strategies.
- ✓ The study limitations resulting from the use of medical reimbursement claims data, including potential misclassifications of diabetes-related complications and lack of clinical biomarkers such as blood glucose, may underestimate rather than overestimate the incidence rates of diabetes-related complications.
- ✓ The incidence estimates of diabetes-related complications may only be generalizable to ethnically Chinese population with type 1 diabetes.

Introduction

It has been estimated that the incidence of type 1 diabetes increases by about 3-5% per year worldwide.[1-3] The annual incidence rate of childhood (< 15 years) type 1 diabetes in Taiwan was 5.3 per 100,000 children in the period 2003-2008.[4] Type 1 diabetes accounts for only 5-10% of the diabetic population, but it remains a devastating chronic disorder with acute complications, including diabetic ketoacidosis (DKA) and hypoglycemia, and chronic complications, which can be divided into microvascular (i.e., retinopathy, neuropathy, nephropathy) and macrovascular complications (i.e., cardiovascular diseases; CVD). Although treatment and care for type 1 diabetes have improved,[5-7] diabetes-related complications are major obstacles to glycemic control for many patients and contribute to most of the increased morbidity and premature mortality in such individuals.[8] The toxicity effect of prolonged chronic hyperglycemia is a leading cause of microvascular and macrovascular diseases among type 1 diabetes patients, with hypertension and dyslipidemia being exacerbating factors.[9]

Assessing the epidemiology of diabetes-related complications is essential for developing preventive strategies and planning treatment protocols to minimize the impact of the complications. However, there is very little longitudinal data (e.g., Pittsburgh Epidemiology

of Childhood-Onset Diabetes Complications (EDC) Study,[10] EURODIAB IDDM Complications Study[11]) on the incidence of complications for type 1 diabetes, and previous estimates widely varied with countries (e.g., European countries,[12] Finland,[13] Denmarks,[14] United States[10]) and entailed different follow-up periods (e.g., 7 years,[12] 12 years,[13] 18 years,[14] and 30 years[10]). In addition, a limited number of diabetes-related complications have been investigated (e.g., microalbuminuria[12, 14] and cardiovascular diseases; CVD[13]), with no previous study targeting an ethnic Chinese population with type 1 diabetes. Ethnic variations in diabetes-related complications have been recognized; Caucasian patients are greatly affected by CVD,[15, 16] while the prevalence of end-stage renal failure (ESRD)[17] and the odds of microalbuminuria and macroaluminuria[18] in Asian populations are much higher compared to those for Caucasian patients. Given the significance of rising life expectancy in recent years among ethnic Chinese patients with type 1 diabetes,[19] it is important to provide precise up-to-date estimates of incidence of its complications and compare them to those for other countries. We therefore utilized a longitudinal population-based cohort of newly diagnosed type 1 diabetes patients who were followed during the period 1999-2013 to evaluate the incidence densities and cumulative incidences of acute and chronic complications to provide contemporary estimates for an ethnic Chinese population. Efforts were also made to examine

whether there were age and sex differences in the incidences of type-1-diabetes-related complications.

Materials and Methods

The Institutional Review Board of National Cheng Kung University Hospital approved the study before commencement (A-ER-103-298).

Data source:

We utilized the Longitudinal Cohort of Diabetes Patients (LHDB) 1996-2013 data from the National Health Insurance Research Database (NHIRD). Taiwan's NHIRD is population-based and derived from the claims data of the National Health Insurance (NHI) program, a mandatory-enrollment, single-payment system that covers over 99% of Taiwan's population.[20] The LHDB is a valid national dataset that consists of a random sample of 120,000 de-identified diabetes incident cases from each calendar year, who were tracked back to 1996 and followed up to 2013 to establish a longitudinal cohort. The LHDB is representative of Taiwan's population with diabetes and provides research opportunity to evaluate long-term health outcomes of patients.[21-26]

Cohort:

From the LHDB, we selected 4,677 patients with a diagnosis of type 1 diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM = 250.x1 or 250.x3) from outpatient files of the LHDB and having received a Catastrophic Illness Card (CIC) for type 1 diabetes (Figure 1) in the period 1999-2012. Because patients with a CIC are eligible for exemption from co-payments, the approval of such a status is subject to evaluation and review by the Bureau of NHI of Taiwan. The CIC patient data are accurate and reliable with a positive predictive value of 98.3% for type 1 diabetes.[19] We further excluded 670 potential type 2 diabetes cases who consumed any oral antihypoglycemic agents (OHAs) after CIC was issued, including sulfonylureas, meglitinides, acarbose, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide-1 receptor agonists, and however, those who used metformin alone, thiazolidinediones alone, or both were retained. Patients who were prescribed metformin, thiazolidinediones, or both were retained because these OHAs are insulin-sensitizers that can be combined with insulin treatments for cases with insulin resistance,[27, 28] which is also seen in patients with type 1 diabetes in Taiwan based on our expert opinions. To estimate the incidence rates of diabetes-related complications, we further selected cases without a history of microvascular or macrovascular diseases before type 1 diabetes diagnosis (Table 1). Study patients were stratified by gender

and age at first type 1 diabetes diagnosis (i.e., early-onset: 0-12 years, late-onset: ≥13 years). The 25th, 50th (median) and 75th percentiles of age in early-onset group were 5, 8, and 10, respectively, with the mean age of 7.69 (standard deviation: 3.22). And, for late-onset group, the 25th, 50th and 75th percentiles of age were 17, 24, and 33, respectively, with the mean age of 26.47 (standard deviation: 11.60).

Diabetes-related complications:

The complications of interest included acute complications, namely DKA (confirmed by hospital admission or emergency room visit for DKA), hypoglycemia (confirmed by defined hypoglycemic events required for outpatient visits or hospitalization for medical assistance or interventions), and chronic complications, namely CVD, nephropathy, retinopathy, and neuropathy. A list of diabetes-related complications and the corresponding ICD-9-CM codes are provided in Supplementary Table 1; this list was confirmed by the expert panel before being applied.

Statistics:

The incidence density of diabetes-related complications was calculated by dividing the number of incident cases with individual complication events by the total person-years observed over 15 years of follow-up (1999-2013). The 95% confidence intervals (CIs) were

calculated assuming a Poisson distribution of cases.[29] Significant differences in incidence density between age-sex subgroups were indicated by a 95% CI for the difference in incidence density between subgroups.[30] Moreover, because a cohort of newly diagnosed type 1 diabetes patients was utilized, we were able to provide visual illustrations about the cumulative incidences of diabetes-related complications by diabetes duration since diabetes onset. The cumulative incidence of diabetes-related complications was estimated by using the life table method (using the SAS LIFETEST procedure) and significant difference in cumulative incidence between subgroups were examined according to K-sample tests.[31] SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for the aforementioned analyses.

Results

The overall and age-sex specific incidence densities of diabetes-related complications are presented in Tables 1 and 2, respectively. The incidence rate of retinopathy (97.74 per 1,000 person-years) was greatest, followed by those of nephropathy (31.36), neuropathy (23.93), and CVD (4.39). Among acute complications, the incidence density of DKA was greatest (121.11 per 1,000 person-years). As shown in Table 2, the incidence densities of retinopathy, DKA, and hospitalized hypoglycemia in females were significantly higher than

those in males. The incidence densities of DKA and outpatient hypoglycemia in the early-onset group (0-12 years) were significantly higher than those noted in the late-onset group (≥13 years), while those of advanced retinopathy (i.e., sight-threatening diabetic retinopathy; STDR), neuropathy, nephropathy, CVD, and hospitalized hypoglycemia in the late-onset group were significantly higher. Figures 2 and 3 show cumulative incidences for acute and chronic complications, respectively, along with diabetes duration. The cumulative incidences at the 12th year after diagnosis were 52.1%, 36.1%, and 4.1% for DKA, outpatient hypoglycemia, and hospitalized hypoglycemia, respectively. For chronic complications, the 12-year cumulative incidence of retinopathy was greatest (65.2%), followed by those of nephropathy (30.2%), neuropathy (23.7%), and CVD (5.2%). Age-sex specific cumulative incidences of diabetes-related complications are illustrated in Supplementary Figure 1.

Discussion

To the best of our knowledge, this is the largest cohort study of ethnically Chinese patients with newly diagnosed type 1 diabetes. We provided up-to-date estimates of the incidence of acute and chronic complications in type 1 diabetes patients followed for a maximum of 15 years. We observed age-gender disparities in the incidence of

diabetes-related complications in type 1 diabetes. Although comparisons of the epidemiology of diabetes-related complications between studies are difficult, as potential determinants of the complications (e.g., age, gender, diabetes duration) differ, the estimates from different studies may reveal some racial or ethnic differences. In the following, we compare our results for ethnically Chinese patients with those reported for other countries or ethnicities.

Acute diabetes-related complications in type 1 diabetes patients

Diabetic ketoacidosis

Among acute complications, hyperglycemic events, including DKA and hyperglycemic hyperosmolar syndrome (HHS), are leading causes of morbidity and mortality among individuals with diabetes,[32] and utilize significant healthcare resources.[33] DKA was the most common acute complication among the Taiwanese population with type 1 diabetes; the incidence density followed for 15 years was 121.11 per 1,000 person-years, and half of the study population (~52%) experienced DKA at 12 years after diabetes diagnosis. Consistent with previous studies from the United States,[34] Australia,[35] and Canada,[36] we found that the incidence of DKA in female patients, especially those with early-onset diabetes (i.e., 0-12 years), was higher than that in male patients. A cohort of 1,234 children with type 1 diabetes in the United States showed that female patients were greatly affected by DKA. A female

preponderance of DKA was observed in a longitudinal study of childhood type 1 diabetes in Australia.[35] Similarly, a Canadian study of childhood type 1 diabetes showed that female sex was a significant predictor of DKA.[36] In fact, insulin omission or intentional insulin under-treatment due to fear of weight gain[37] and high prevalence of eating disorders[38] and psychiatric disorders[34] among female type 1 diabetes patients have been recognized as precipitating causes of DKA. Hence, effective interventions such as health education and communication for type 1 diabetes females are needed to reduce the incidence of DKA.

Hypoglycemia

Increased hypoglycemic events have been recognized as a result of the undesired effects of intensive insulin therapy with strict glycemic control.[39] The present study showed that the incidence rates of hospitalized and outpatient hypoglycemia in the Taiwanese population with type 1 diabetes were 3.89 and 39.93 per 1,000 person-years, respectively, which are much lower than that reported in type 1 diabetes children (0-19 years) in the United States (incidence of severe hypoglycemia: 190 per 1,000 person-years).[34] Such discrepancies in international data may be explained by different definitions and assessment approaches for hypoglycemic events. We targeted hospital admissions for hypoglycemia based on ICD-9 CM codes, whereas the United States study used patients' reported survey data and classified

severe hypoglycemia as acute episodes requiring the assistance of another person for treatment reported in the preceding 3 months.[40]

Moreover, we observed that early-onset patients were greatly affected by acute complications (i.e., DKA, hypoglycemia). It has been documented that among young children with type 1 diabetes, inconsistent eating patterns and lesser ability to recognize and report acute symptoms make it difficult to achieve glycemic control, leading to glycemic fluctuations that cause multiple episodes of hyperglycemia (i.e., DKA) and hypoglycemia.[41] Frequent exposures to hyperglycemia and hypoglycemia in early-onset type 1 diabetes patients could lead to a range of neurocognitive dysfunctions and brain changes.[42] Also, structural brain changes in type 1 diabetes children may occur due to recurrent hypoglycemia.[43] Hence, given the high rates of acute complications and associated serious consequences, effective management protocols and identification and treatment of precipitating causes are needed.[44] In particular, regular glycemic monitoring and identification of risk factors in young type 1 diabetes patients are needed to reduce the frequency and severity of DKA and hypoglycemia.

Chronic diabetes-related complications in type 1 diabetes

Diabetic retinopathy

Diabetic retinopathy is the main cause of blindness in the adult population.[45] Almost all type 1 diabetes patients develop evident retinopathy in the first 20 years of diagnosis.[46] The present study showed that more than half (~69%) of type 1 diabetes patients experienced some form of diabetic retinopathy at 12 years after diagnosis. We observed that the incidence density of diabetes retinopathy is greatest among chronic complications in Taiwanese type 1 diabetes patients (4.53 per 100 person-years over a period of 15 years of follow-up). As compared to the incident density of proliferative retinopathy (19.5 per 1,000 person-years) in the Pittsburgh EDC Study of type 1 diabetes patients with a mean age of 28 years and diabetes duration of 19 years at baseline examination,[10] our estimate (5.87 per 1,000 person-year) based on a cohort of newly diagnosed type 1 diabetes patients is lower. Such a difference between studies may be explained by diabetes duration and age at baseline of study examination. Moreover, comparing the prevalence of STDR in type 1 diabetes patients in this study (2.00 % for women and 1.66 % for men) with that previously observed in Taiwanese type 2 diabetes patients (2.75% for women and 2.87% for men)[47] reveals a slightly lower advanced diabetic retinopathy (i.e., STDR) in the type 1 diabetes versus type 2 diabetes patients. However, the lower rate of STDR in our study may be due to the other study's inclusion of prevalent type 2 diabetes cases with longer diabetes duration[47] as compared to

incident type 1 diabetes targeted in this study.

Consistent with previous studies,[48, 49] the present study demonstrated a female preponderance in diabetic retinopathy. A large cohort of 8,114 type 1 diabetes patients and families assembled over 25 years from the United States showed that females had 1.7 fold higher retinopathy risk ($p < 0.001$) as compared to that of males.[48] Also, a cross-sectional study of 247 Italian type 1 diabetes patients showed a significant relationship between diabetic retinopathy and female gender ($p = 0.01$).[49] Although exact hormone, genetic, lifestyle, or environmental factors are unclear, a differential effect of sex steroid hormones has been proposed to explain this gender discrepancy.[50] Also, age at diabetes onset has been shown to be associated with the development of diabetic retinopathy.[49, 51] An early age at onset (5-14 years) appears to modify the long-term risk of proliferative retinopathy.[51] Consistent with other studies, we observed lower incidence of diabetic retinopathy in early-onset patients as compared to that in late-onset patients. Nevertheless, given a high rate of diabetes retinopathy observed among Taiwanese type 1 diabetes patients, early detection using routine eye examination, control for risk factors of diabetic retinopathy (e,g., hypertension, hyperglycemia, hyperlipidemia),[9] as well as development of tailored intervention strategies for age-sex subgroups are important.

Diabetic nephropathy

Our results show that diabetic nephropathy is the second most common microvascular complication among the Taiwanese population with type 1 diabetes. Without interventions, diabetes patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy.[52] Diabetic nephropathy is a leading cause of ESRD among patients with diabetes.[52] As estimated, individuals with type 1 diabetes face a 20-50% chance of developing ESDR that requires dialysis or renal transplantation.[53] The Pittsburgh EDC Study reported that the incidence density of renal failure (based on self-reported renal transplantation and dialysis) was 6.3 per 1,000 person-years over 12 years of follow-up,[10] while the present study based on ICD-9 codes of renal failure found that the incidence of renal failure was 1.31 per 1,000 person-years over 15 years of follow-up. Of note, the EDC study enrolled more advanced type 1 diabetes cases (i.e., mean age of 28 years and diabetes duration of 19 years at baseline examination[10]) than those in our study (i.e., newly diagnosed type 1 diabetes cases in 2000-2012), which may explain the higher rate of renal failure in the EDC study. A large inception cohort study of Danish patients newly diagnosed with type 1 diabetes followed for a median of 18 years reported that the cumulative incidences of persistent microalbuminuria and macroalbuminuria were 33.6% and 14.6%, respectively,

while the present study found that overall cumulative incidence of any form of diabetic nephropathy was 30.2% at 12 years after diabetes diagnosis. Moreover, early-onset diabetes appears to be protective for developing diabetic nephropathy[12, 54-56] and may delay the time until microalbuminuria.[56] Consistently, we found that late-onset diabetes patients were more affected by diabetic nephropathy than were early-onset patients. Nevertheless, given the fact that Taiwan has the highest number of patients undergoing renal dialysis in the world, where diabetes contributes to about 40 % of end-stage renal failure cases,[57] it is critical for routine annual screening of clinical signs of diabetic nephropathy (i.e., proteinuria, microalbuminuria), optimal control of glycemia and risk factors (e.g., retinopathy smoking, dyslipidemia, hypertension[14, 58, 59]), and early intervening medications for prevention (e.g., angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker for those with comorbid hypertension).[9]

Diabetic neuropathy

Diabetic neuropathy refers to the presence of symptoms, signs, or both of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.[60] Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies.[61] The epidemiological data of diabetic

neuropathy is very limited. A study of 467 Italian type 1 diabetes patients showed that the prevalence rates of asymptomatic and symptomatic neuropathy were 7.2% and 21.3%, respectively.[62] The present study is the first study to provide epidemiology data on diabetic neuropathy among ethnically Chinese patients with type 1 diabetes from Asia. We found that the incidence rate was 23.93 per 1,000 person-years over 15 years of follow-up, and that the cumulative incidence was 23.7% at 12 years after diabetes diagnosis. We also observed that the incidence of diabetic neuropathy in late-onset patients were much higher than that in early-onset patients. Similarly, the Italian study of type 1 diabetes showed that the prevalence of diabetic neuropathy was higher in patients at older ages.[62] Since diabetic neuropathy contributes to considerable disabilities and mortality, it is critical for clinicians to understand its manifestations, prevention, and treatment.[9] Early prevention strategies that control hypertension and hyperglycemia and identify patients with peripheral neuropathy or peripheral vascular disease and annual screening for these conditions are strongly recommended.[9]

Cardiovascular diseases

CVD is a leading cause of mortality in patients with type 1 diabetes[63, 64] and accounts for the greatest proportion of healthcare spending for patients with diabetes.[64, 65] As compared to

patients without diabetes, type 1 diabetes increases the risk of CVD by ten fold,[63, 66] which contributes to two-thirds of mortality in patients with type 1 diabetes.[67, 68] The Pittsburgh EDC Study showed an incidence density of 3.6 per 1,000 person-years for coronary heart diseases (defined as coronary-artery-disease-related death, a history of myocardial infarction, angiographic stenosis ≥ 50% including revascularization) over a period of 12 years,[10] while the present study found that the incidence density for a broader category of CVD (including myocardial infarction, ischemic heart diseases, heart failure, stroke, and arrhythmia, as shown in Supplementary Table 1) in the Taiwanese population with type 1 diabetes within 15 years of follow-up was 4.39 per 1,000 person-years. The cumulative incidences of CVD (including only stroke and coronary heart disease) at 12 years after diabetes was diagnosed was 1-2% among Finnish type 1 diabetes patients,[13] which is lower than that for the Taiwanese type 1 diabetes patients in the present study (~5.2%). Moreover, we found that late-onset patients were greatly affected by CVD. In fact, old age is recognized as a predictor of vascular diseases,[63] which may be explained by the calcification of extremity arteries and hypertension in older age patients, which are risk factors of macrovascular diseases.[69]

Methodological concerns

Some limitations of this study should be acknowledged. The classification of

diabetes-related complications based on the ICD-9 CM codes in claims data may underestimate the occurrence of the complications. For example, patients experiencing clinical symptoms/signs of diabetes-related complications (e.g., hypoglycemia) may not see doctors if they can tolerate them. Also, the claims data do not capture clinical/minor symptoms or signs of diabetes-related complications such as minor microalbuminuria. The glycemic biomarkers such as blood glucose were not available from the claims data so the identification of hyperglycemia or hypoglycemia was only based on the ICD-9 CM diagnosis codes. So, we might under-estimate the incidence of hypoglycemic events and may not be able to disentangle the severity of hypoglycemia. However, the claims records capture defined diabetes-related complications that are required for medical assistance or treatments, which lead to more conservative estimates and reveal important manifestations of diabetes-related complications for clinical attention. Moreover, based on our operational definition for hospitalized hypoglycemia (i.e., any one of diagnosis codes with hypoglycemia from the five diagnosis codes in the inpatient files of the NHIRD), two types of hypoglycemic events could be included: (1) hospital admission for hypoglycemia, and (2) other reasons for hospital admission (e.g., DKA), and then hypoglycemia happened during hospitalization. It is difficult to differentiate these two types of hypoglycemic events based on

the retrospective claims data we utilized. However, in the clinical practice in Taiwan, the first code from the five diagnosis codes in hospitalization is typically to be the main/primary reason for hospital admission. With this regard, we re-run the analyses for hospitalized hypoglycemia which was identified from the first diagnosis code in hospitalization. The results were provided in the Supplementary Table 2, and Supplementary Figures 2 and 3. These re-analytical results may also ease the concern that patients who came to hospital primarily for reasons that may induce hypoglycemia during hospitalization. Lastly, the generalizability of our study results may be limited to ethnically Chinese populations. In addition, our results may represent only ethnically Chinese patients with type 1 diabetes in Taiwan.

Conclusions

Utilizing an incident cohort of type 1 diabetes patients diagnosed during the period 1999-2012 with a maximum of 15 years of follow-up, we found that most type 1 diabetes patients were affected by DKA and retinopathy, which highlight the critical need to identify precipitating causes and modifiable factors for developing preventive strategies and intervening treatment protocols to minimize the impact of these complications. Age and sex discrepancies appear in epidemiological data of diabetes-related complications; late-onset

diabetes females were greatly affected by advanced retinopathy (i.e., STDR) and hospitalized hypoglycemia, while early-onset females had a high incidence of DKA. Chronic diabetes-related complications were more common in late-onset type 1 diabetes patients, while early-onset individuals were most affected by acute complications. More attention should be given to identify potential risk factors and contributors to such age-sex differences in diabetes-related complications. Population-based data on the incidence of diabetes-related complications from this study are important for clinicians to recognize the need for diagnostic awareness and for policy-markers to develop effective treatments for patients with type 1 diabetes.

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Table 1: Overall incidence density of diabetes-related complications among patients with type 1 diabetes between 1999 and 2013

	Retinopathy	Proliferative retinopathy	STDR	Neuropathy	Nephropathy	Renal failure	CVD	DKA	Outpatient hypoglycemia	Hospitalized hypoglycemia
No. of cases*	3,359	3,970	3,983	3,742	3,634	4,003	3,916	2,205	3,934	3,987
No. of cases with event**	1,532	157	90	558	688	36	117	996	913	105
Follow-up time (person-years)†	15,675	26,733	27,139	23,320	21,936	27,491	26,664	8,224	22,865	26,968
Incidence density (1,000 person-years) (95% CI)	97.74 (92.9-102.8)	5.87 (5.0-6.9)	3.32 (2.7-4.1)	23.93 (22.0-26.0)	31.36 (29.1-33.8)	1.31 (0.9-1.8)	4.39 (3.6-5.3)	121.11 (113.7-128.9)	39.93 (37.4-42.6)	3.89 (3.2-4.7)

* No. of cases refers to the number of patients who had no complication of interest in the baseline year (one year before diagnosis date).

** No. of cases with event refers to the number of patients who had incident events after type 1 diabetes was confirmed.

† Cumulative follow-up time (person-years) was calculated as the sum of follow-up years during observation period.

Note: Patients with type 1 diabetes were retrieved from incidence cases from 2000 to 2012. Follow-up time started from the first diagnosis date to the time the event occurred, death, discontinued enrollment from Taiwan's National Health Insurance Program, or the end of 2013, whichever came first.

Abbreviations: STDR: sight-threatening diabetic retinopathy, CVD: cardiovascular disease, DKA: diabetic ketoacidosis, CI: confidence interval.

Table 2: Incidence density of diabetes-related complications by age and sex among patients with type 1 diabetes between 1999 and 2013

	Retinopathy	Proliferative retinopathy	STDR	Neuropathy	Nephropathy	Renal failure	CVD	DKA	Outpatient hypoglycemia	Hospitalized hypoglycemia
Male										
No. of cases*										
All male	1,618	1,886	1,892	1,778	1,695	1,901	1859	1,073	1,872	1,902
Early-onset (0-12 years)	654	719	719	714	700	719	712	396	718	719
Late-onset (≥13 years)	964	1,167	1,173	1,064	995	1,182	1,147	677	1,154	1,183
No. of cases with event**										
All male	693	64	34	261	332	15	60	447	452	28
Early onset	305	14	1	37	86	1	7	239	202	11
Late onset	388	50	33	224	246	14	53	208	250	17
Follow-up time (person-years)†										
All male	7,813	12,908	13,102	11,345	10,403	13,248	12,798	4,322	11,025	13,115
Early-onset	3,333	5,290	5,368	5,180	4,817	5,358	5,280	1,317	4,277	5,297
Late-onset	4,480	7,618	7,734	6,165	5,586	7,891	7,518	3,005	6,749	7,818
Incidence density (1,000 person-years) (95% CI)										
All male	88.70 (82.2-95.6)	4.96 (3.8-6.3)	2.60 (1.8-3.6)	23.01 (20.3-26.0)	31.91 (28.6-35.5)	1.13 (0.6-1.9)	4.69 (3.6-6.0)	103.43 (94.1-113.5)	41.00 (37.3-45.0)	2.13 (1.4-3.1)
Early-onset	91.52	2.65	0.19	7.14	17.85	0.19	1.33	181.53	47.23	2.08

	(81.5-102.4)	(1.4-4.4)	(0.0-1.0)	(5.0-9.8)	(14.3-22.0)	(0.0-1.0)	(0.5-2.7)	(159.2-206.1)	(40.9-54.2)	(1.0-3.7)
Late-onset	86.60	6.56	4.27	36.34	44.04	1.77	7.05	69.22	37.05	2.17
	(78.2-95.7)	(4.9-8.7)	(2.9-6.0)	(31.7-41.4)	(38.7-49.9)	(1.0-3.0)	(5.3-9.2)	(60.1-79.3)	(32.6-41.9)	(1.3-3.5)
95% CI of incidence density difference for male, early vs. late-onset	**-8.5 to 18.3**	**-6.4 to -1.4‡**	**-5.9 to -2.3‡**	**-34.8 to -23.6‡**	**-33.1 to -19.3‡**	**-2.8 to -0.4‡**	**-8.1 to -3.3‡**	**91.5 to 133.1‡**	**2.4 to 17.9‡**	**-1.7 to 1.5**
Female										
No. of cases*										
All female	1,741	2,084	2,091	1,964	1,939	2,102	2,057	1,132	2,062	2,085
Early-onset	721	777	777	772	764	777	773	413	774	774
Late-onset	1,020	1,307	1,314	1,192	1,175	1,325	1,284	719	1,288	1,311
No. of cases with event**										
All female	839	93	56	297	356	21	57	549	461	77
Early-onset	358	18	6	50	109	1	11	277	229	21
Late-onset	481	75	50	247	247	20	46	272	232	56
Follow-up time (person-years)†										
All female	7,862	13,825	14,037	11,976	11,533	14,243	13,866	3,902	11,840	13,853
Early-onset	3,616	5,848	5,910	5,610	5,283	5,927	5,871	1,183	4,642	5,777
Late-onset	4,246	7,977	8,127	6,365	6,250	8,317	7,995	2,719	7,199	8,076
Incidence density (1,000 person-years) (95% CI)										

All female	106.72	6.73	3.99	24.80	30.87	1.47	4.11	140.69	38.94	5.56
	(99.6-114.2)	(5.4-8.2)	(3.0-5.2)	(22.1-27.8)	(27.7-34.2)	(0.9-2.3)	(3.1-5.3)	(129.2-153.0)	(35.5-42.7)	(4.4-6.9)
Early-onset	99.01	3.08	1.02	8.91	20.63	0.17	1.87	234.05	49.34	3.63
	(89.0-109.8)	(1.8-4.9)	(0.4-2.2)	(6.6-11.8)	(16.9-24.9)	(0.0-0.9)	(0.9-3.4)	(207.3-263.3)	(43.1-56.2)	(2.3-5.6)
Late-onset	113.29	9.40	6.15	38.80	39.52	2.40	5.75	100.05	32.23	6.93
	(103.4-123.9)	(7.4-11.8)	(4.6-8.1)	(34.1-44.0)	(34.7-44.8)	(1.5-3.7)	(4.2-7.7)	(88.5-112.7)	(28.2-36.7)	(5.2-9.0)
95% CI of incidence density difference for female, early vs. late-onset	**-28.8 to 0.2**	**-9.1 to -3.6‡**	**-7.3 to -3.0‡**	**-35.5 to -24.2‡**	**-25.3 to -12.5‡**	**-3.5 to -1.0‡**	**-6.0 to -1.7‡**	**108.4 to 159.6‡**	**9.8 to 24.4‡**	**-5.8 to -0.8‡**
95% CI of incidence density difference for male vs. female	**-27.8 to -8.2‡**	**-3.6 to 0.1**	**-2.8 to -0.02‡**	**-5.8 to 2.2**	**-3.6 to 5.7**	**-1.2 to 0.5**	**-1.0 to 2.2**	**-52.3 to -22.2‡**	**-3.1 to 7.2**	**-4.9 to -1.9‡**

* No. of cases refers to the number of patients who had no complication of interest in the baseline year (one year before diagnosis date).

** No. of cases with event refers to the number of patients who had incident events after type 1 diabetes was confirmed.

† Cumulative follow-up time (person-years) was calculated as the sum of follow-up years during observation period.

Note: Patients with type 1 diabetes were retrieved from incidence cases from 2000 to 2012. Follow-up time started from the first diagnosis date to the time the event occurred, death, discontinued enrollment from Taiwan's National Health Insurance Program, or the end of 2013, whichever came first.

Abbreviations: STDR: sight-threatening diabetic retinopathy, CVD: cardiovascular disease, DKA: diabetic ketoacidosis, CI: confidence interval. ‡ $p < 0.05$

Figure 1. Flowchart of study cohort selection

Figure 2: Cumulative incidences of diabetic ketoacidosis, mild hypoglycemia according to the duration of diabetes in patients with type 1 diabetes (shadow area indicates 95 % confidence interval)

Figure 3: Cumulative incidences of retinopathy, sight-threatening diabetic retinopathy, neuropathy, nephropathy, renal failure, and cardiovascular diseases according to the duration of diabetes in patients with type 1 diabetes (shadow area indicates 95 % confidence interval)

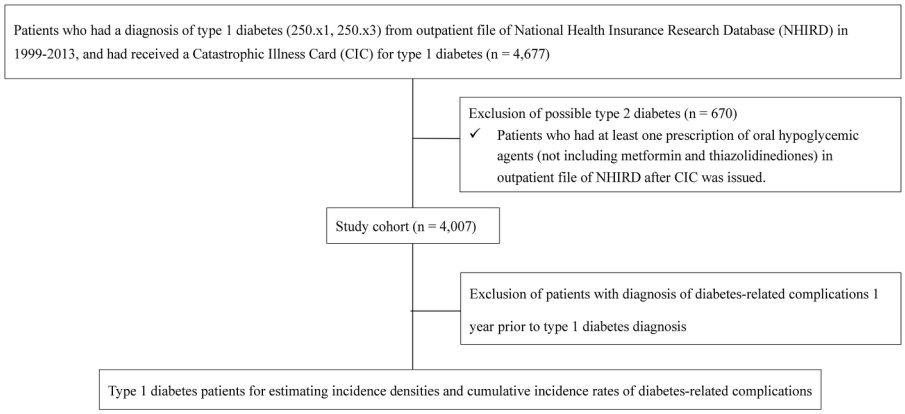

Figure 1. Flowchart of study cohort selection

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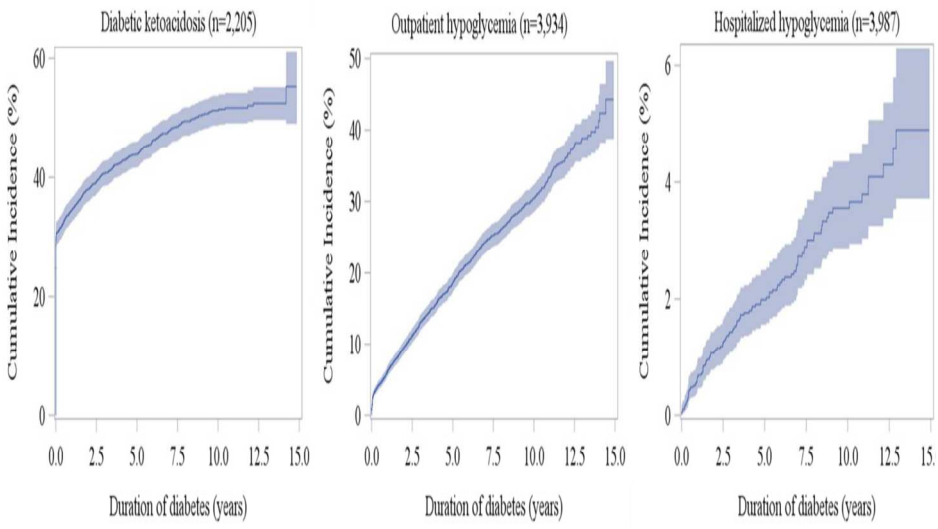

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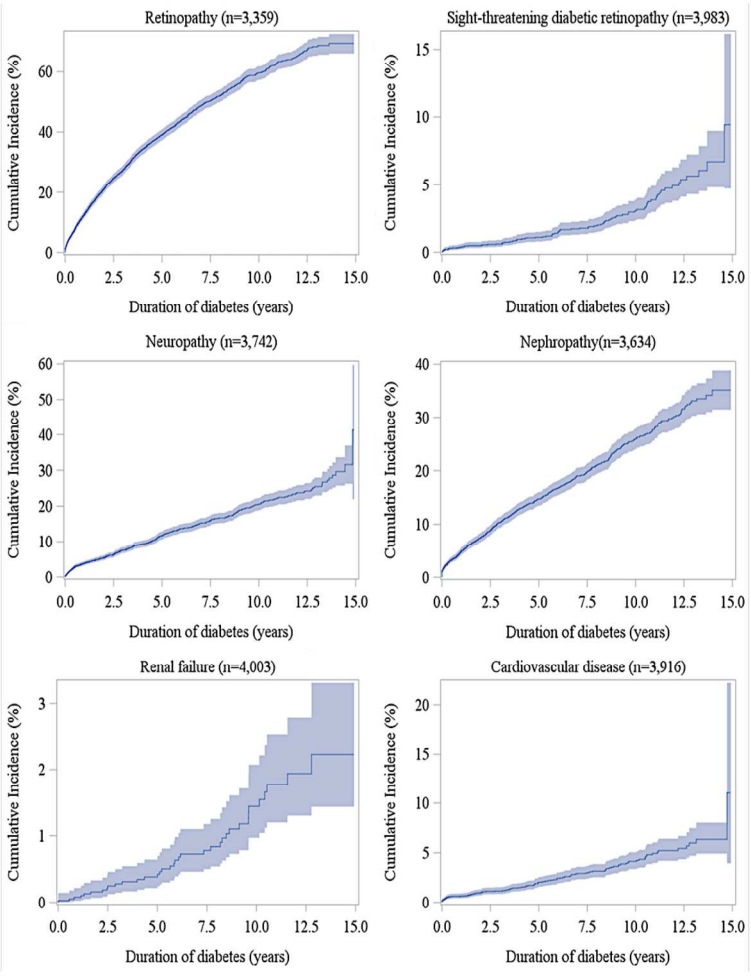


Figure 3: Cumulative incidences of retinopathy, sight-threatening diabetic retinopathy, neuropathy, nephropathy, renal failure, and cardiovascular diseases according to the duration of diabetes in patients with type 1 diabetes (shadow area indicates 95 % confidence interval)

297x420mm (300 x 300 DPI)

Supplementary Table 1: Diabetes-related acute and chronic complications

Complications	ICD-9-CM disease codes	ICD-9-CM procedure codes	NHI procedure codes
CVD (cardiovascular disease and cerebrovascular disease)[a,b]			
Acute myocardial infarction	410, 412*	---	---
Ischemic heart disease	411, 413, 414, V45.81, V45.82	00.66, 36.0, 36.1, 36.2, 36.3, 36.9, 88.5	---
Heart failure	428		---
Stroke	430-437, 438*, V12.54	00.61, 00.63, 38.11, 38.12	---
Cardiogenic shock	785.51	---	---
Sudden cardiac arrest	V12.53	---	---
Arteriosclerotic cardiovascular disease	429.2	---	---
Arrhythmia	426, 427	---	---
Microvascular complications[a,c]			
Nephropathy	250.4, 403, 404, 580, 581, 582, 583, 584, 585, 586, 587, 588, 593, 791.0, V13.03, V42.0, V45.1, V56	38.95, 39.27, 39.42, 39.95, 54.98, 55.4, 55.5, 55.6	---
Renal failure (dialysis or transplantation)[d]	V45.1, V56	39.95, 54.98 55.6	---
Retinopathy	250.5, 361, 362, 364, 365, 366, 368, 369, 377, 379.2	12.41, 12.73, 14.23, 14.24, 14.25, 14.33, 14.34, 14.35, 14.53, 14.54, 14.55, 16.92, 16.99	86206B, 86207B, 60001C, 60002C*, 60003C, 60004C*
Proliferative retinopathy[d]	362.02	---	60001C, 60002C*, 60003C, 60004C*
Sight-threatening diabetic retinopathy[e]	---	---	86206B, 86207B, 60001C, 60002C*, 60003C, 60004C*
Neuropathy	250.6, 302.72, 337.1, 354, 355, 357.2, 358.1, 607.84, 713.5, 729.2	---	---
Metabolic complications			
Diabetic ketoacidosis[a]	250.1	---	---
Hypoglycemia[a,f]	251.0, 251.1, 251.2, 270.3, 775.0, 775.6	---	---

*For identifying prevalent cases only. a: Nutr Metab Cardiovasc Dis. 2014;24(1):10-7. b: Pharmacoepidemiol Drug Saf. 2009;18(6):497-503. c: Diabetes Care. 2008;31(3):596-615. d: Diabetes. 2006;55(5):1463-9. e: JAMA Ophthalmol. 2014;132(8):922-928. f: BMC Endocr Disord. 2008;8:4. Abbreviations: ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification, NHI: Taiwan National Health Insurance.

Supplementary Table 2: Incidence density of hospitalized hypoglycemia among patients with incident type 1 diabetes diagnosed between 1999 and 2013 (using primary diagnosis to define hospitalization for hypoglycemia)

	Overall patients	Male subgroup			Female subgroup		
		Overall male‡	Male early-onset (0-12 years)‡	Male late-onset (≥13 years)	Overall female	Female early-onset (0-12 years)‡	Female late-onset (≥13 years)
No. of cases*	4,001	1,903	719	1,184	2,098	777	1,321
No. of cases with event	36	12	4	8	24	6	18
Follow-up time (person-years)†	27,374	13,205	5,327	7,878	14,169	5,890	8,280
Incidence density (1,000 person-years) (95% CI)	1.32 (0.9-1.8)	0.91 (0.5-1.6)	0.75 (0.2-1.9)	1.02 (0.4-2.0)	1.69 (1.1-2.5)	1.02 (0.4-2.2)	2.17 (1.3-3.4)

* No. of cases refers to the number of patients who had no complication event of interest before type 1 diabetes was confirmed.

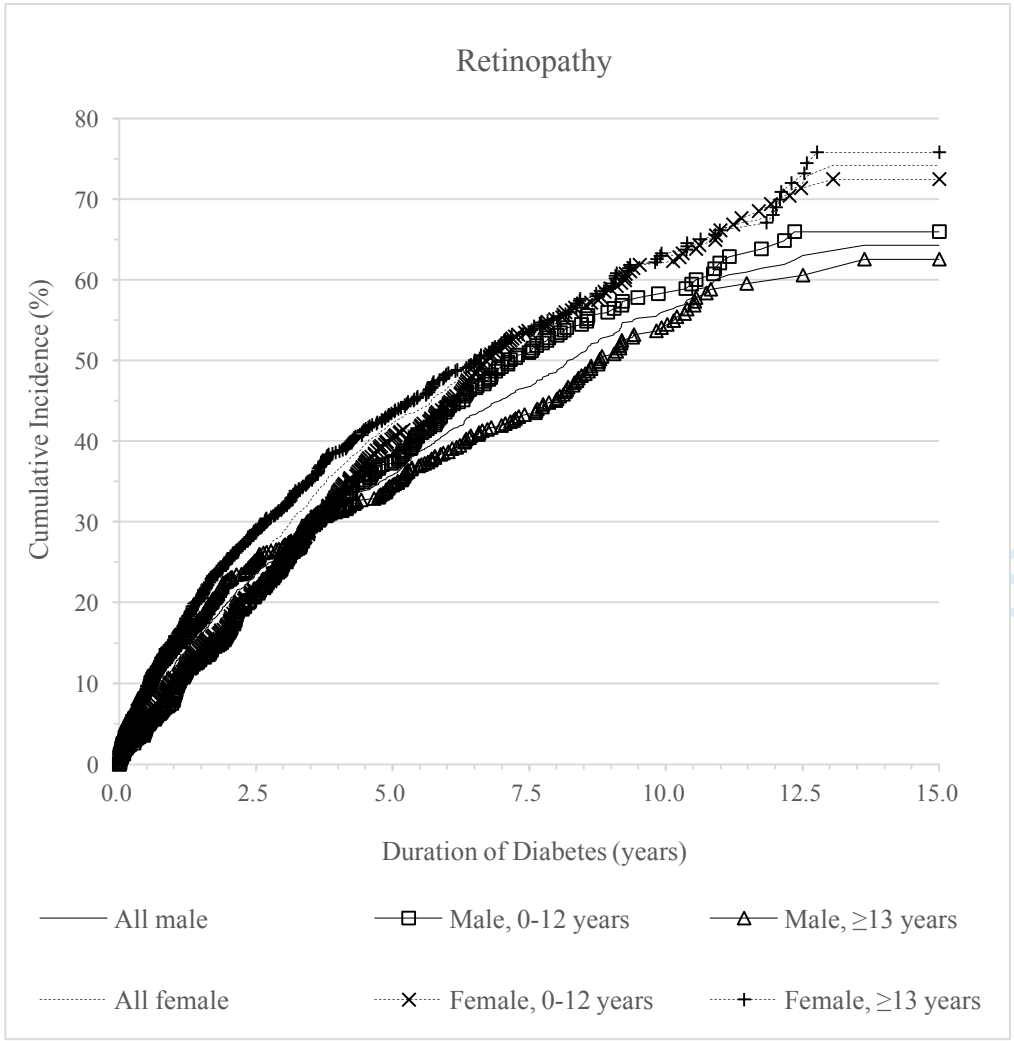
† Cumulative follow-up time (person-years) was calculated as the sum of follow-up years during observation period.

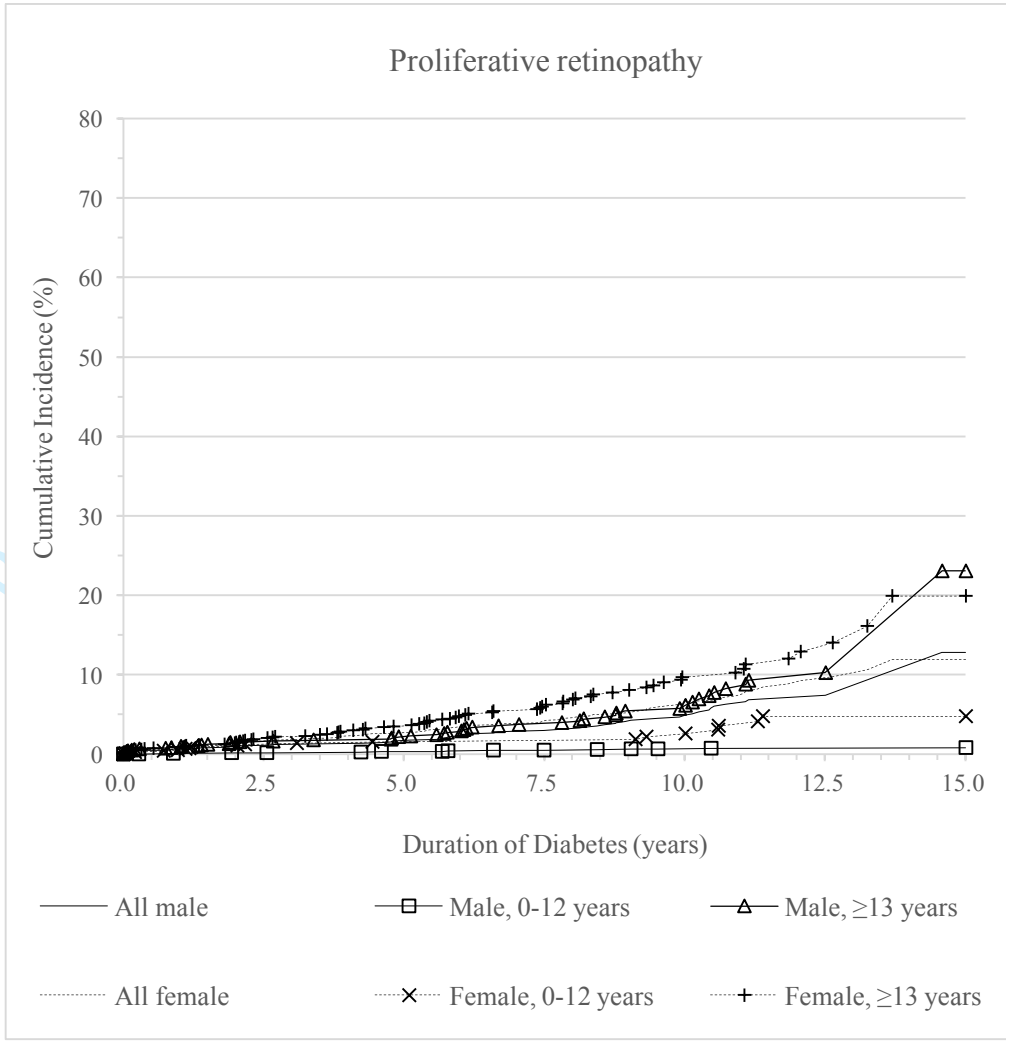
Note: Patients with type 1 diabetes were retrieved from incidence cases from 2000 to 2012. Follow-up time started from the first diagnosis date to the time the event occurred, death, discontinued enrollment from Taiwan's National Health Insurance Program, or the end of 2013, whichever came first.

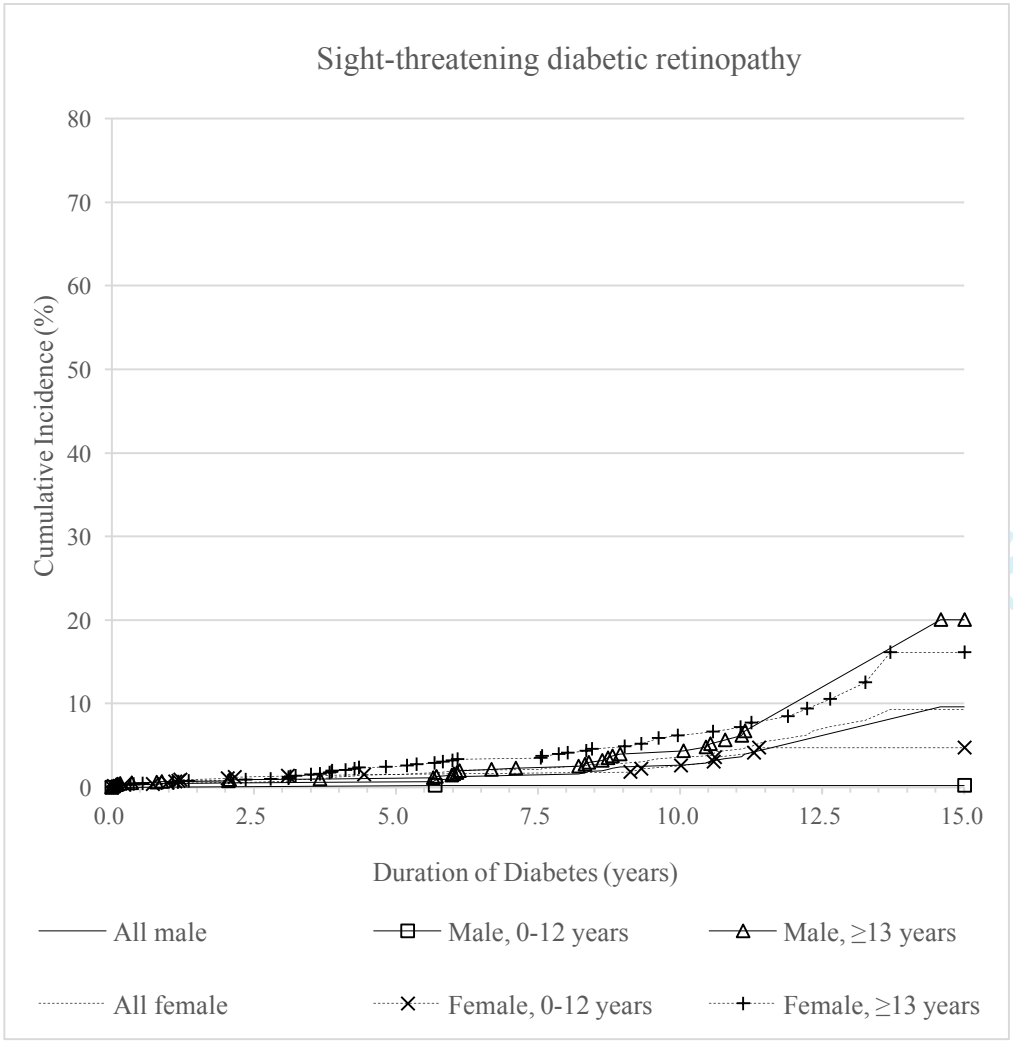
‡ 95% CI of incidence density difference for male vs. female was [-1.6 to 0.1]; in male subgroup, early vs. late-onset was [-1.3 to 0.8]; and in female subgroup, early vs. late-onset was [-2.5 to 0.2].

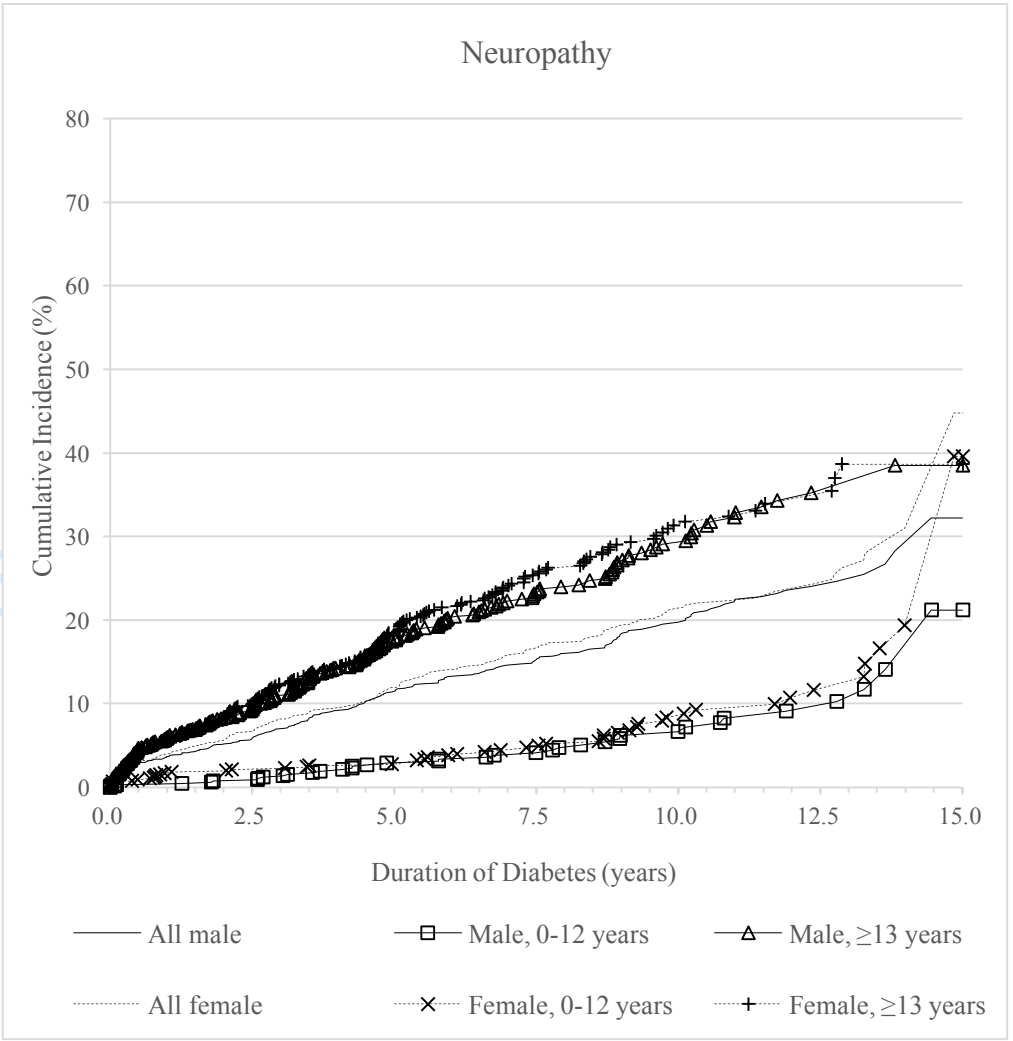
Abbreviations: STDR: sight-threatening diabetic retinopathy, CVD: cardiovascular disease, DKA: diabetic ketoacidosis, CI: confidence interval.

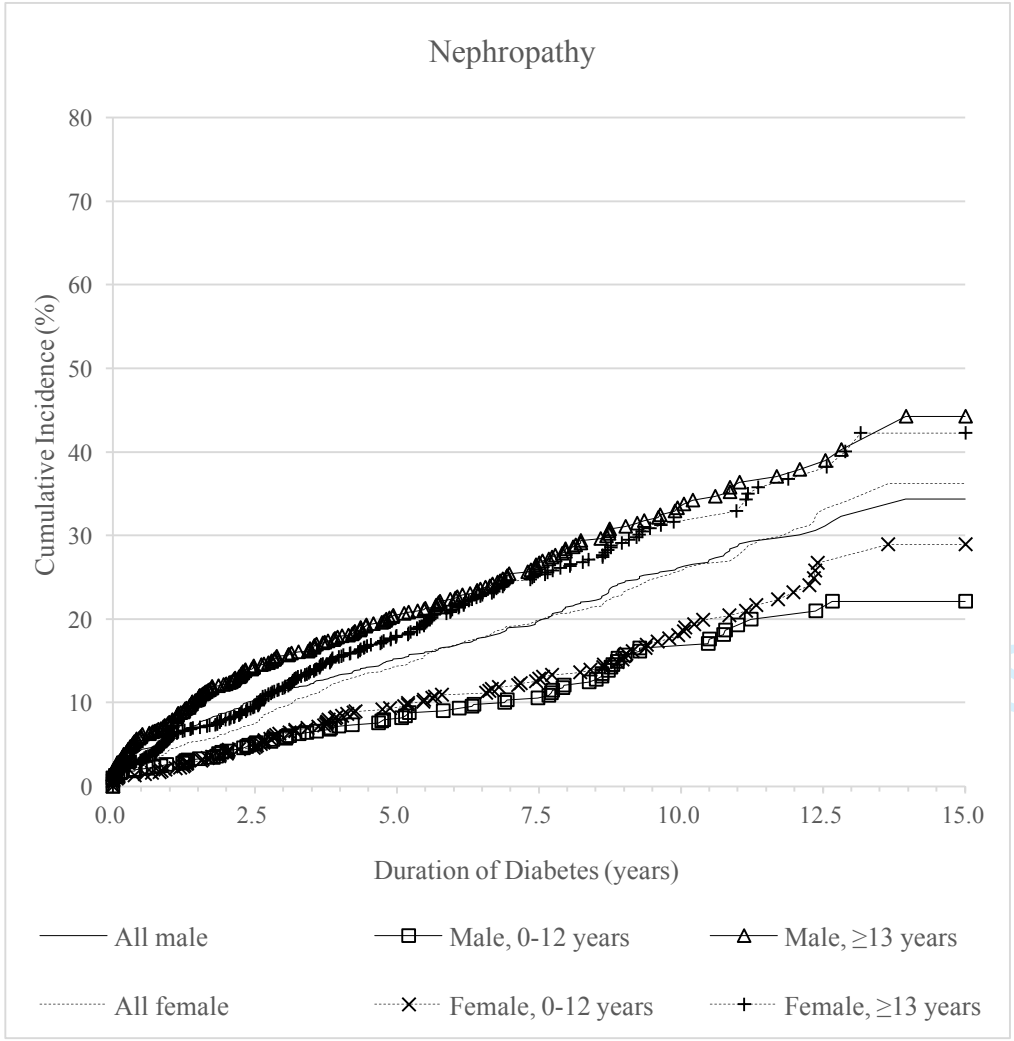
Supplementary Figure 1: Age-sex-specific cumulative incidences of diabetes complications according to duration of diabetes in patients with type 1 diabetes (early-onset: 0-12 years, late-onset: ≥13 years)

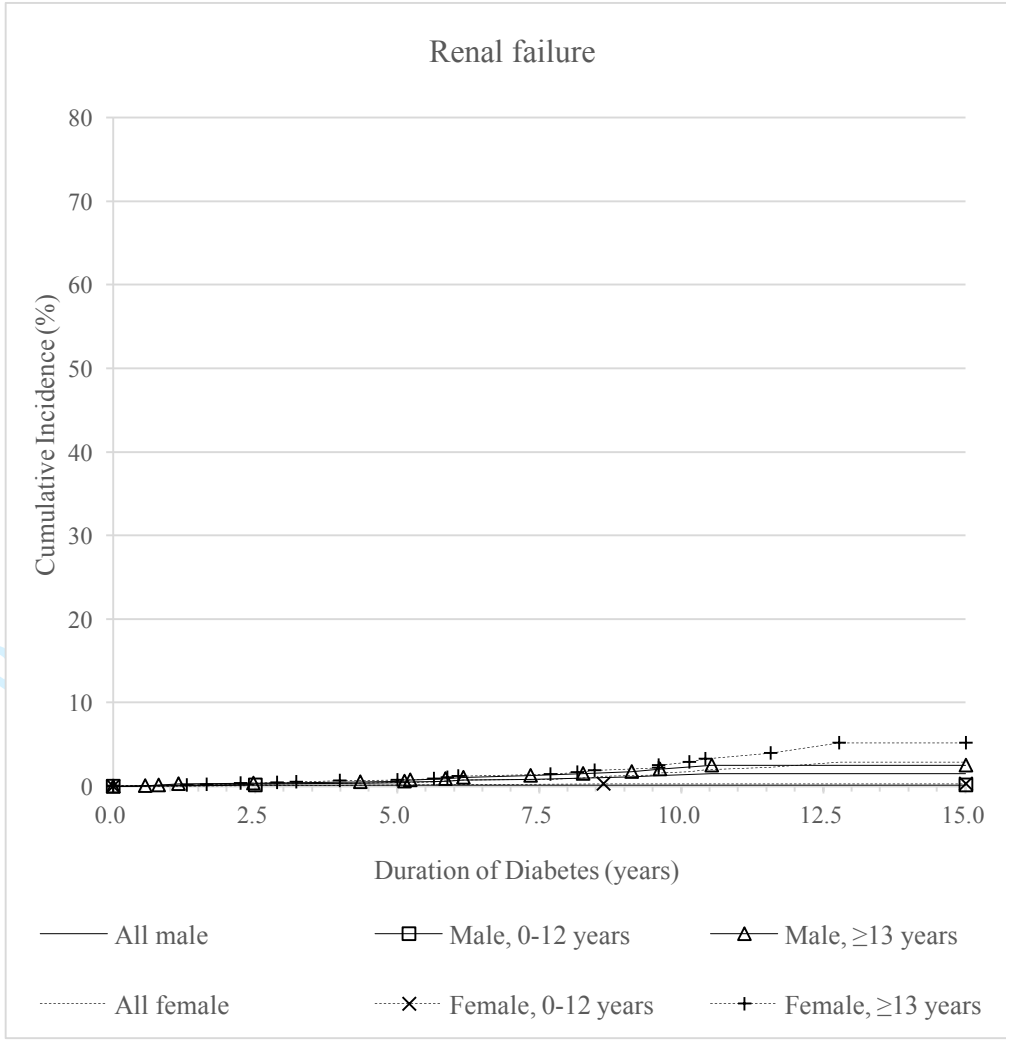


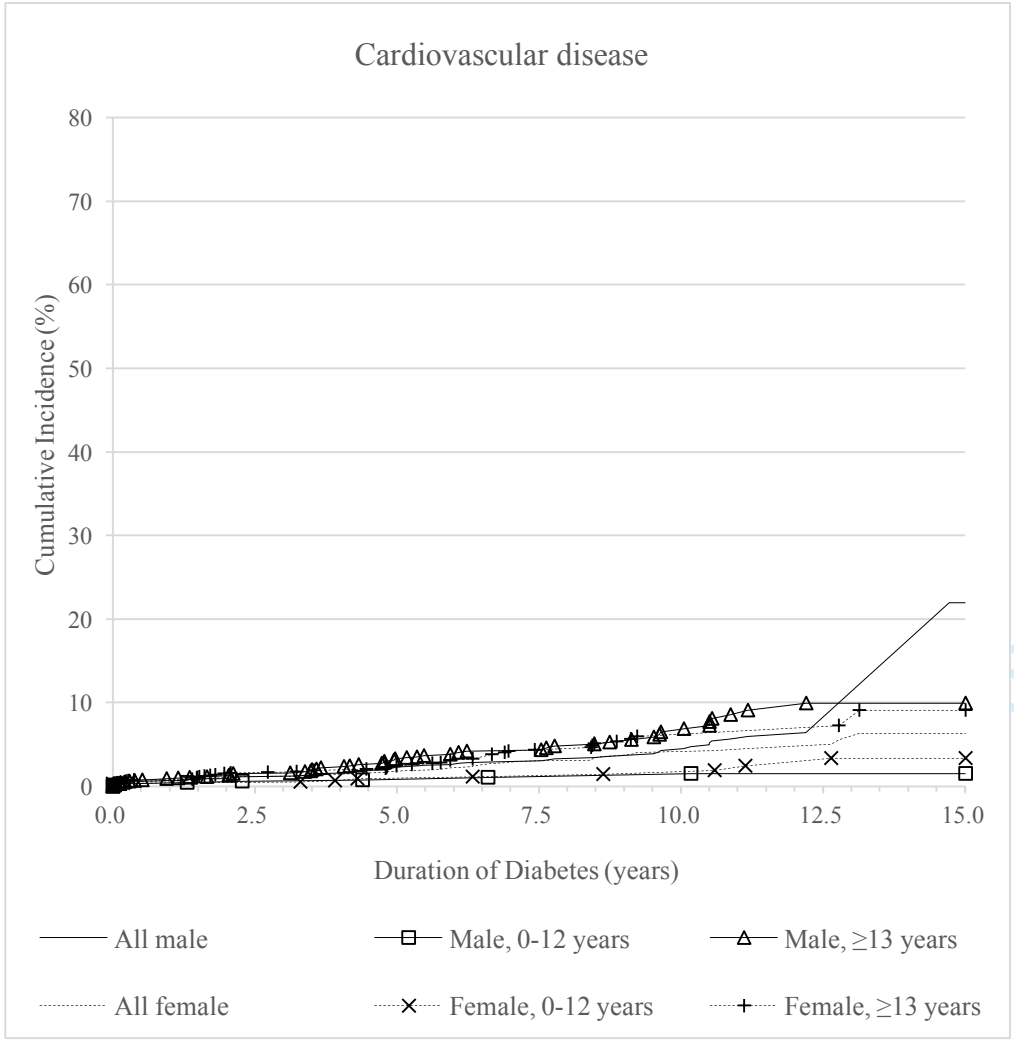


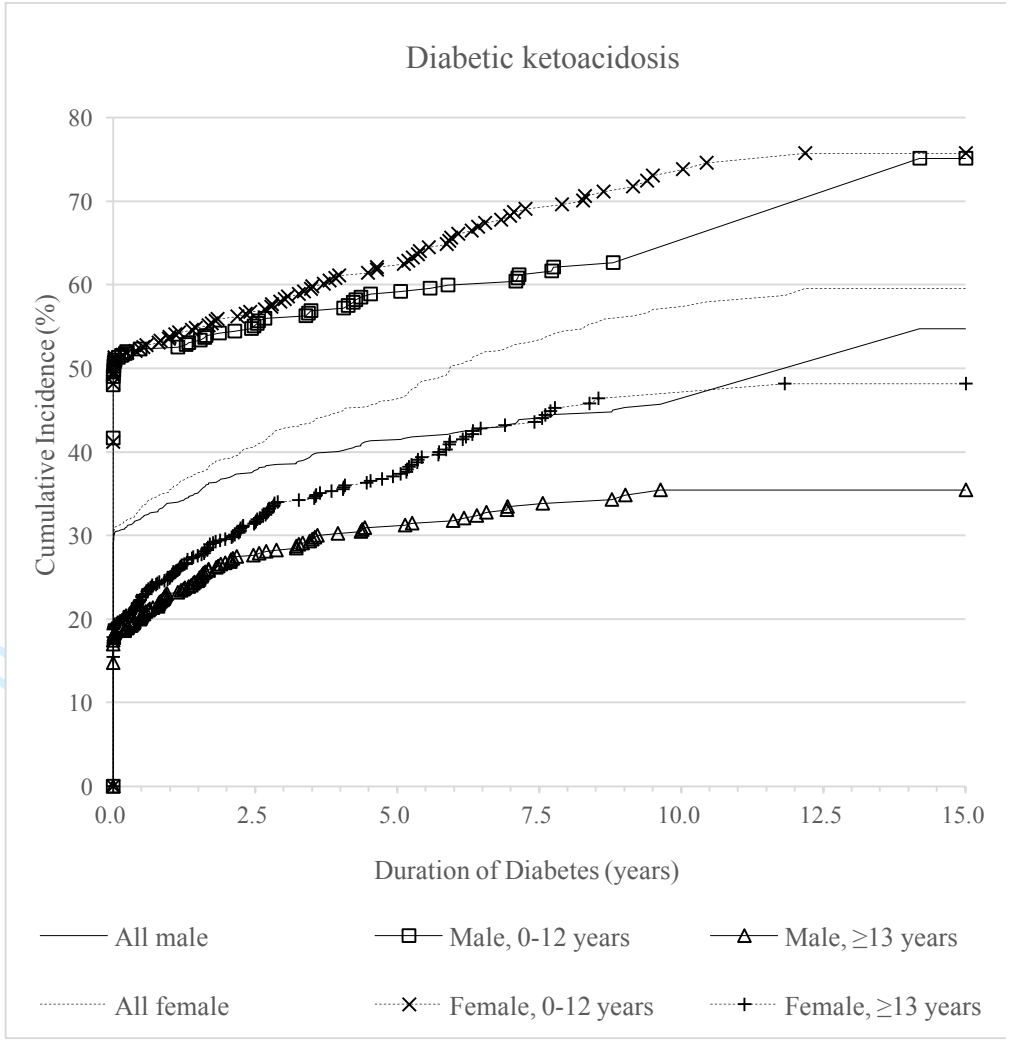

Sight-threatening diabetic retinopathy
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years

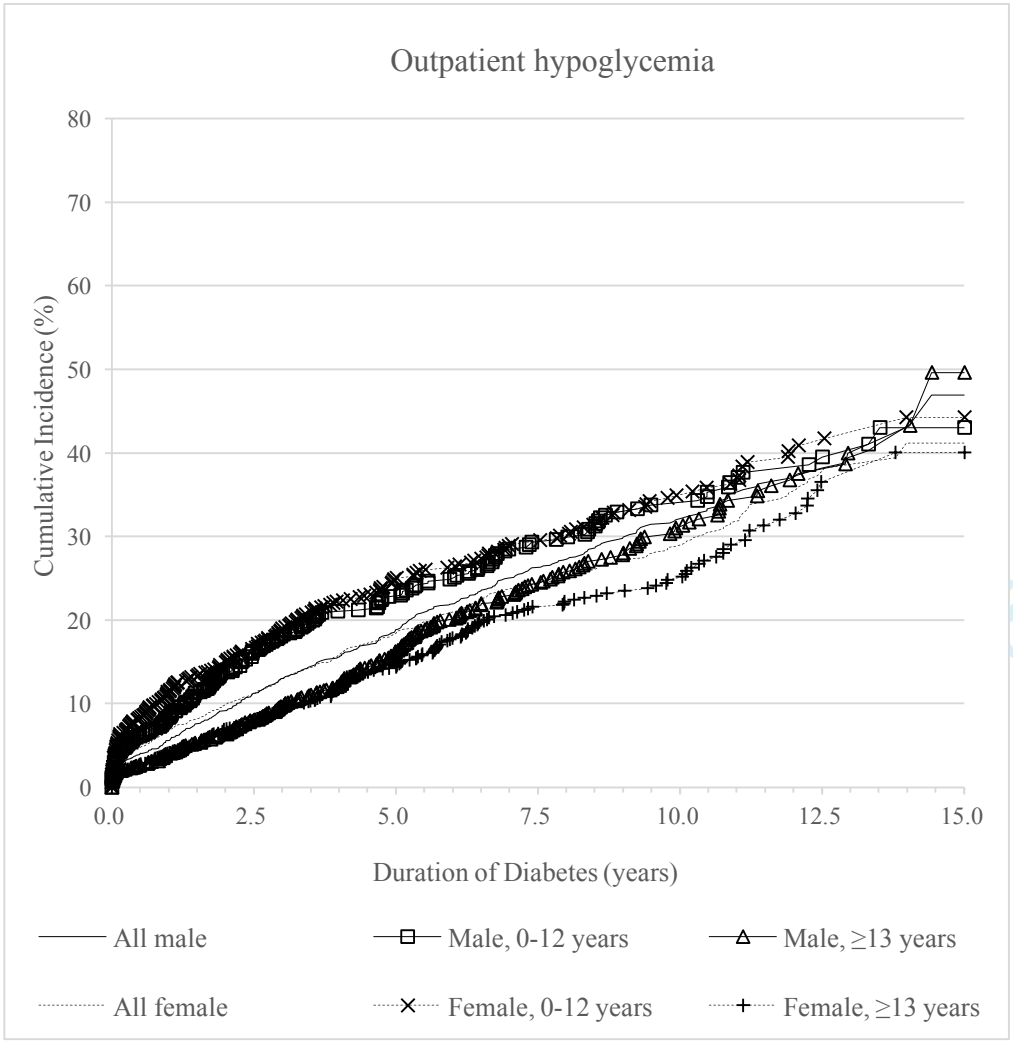

Neuropathy
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years

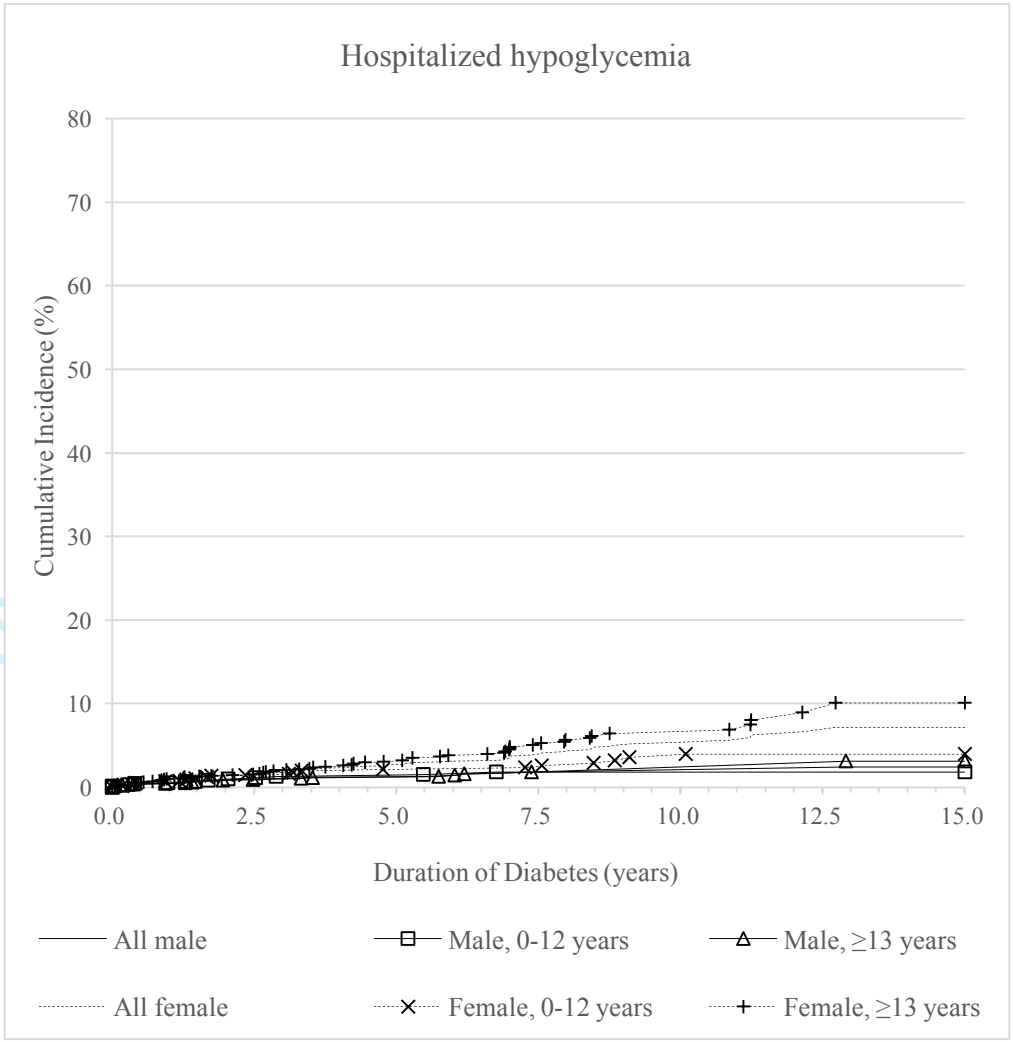

Nephropathy
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Renal failure
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Cardiovascular disease
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Diabetic ketoacidosis
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years





Note:

p value for comparison of cumulative incidence of retinopathy for male vs. female was 0.0006, for male, early vs. late-onset was 0.4553, for female, early vs. late-onset was 0.0908.

p value for comparison of cumulative incidence of proliferative retinopathy for male vs. female was 0.0567, for male, early vs. late-onset was 0.0013, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of sight-threatening diabetic retinopathy for male vs. female was 0.0405, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of neuropathy for male vs. female was 0.4050, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of nephropathy for male vs. female was 0.6191, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of renal failure for male vs. female was 0.4222, for male, early vs. late-onset was 0.0078, for female, early vs. late-onset was 0.0003.

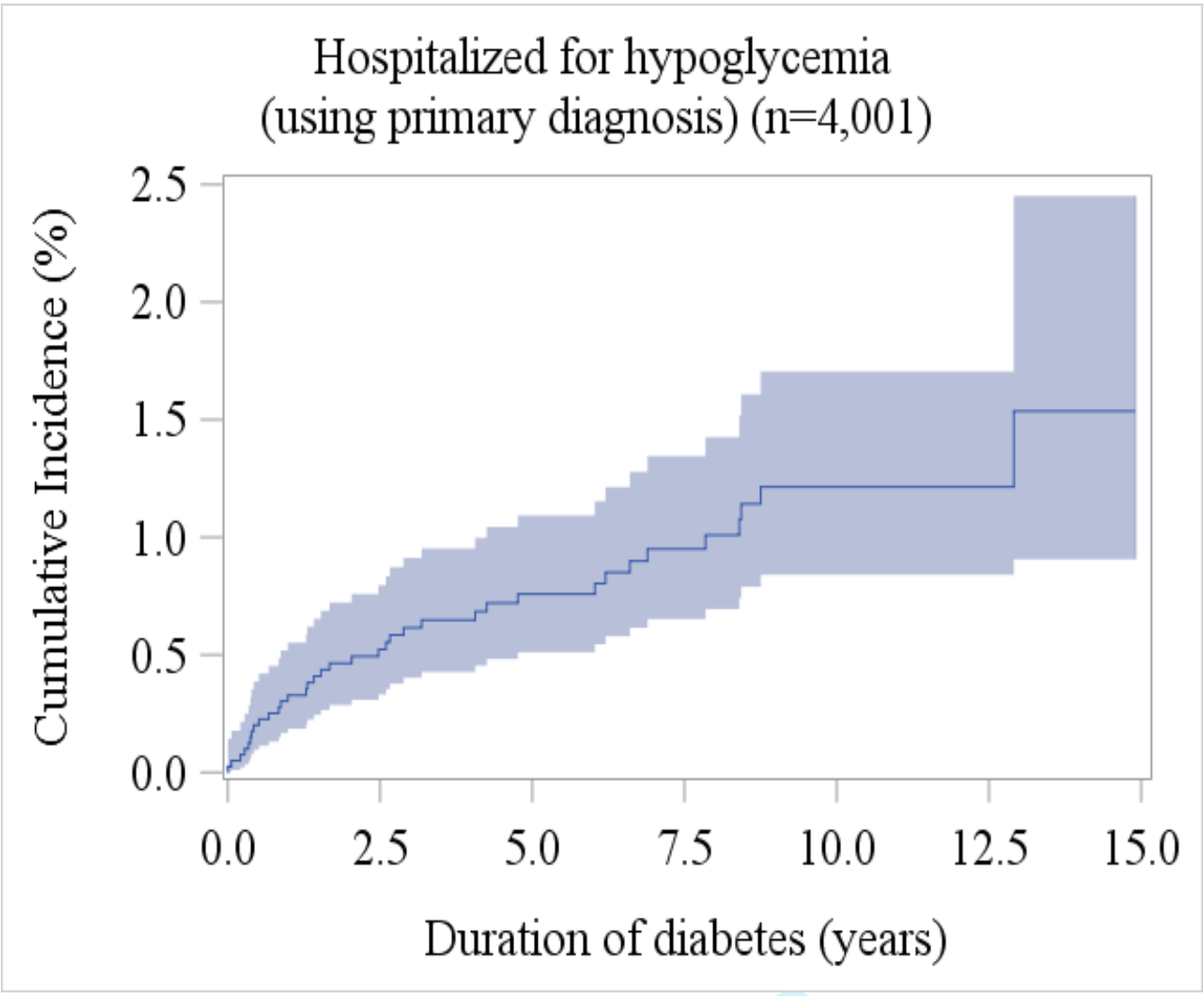
p value for comparison of cumulative incidence of cardiovascular disease for male vs. female was 0.4655, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was 0.0004.

p value for comparison of cumulative incidence of diabetic ketoacidosis for male vs. female was 0.0015, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was <.0001.

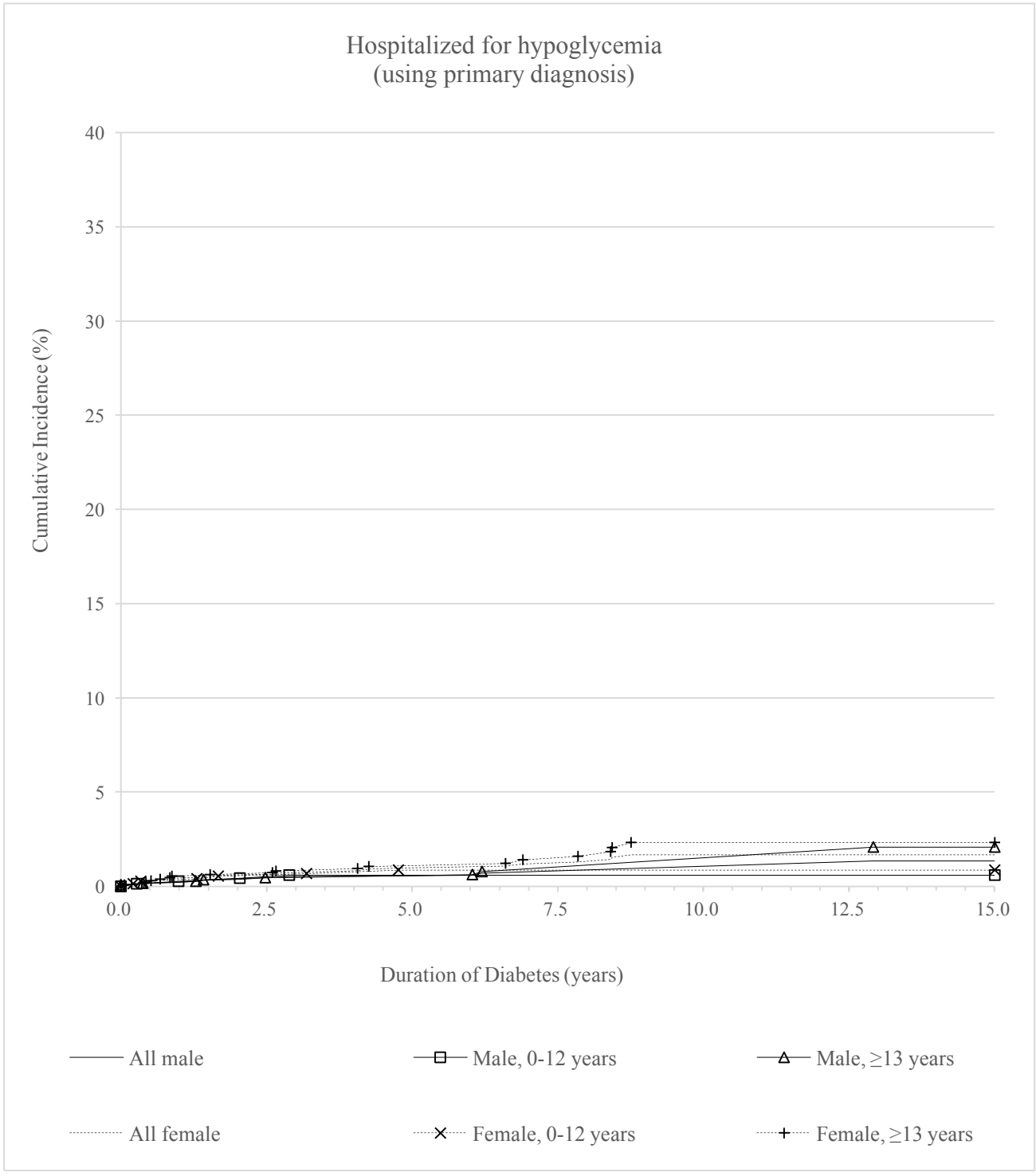
p value for comparison of cumulative incidence of outpatient hypoglycemia for male vs. female was 0.4095 for male, early vs. late-onset was 0.0097, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of hospitalized hypoglycemia for male vs. female was <.0001, for male, early vs. late-onset was 0.9600, for female, early vs. late-onset was 0.0113.

Supplementary Figure 2: Cumulative incidence of hospitalized for hypoglycemia according to the duration of diabetes in patients with type 1 diabetes (shadow area indicates 95 % confidence interval)



Supplementary Figure 3: Age-sex-specific cumulative incidences of hospitalized for hypoglycemia according to duration of diabetes in patients with type 1 diabetes (early-onset: 0-12 years, late-onset: ≥13 years)



Note:

p value for comparison of cumulative incidence for male vs. female was 0.0782, for male, early vs. late-onset was 0.6272, for female, early vs. late-onset was 0.1326.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7, 8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7, 8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	9, 10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9, 10

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11
		(*b*) Report category boundaries when continuous variables were categorized	10, 11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Incidence of diabetes-related complications in Chinese patients with type 1 diabetes: A population-based longitudinal cohort study in Taiwan

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Secondary Subject Heading:	Epidemiology, Health services research
Keywords:	DIABETES & ENDOCRINOLOGY, EPIDEMIOLOGY, Diabetic neuropathy < DIABETES & ENDOCRINOLOGY

Incidence of diabetes-related complications in Chinese patients with type 1 diabetes: A population-based longitudinal cohort study in Taiwan

Huang-Tz Ou PhD[1,2,*], Tsung-Ying Lee MS[1], Chung-Yi Li PhD[3,4], Jin-Shang Wu MD[5,6], Zih-Jie Sun MD[6,7]

[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2]Department of Pharmacy, College of Medicine, National Cheng Kung University Tainan, Taiwan
[3]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[4]Department of Public Health, China Medical University, Taichung, Taiwan
[5]Department of Family Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[6]Department of Family Medicine, National Cheng Kung University Hospital, Tainan, Taiwan
[7]Department of Family Medicine, National Cheng Kung University Hospital, Dou-Liou Branch, Dou-Liou, Taiwan

Corresponding author
Huang-Tz Ou, PhD
Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University,
1 University Road, Tainan 7010, Taiwan
Phone: +886-6-2353535 ext.5685
Fax: +886-6-2373149
Email: huangtz@mail.ncku.edu.tw

Abstract

Objective: To estimate the incidence densities and cumulative incidence of diabetes-related complications in patients with type 1 diabetes for a maximum of 15-year follow-up. The estimations were further stratified by gender and age at diagnosis (i.e., early-onset: 0-12 years, late-onset: ≥13 years).

Design: A population-based retrospective longitudinal cohort study.

Setting: Taiwan's National Health Insurance medical claims.

Participants: 4,007 patients newly-diagnosed with type 1 diabetes were identified during 1999-2012.

Outcome measures: Acute complications included diabetic ketoacidosis (DKA) and hypoglycemia. Chronic complications were cardiovascular diseases (CVD), retinopathy, neuropathy, and nephropathy.

Results: The incidence density of retinopathy was greatest (97.74 per 1,000 person-years), followed by those of nephropathy (31.36), neuropathy (23.93), and CVD (4.39). Among acute complications, the incidence density of DKA was greatest (121.11 per 1,000 person-years). The cumulative incidences of acute complications after 12 years following diagnosis were estimated to be 52.1%, 36.1%, and 4.1% for DKA, outpatient hypoglycemia,

and hospitalized hypoglycemia, respectively. For chronic complications, the cumulative incidence of retinopathy after 12 years following diagnosis was greatest (65.2%), followed by those of nephropathy (30.2%), neuropathy (23.7%), and CVD (4.1%). Females with late-onset diabetes were greatly affected by advanced retinopathy (i.e., sight-threatening diabetic retinopathy) and hospitalized hypoglycemia, whereas those with early-onset diabetes were more vulnerable to DKA. Chronic complications were more commonly seen in late-onset diabetes, whereas early-onset diabetes were most affected by acute complications.

Conclusions: Ethnically Chinese patients with type 1 diabetes were greatly affected by DKA and retinopathy. The incidence of diabetes-related complications after diagnosis differed by age and sex.

Strengths and limitations of this study

- ✓ This is the largest longitudinal cohort study of ethnically Chinese patients with type 1 diabetes followed for a maximum of 15 years to provide up-to-date incidence estimates of acute and chronic complications.
- ✓ The analyses stratified by gender and age at diabetes-onset indicated significant age-gender disparities in the epidemiological data of diabetes-related complications in type 1 diabetes, which highlight importance for clinical attention and developing preventive strategies.
- ✓ The study limitations resulting from the use of medical reimbursement claims data, including potential misclassifications of diabetes-related complications and lack of clinical biomarkers such as blood glucose, may underestimate rather than overestimate the incidence rates of diabetes-related complications.
- ✓ The incidence estimates of diabetes-related complications may only be generalizable to ethnically Chinese population with type 1 diabetes.

Introduction

It has been estimated that the incidence of type 1 diabetes increases by about 3-5% per year worldwide.[1-3] The annual incidence rate of childhood (< 15 years) type 1 diabetes in Taiwan was 5.3 per 100,000 children in the period 2003-2008.[4] Type 1 diabetes accounts for only 5-10% of the diabetic population, but it remains a devastating chronic disorder with acute complications, including diabetic ketoacidosis (DKA) and hypoglycemia, and chronic complications, which can be divided into microvascular (i.e., retinopathy, neuropathy, nephropathy) and macrovascular complications (i.e., cardiovascular diseases; CVD). Although treatment and care for type 1 diabetes have improved,[5-7] diabetes-related complications are major obstacles to glycemic control for many patients and contribute to most of the increased morbidity and premature mortality in such individuals.[8] The toxicity effect of prolonged chronic hyperglycemia is a leading cause of microvascular and macrovascular diseases among type 1 diabetes patients, with hypertension and dyslipidemia being exacerbating factors.[9]

Assessing the epidemiology of diabetes-related complications is essential for developing preventive strategies and planning treatment protocols to minimize the impact of the complications. However, there is very little longitudinal data (e.g., Pittsburgh Epidemiology

of Childhood-Onset Diabetes Complications (EDC) Study,[10] EURODIAB IDDM Complications Study[11]) on the incidence of complications for type 1 diabetes, and previous estimates widely varied with countries (e.g., European countries,[12] Finland,[13] Denmarks,[14] United States[10]) and entailed different follow-up periods (e.g., 7 years,[12] 12 years,[13] 18 years,[14] and 30 years[10]). In addition, a limited number of diabetes-related complications have been investigated (e.g., microalbuminuria[12, 14] and cardiovascular diseases; CVD[13]), with no previous study targeting an ethnic Chinese population with type 1 diabetes. Ethnic variations in diabetes-related complications have been recognized; Caucasian patients are greatly affected by CVD,[15, 16] while the prevalence of end-stage renal failure (ESRD)[17] and the odds of microalbuminuria and macroaluminuria[18] in Asian populations are much higher compared to those for Caucasian patients. Given the significance of rising life expectancy in recent years among ethnic Chinese patients with type 1 diabetes,[19] it is important to provide precise up-to-date estimates of incidence of its complications and compare them to those for other countries. We therefore utilized a longitudinal population-based cohort of newly diagnosed type 1 diabetes patients who were followed during the period 1999-2013 to evaluate the incidence densities and cumulative incidences of acute and chronic complications to provide contemporary estimates for an ethnic Chinese population. Efforts were also made to examine

whether there were age and sex differences in the incidences of type-1-diabetes-related complications.

Materials and Methods

The Institutional Review Board of National Cheng Kung University Hospital approved the study before commencement (A-ER-103-298).

Data source:

We utilized the Longitudinal Cohort of Diabetes Patients (LHDB) 1996-2013 data from the National Health Insurance Research Database (NHIRD). Taiwan's NHIRD is population-based and derived from the claims data of the National Health Insurance (NHI) program, a mandatory-enrollment, single-payment system that covers over 99% of Taiwan's population.[20] The LHDB is a valid national dataset that consists of a random sample of 120,000 de-identified diabetes incident cases from each calendar year, who were tracked back to 1996 and followed up to 2013 to establish a longitudinal cohort. The LHDB is representative of Taiwan's population with diabetes and provides research opportunity to evaluate long-term health outcomes of patients.[21-26]

Cohort:

From the LHDB, we selected 4,677 patients with a diagnosis of type 1 diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9-CM = 250.x1 or 250.x3) from outpatient files of the LHDB and having received a Catastrophic Illness Card (CIC) for type 1 diabetes (Figure 1) in the period 1999-2012. Because patients with a CIC are eligible for exemption from co-payments, the approval of such a status is subject to evaluation and review by the Bureau of NHI of Taiwan. The CIC patient data are accurate and reliable with a positive predictive value of 98.3% for type 1 diabetes.[19] We further excluded 670 potential type 2 diabetes cases who consumed any oral antihypoglycemic agents (OHAs) after CIC was issued, including sulfonylureas, meglitinides, acarbose, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide-1 receptor agonists, and however, those who used metformin alone, thiazolidinediones alone, or both were retained. Patients who were prescribed metformin, thiazolidinediones, or both were retained because these OHAs are insulin-sensitizers that can be combined with insulin treatments for cases with insulin resistance,[27, 28] which is also seen in patients with type 1 diabetes in Taiwan based on our expert opinions. To estimate the incidence rates of diabetes-related complications, we further selected cases without a history of the complication before type 1 diabetes diagnosis (Table 1). Study patients were stratified by gender and age at first type 1

diabetes diagnosis (i.e., early-onset: 0-12 years, late-onset: ≥13 years). The 25th, 50th (median) and 75th percentiles of age in early-onset group were 5, 8, and 10, respectively, with the mean age of 7.69 (standard deviation: 3.22). And, for late-onset group, the 25th, 50th and 75th percentiles of age were 17, 24, and 33, respectively, with the mean age of 26.47 (standard deviation: 11.60).

Diabetes-related complications:

The complications of interest included acute complications, namely DKA (confirmed by hospital admission or emergency room visit for DKA), hypoglycemia (confirmed by defined hypoglycemic events required for outpatient visits or hospitalization for medical assistance or interventions), and chronic complications, namely CVD, nephropathy, retinopathy, and neuropathy. A list of diabetes-related complications and the corresponding ICD-9-CM codes are provided in Supplementary Table 1; this list was confirmed by the expert panel before being applied.

Statistics:

The incidence density of diabetes-related complications was calculated by dividing the number of incident cases with individual complication events by the total person-years observed over 15 years of follow-up (1999-2013). The 95% confidence intervals (CIs) were

calculated assuming a Poisson distribution of cases.[29] Significant differences in incidence density between age-sex subgroups were indicated by a 95% CI for the difference in incidence density between subgroups.[30] Moreover, because a cohort of newly diagnosed type 1 diabetes patients was utilized, we were able to provide visual illustrations about the cumulative incidences of diabetes-related complications by diabetes duration since diabetes onset. The cumulative incidence of diabetes-related complications was estimated by using the life table method (using the SAS LIFETEST procedure) and significant difference in cumulative incidence between subgroups were examined according to K-sample tests.[31] SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for the aforementioned analyses.

Results

The median (25th and 75th percentiles) for the overall follow-up times (defined as the time from diabetes diagnosis to death, loss-to-follow-up, or the end of study period, whichever came first) are 6.74 years (3.43 and 10.02 years). The overall and age-sex specific incidence densities of diabetes-related complications are presented in Tables 1 and 2, respectively. The incidence rate of retinopathy (97.74 per 1,000 person-years) was greatest, followed by those of nephropathy (31.36), neuropathy (23.93), and CVD (4.39). Among

acute complications, the incidence density of DKA was greatest (121.11 per 1,000 person-years). As shown in Table 2, the incidence densities of retinopathy, DKA, and hospitalized hypoglycemia in females were significantly higher than those in males. The incidence densities of DKA and outpatient hypoglycemia in the early-onset group (0-12 years) were significantly higher than those noted in the late-onset group (≥13 years), while those of advanced retinopathy (i.e., sight-threatening diabetic retinopathy; STDR), neuropathy, nephropathy, CVD, and hospitalized hypoglycemia in the late-onset group were significantly higher. Figures 2 and 3 show cumulative incidences for acute and chronic complications, respectively, along with diabetes duration. The cumulative incidences at the 12th year after diagnosis were 52.1%, 36.1%, and 4.1% for DKA, outpatient hypoglycemia, and hospitalized hypoglycemia, respectively. For chronic complications, the 12-year cumulative incidence of retinopathy was greatest (65.2%), followed by those of nephropathy (30.2%), neuropathy (23.7%), and CVD (5.2%). Age-sex specific cumulative incidences of diabetes-related complications are illustrated in Supplementary Figure 1.

Discussion

To the best of our knowledge, this is the largest cohort study of ethnically Chinese

patients with newly diagnosed type 1 diabetes. We provided up-to-date estimates of the incidence of acute and chronic complications in type 1 diabetes patients followed for a maximum of 15 years. We observed age-gender disparities in the incidence of diabetes-related complications in type 1 diabetes. Although comparisons of the epidemiology of diabetes-related complications between studies are difficult, as potential determinants of the complications (e.g., age, gender, diabetes duration) differ, the estimates from different studies may reveal some racial or ethnic differences. In the following, we compare our results for ethnically Chinese patients with those reported for other countries or ethnicities.

Acute diabetes-related complications in type 1 diabetes patients

Diabetic ketoacidosis

Among acute complications, hyperglycemic events, including DKA and hyperglycemic hyperosmolar syndrome (HHS), are leading causes of morbidity and mortality among individuals with diabetes,[32] and utilize significant healthcare resources.[33] DKA was the most common acute complication among the Taiwanese population with type 1 diabetes; the incidence density followed for 15 years was 121.11 per 1,000 person-years, and half of the study population (~52%) experienced DKA at 12 years after diabetes diagnosis. Consistent with previous studies from the United States,[34] Australia,[35] and Canada,[36] we found that the

incidence of DKA in female patients, especially those with early-onset diabetes (i.e., 0-12 years), was higher than that in male patients. A cohort of 1,234 children with type 1 diabetes in the United States showed that female patients were greatly affected by DKA. A female preponderance of DKA was observed in a longitudinal study of childhood type 1 diabetes in Australia.[35] Similarly, a Canadian study of childhood type 1 diabetes showed that female sex was a significant predictor of DKA.[36] In fact, insulin omission or intentional insulin under-treatment due to fear of weight gain[37] and high prevalence of eating disorders[38] and psychiatric disorders[34] among female type 1 diabetes patients have been recognized as precipitating causes of DKA. Hence, effective interventions such as health education and communication for type 1 diabetes females are needed to reduce the incidence of DKA.

Hypoglycemia

Increased hypoglycemic events have been recognized as a result of the undesired effects of intensive insulin therapy with strict glycemic control.[39] The present study showed that the incidence rates of hospitalized and outpatient hypoglycemia in the Taiwanese population with type 1 diabetes were 3.89 and 39.93 per 1,000 person-years, respectively, which are much lower than that reported in type 1 diabetes children (0-19 years) in the United States (incidence of severe hypoglycemia: 190 per 1,000 person-years).[34] Such discrepancies in

international data may be explained by different definitions and assessment approaches for hypoglycemic events. We targeted hospital admissions for hypoglycemia based on ICD-9 CM codes, whereas the United States study used patients' reported survey data and classified severe hypoglycemia as acute episodes requiring the assistance of another person for treatment reported in the preceding 3 months.[40]

Moreover, we observed that early-onset patients were greatly affected by acute complications (i.e., DKA, hypoglycemia). It has been documented that among young children with type 1 diabetes, inconsistent eating patterns and lesser ability to recognize and report acute symptoms make it difficult to achieve glycemic control, leading to glycemic fluctuations that cause multiple episodes of hyperglycemia (i.e., DKA) and hypoglycemia.[41] Frequent exposures to hyperglycemia and hypoglycemia in early-onset type 1 diabetes patients could lead to a range of neurocognitive dysfunctions and brain changes.[42] Also, structural brain changes in type 1 diabetes children may occur due to recurrent hypoglycemia.[43] Hence, given the high rates of acute complications and associated serious consequences, effective management protocols and identification and treatment of precipitating causes are needed.[44] In particular, regular glycemic monitoring and identification of risk factors in young type 1 diabetes patients are needed to reduce the

frequency and severity of DKA and hypoglycemia.

Chronic diabetes-related complications in type 1 diabetes

Diabetic retinopathy

Diabetic retinopathy is the main cause of blindness in the adult population.[45] Almost all type 1 diabetes patients develop evident retinopathy in the first 20 years of diagnosis.[46] The present study showed that more than half (~69%) of type 1 diabetes patients experienced some form of diabetic retinopathy at 12 years after diagnosis. We observed that the incidence density of diabetes retinopathy is greatest among chronic complications in Taiwanese type 1 diabetes patients (4.53 per 100 person-years over a period of 15 years of follow-up). As compared to the incident density of proliferative retinopathy (19.5 per 1,000 person-years) in the Pittsburgh EDC Study of type 1 diabetes patients with a mean age of 28 years and diabetes duration of 19 years at baseline examination,[10] our estimate (5.87 per 1,000 person-year) based on a cohort of newly diagnosed type 1 diabetes patients is lower. Such a difference between studies may be explained by diabetes duration and age at baseline of study examination. Moreover, comparing the prevalence of STDR in type 1 diabetes patients in this study (2.00 % for women and 1.66 % for men) with that previously observed in Taiwanese type 2 diabetes patients (2.75% for women and 2.87% for men)[47] reveals a slightly

lower advanced diabetic retinopathy (i.e., STDR) in the type 1 diabetes versus type 2 diabetes patients. However, the lower rate of STDR in our study may be due to the other study's inclusion of prevalent type 2 diabetes cases with longer diabetes duration[47] as compared to incident type 1 diabetes targeted in this study.

Consistent with previous studies,[48, 49] the present study demonstrated a female preponderance in diabetic retinopathy. A large cohort of 8,114 type 1 diabetes patients and families assembled over 25 years from the United States showed that females had 1.7 fold higher retinopathy risk ($p < 0.001$) as compared to that of males.[48] Also, a cross-sectional study of 247 Italian type 1 diabetes patients showed a significant relationship between diabetic retinopathy and female gender ($p = 0.01$).[49] Although exact hormone, genetic, lifestyle, or environmental factors are unclear, a differential effect of sex steroid hormones has been proposed to explain this gender discrepancy.[50] Also, age at diabetes onset has been shown to be associated with the development of diabetic retinopathy.[49, 51] An early age at onset (5-14 years) appears to modify the long-term risk of proliferative retinopathy.[51] Consistent with other studies, we observed lower incidence of diabetic retinopathy in early-onset patients as compared to that in late-onset patients. Nevertheless, given a high rate of diabetes retinopathy observed among Taiwanese type 1 diabetes patients, early detection

using routine eye examination, control for risk factors of diabetic retinopathy (e,g., hypertension, hyperglycemia, hyperlipidemia),[9] as well as development of tailored intervention strategies for age-sex subgroups are important.

Diabetic nephropathy

Our results show that diabetic nephropathy is the second most common microvascular complication among the Taiwanese population with type 1 diabetes. Without interventions, diabetes patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy.[52] Diabetic nephropathy is a leading cause of ESRD among patients with diabetes.[52] As estimated, individuals with type 1 diabetes face a 20-50% chance of developing ESDR that requires dialysis or renal transplantation.[53] The Pittsburgh EDC Study reported that the incidence density of renal failure (based on self-reported renal transplantation and dialysis) was 6.3 per 1,000 person-years over 12 years of follow-up,[10] while the present study based on ICD-9 codes of renal failure found that the incidence of renal failure was 1.31 per 1,000 person-years over 15 years of follow-up. Of note, the EDC study enrolled more advanced type 1 diabetes cases (i.e., mean age of 28 years and diabetes duration of 19 years at baseline examination[10]) than those in our study (i.e., newly diagnosed type 1 diabetes cases in 2000-2012), which may explain the higher rate of renal failure in the

EDC study. A large inception cohort study of Danish patients newly diagnosed with type 1 diabetes followed for a median of 18 years reported that the cumulative incidences of persistent microalbuminuria and macroalbuminuria were 33.6% and 14.6%, respectively, while the present study found that overall cumulative incidence of any form of diabetic nephropathy was 30.2% at 12 years after diabetes diagnosis. Moreover, early-onset diabetes appears to be protective for developing diabetic nephropathy[12, 54-56] and may delay the time until microalbuminuria.[56] Consistently, we found that late-onset diabetes patients were more affected by diabetic nephropathy than were early-onset patients. Nevertheless, given the fact that Taiwan has the highest number of patients undergoing renal dialysis in the world, where diabetes contributes to about 40 % of end-stage renal failure cases,[57] it is critical for routine annual screening of clinical signs of diabetic nephropathy (i.e., proteinuria, microalbuminuria), optimal control of glycemia and risk factors (e.g., retinopathy smoking, dyslipidemia, hypertension[14, 58, 59]), and early intervening medications for prevention (e.g., angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker for those with comorbid hypertension).[9]

Diabetic neuropathy

Diabetic neuropathy refers to the presence of symptoms, signs, or both of peripheral

nerve dysfunction in people with diabetes after the exclusion of other causes.[60] Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies.[61] The epidemiological data of diabetic neuropathy is very limited. A study of 467 Italian type 1 diabetes patients showed that the prevalence rates of asymptomatic and symptomatic neuropathy were 7.2% and 21.3%, respectively.[62] The present study is the first study to provide epidemiology data on diabetic neuropathy among ethnically Chinese patients with type 1 diabetes from Asia. We found that the incidence rate was 23.93 per 1,000 person-years over 15 years of follow-up, and that the cumulative incidence was 23.7% at 12 years after diabetes diagnosis. We also observed that the incidence of diabetic neuropathy in late-onset patients were much higher than that in early-onset patients. Similarly, the Italian study of type 1 diabetes showed that the prevalence of diabetic neuropathy was higher in patients at older ages.[62] Since diabetic neuropathy contributes to considerable disabilities and mortality, it is critical for clinicians to understand its manifestations, prevention, and treatment.[9] Early prevention strategies that control hypertension and hyperglycemia and identify patients with peripheral neuropathy or peripheral vascular disease and annual screening for these conditions are strongly recommended.[9]

Cardiovascular diseases

CVD is a leading cause of mortality in patients with type 1 diabetes[63, 64] and accounts for the greatest proportion of healthcare spending for patients with diabetes.[64, 65] As compared to patients without diabetes, type 1 diabetes increases the risk of CVD by ten fold,[63, 66] which contributes to two-thirds of mortality in patients with type 1 diabetes.[67, 68] The Pittsburgh EDC Study showed an incidence density of 3.6 per 1,000 person-years for coronary heart diseases (defined as coronary-artery-disease-related death, a history of myocardial infarction, angiographic stenosis ≥ 50% including revascularization) over a period of 12 years,[10] while the present study found that the incidence density for a broader category of CVD (including myocardial infarction, ischemic heart diseases, heart failure, stroke, and arrhythmia, as shown in Supplementary Table 1) in the Taiwanese population with type 1 diabetes within 15 years of follow-up was 4.39 per 1,000 person-years. The cumulative incidences of CVD (including only stroke and coronary heart disease) at 12 years after diabetes was diagnosed was 1-2% among Finnish type 1 diabetes patients,[13] which is lower than that for the Taiwanese type 1 diabetes patients in the present study (~5.2%). Moreover, we found that late-onset patients were greatly affected by CVD. In fact, old age is recognized as a predictor of vascular diseases,[63] which may be explained by the calcification of extremity arteries and hypertension

in older age patients, which are risk factors of macrovascular diseases.[69]

Methodological concerns

Some limitations of this study should be acknowledged. The classification of diabetes-related complications based on the ICD-9 CM codes in claims data may underestimate the occurrence of the complications. For example, patients experiencing clinical symptoms/signs of diabetes-related complications (e.g., hypoglycemia) may not see doctors if they can tolerate them. Also, the claims data do not capture clinical/minor symptoms or signs of diabetes-related complications such as minor microalbuminuria. The glycemic biomarkers such as blood glucose were not available from the claims data so the identification of hyperglycemia or hypoglycemia was only based on the ICD-9 CM diagnosis codes. So, we might under-estimate the incidence of hypoglycemic events and may not be able to disentangle the severity of hypoglycemia. However, the claims records capture defined diabetes-related complications that are required for medical assistance or treatments, which lead to more conservative estimates and reveal important manifestations of diabetes-related complications for clinical attention. Moreover, based on our operational definition for hospitalized hypoglycemia (i.e., any one of diagnosis codes with hypoglycemia from the five diagnosis codes in the inpatient files of the NHIRD), two types of

hypoglycemic events could be included: (1) hospital admission for hypoglycemia, and (2) other reasons for hospital admission (e.g., DKA), and then hypoglycemia happened during hospitalization. It is difficult to differentiate these two types of hypoglycemic events based on the retrospective claims data we utilized. However, in the clinical practice in Taiwan, the first code from the five diagnosis codes in hospitalization is typically to be the main/primary reason for hospital admission. With this regard, we re-run the analyses for hospitalized hypoglycemia which was identified from the first diagnosis code in hospitalization. The results were provided in the Supplementary Table 2, and Supplementary Figures 2 and 3. These re-analytical results may also ease the concern that patients who came to hospital primarily for reasons that may induce hypoglycemia during hospitalization. Lastly, the generalizability of our study results may be limited to ethnically Chinese populations. In addition, our results may represent only ethnically Chinese patients with type 1 diabetes in Taiwan.

Conclusions

Utilizing an incident cohort of type 1 diabetes patients diagnosed during the period 1999-2012 with a maximum of 15 years of follow-up, we found that most type 1 diabetes patients were affected by DKA and retinopathy, which highlight the critical need to identify

precipitating causes and modifiable factors for developing preventive strategies and intervening treatment protocols to minimize the impact of these complications. Age and sex discrepancies appear in epidemiological data of diabetes-related complications; late-onset diabetes females were greatly affected by advanced retinopathy (i.e., STDR) and hospitalized hypoglycemia, while early-onset females had a high incidence of DKA. Chronic diabetes-related complications were more common in late-onset type 1 diabetes patients, while early-onset individuals were most affected by acute complications. More attention should be given to identify potential risk factors and contributors to such age-sex differences in diabetes-related complications. Population-based data on the incidence of diabetes-related complications from this study are important for clinicians to recognize the need for diagnostic awareness and for policy-markers to develop effective treatments for patients with type 1 diabetes.

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Table 1: Overall incidence density of diabetes-related complications among patients with type 1 diabetes between 1999 and 2013

	Retinopathy	Proliferative retinopathy	STDR	Neuropathy	Nephropathy	Renal failure	CVD	DKA	Outpatient hypoglycemia	Hospitalized hypoglycemia
No. of cases*	3,359	3,970	3,983	3,742	3,634	4,003	3,916	2,205	3,934	3,987
No. of cases with event**	1,532	157	90	558	688	36	117	996	913	105
Follow-up time (person-years)†	15,675	26,733	27,139	23,320	21,936	27,491	26,664	8,224	22,865	26,968
Incidence density (1,000 person-years) (95% CI)	97.74 (92.9-102.8)	5.87 (5.0-6.9)	3.32 (2.7-4.1)	23.93 (22.0-26.0)	31.36 (29.1-33.8)	1.31 (0.9-1.8)	4.39 (3.6-5.3)	121.11 (113.7-128.9)	39.93 (37.4-42.6)	3.89 (3.2-4.7)

* No. of cases refers to the number of patients who had no complication of interest in the baseline year (one year before diagnosis date).

** No. of cases with event refers to the number of patients who had incident events after type 1 diabetes was confirmed.

† Cumulative follow-up time (person-years) was calculated as the sum of follow-up years during observation period.

Note: Patients with type 1 diabetes were retrieved from incidence cases from 2000 to 2012. Follow-up time started from the first diagnosis date to the time the event occurred, death, discontinued enrollment from Taiwan's National Health Insurance Program, or the end of 2013, whichever came first.

Abbreviations: STDR: sight-threatening diabetic retinopathy, CVD: cardiovascular disease, DKA: diabetic ketoacidosis, CI: confidence interval.

Table 2: Incidence density of diabetes-related complications by age and sex among patients with type 1 diabetes between 1999 and 2013

	Retinopathy	Proliferative retinopathy	STDR	Neuropathy	Nephropathy	Renal failure	CVD	DKA	Outpatient hypoglycemia	Hospitalized hypoglycemia
Male										
No. of cases*										
All male	1,618	1,886	1,892	1,778	1,695	1,901	1859	1,073	1,872	1,902
Early-onset (0-12 years)	654	719	719	714	700	719	712	396	718	719
Late-onset (≥13 years)	964	1,167	1,173	1,064	995	1,182	1,147	677	1,154	1,183
No. of cases with event**										
All male	693	64	34	261	332	15	60	447	452	28
Early onset	305	14	1	37	86	1	7	239	202	11
Late onset	388	50	33	224	246	14	53	208	250	17
Follow-up time (person-years)†										
All male	7,813	12,908	13,102	11,345	10,403	13,248	12,798	4,322	11,025	13,115
Early-onset	3,333	5,290	5,368	5,180	4,817	5,358	5,280	1,317	4,277	5,297
Late-onset	4,480	7,618	7,734	6,165	5,586	7,891	7,518	3,005	6,749	7,818
Incidence density (1,000 person-years) (95% CI)										
All male	88.70 (82.2-95.6)	4.96 (3.8-6.3)	2.60 (1.8-3.6)	23.01 (20.3-26.0)	31.91 (28.6-35.5)	1.13 (0.6-1.9)	4.69 (3.6-6.0)	103.43 (94.1-113.5)	41.00 (37.3-45.0)	2.13 (1.4-3.1)
Early-onset	91.52	2.65	0.19	7.14	17.85	0.19	1.33	181.53	47.23	2.08

	(81.5-102.4)	(1.4-4.4)	(0.0-1.0)	(5.0-9.8)	(14.3-22.0)	(0.0-1.0)	(0.5-2.7)	(159.2-206.1)	(40.9-54.2)	(1.0-3.7)
Late-onset	86.60	6.56	4.27	36.34	44.04	1.77	7.05	69.22	37.05	2.17
	(78.2-95.7)	(4.9-8.7)	(2.9-6.0)	(31.7-41.4)	(38.7-49.9)	(1.0-3.0)	(5.3-9.2)	(60.1-79.3)	(32.6-41.9)	(1.3-3.5)
95% CI of incidence density difference for male, early vs. late-onset	**-8.5 to 18.3**	**-6.4 to -1.4‡**	**-5.9 to -2.3‡**	**-34.8 to -23.6‡**	**-33.1 to -19.3‡**	**-2.8 to -0.4‡**	**-8.1 to -3.3‡**	**91.5 to 133.1‡**	**2.4 to 17.9‡**	**-1.7 to 1.5**
Female										
No. of cases*										
All female	1,741	2,084	2,091	1,964	1,939	2,102	2,057	1,132	2,062	2,085
Early-onset	721	777	777	772	764	777	773	413	774	774
Late-onset	1,020	1,307	1,314	1,192	1,175	1,325	1,284	719	1,288	1,311
No. of cases with event**										
All female	839	93	56	297	356	21	57	549	461	77
Early-onset	358	18	6	50	109	1	11	277	229	21
Late-onset	481	75	50	247	247	20	46	272	232	56
Follow-up time (person-years)†										
All female	7,862	13,825	14,037	11,976	11,533	14,243	13,866	3,902	11,840	13,853
Early-onset	3,616	5,848	5,910	5,610	5,283	5,927	5,871	1,183	4,642	5,777
Late-onset	4,246	7,977	8,127	6,365	6,250	8,317	7,995	2,719	7,199	8,076
Incidence density (1,000 person-years) (95% CI)										

All female	106.72	6.73	3.99	24.80	30.87	1.47	4.11	140.69	38.94	5.56
	(99.6-114.2)	(5.4-8.2)	(3.0-5.2)	(22.1-27.8)	(27.7-34.2)	(0.9-2.3)	(3.1-5.3)	(129.2-153.0)	(35.5-42.7)	(4.4-6.9)
Early-onset	99.01	3.08	1.02	8.91	20.63	0.17	1.87	234.05	49.34	3.63
	(89.0-109.8)	(1.8-4.9)	(0.4-2.2)	(6.6-11.8)	(16.9-24.9)	(0.0-0.9)	(0.9-3.4)	(207.3-263.3)	(43.1-56.2)	(2.3-5.6)
Late-onset	113.29	9.40	6.15	38.80	39.52	2.40	5.75	100.05	32.23	6.93
	(103.4-123.9)	(7.4-11.8)	(4.6-8.1)	(34.1-44.0)	(34.7-44.8)	(1.5-3.7)	(4.2-7.7)	(88.5-112.7)	(28.2-36.7)	(5.2-9.0)
95% CI of incidence density difference for female, early vs. late-onset	**-28.8 to 0.2**	**-9.1 to -3.6‡**	**-7.3 to -3.0‡**	**-35.5 to -24.2‡**	**-25.3 to -12.5‡**	**-3.5 to -1.0‡**	**-6.0 to -1.7‡**	**108.4 to 159.6‡**	**9.8 to 24.4‡**	**-5.8 to -0.8‡**
95% CI of incidence density difference for male vs. female	**-27.8 to -8.2‡**	**-3.6 to 0.1**	**-2.8 to -0.02‡**	**-5.8 to 2.2**	**-3.6 to 5.7**	**-1.2 to 0.5**	**-1.0 to 2.2**	**-52.3 to -22.2‡**	**-3.1 to 7.2**	**-4.9 to -1.9‡**

* No. of cases refers to the number of patients who had no complication of interest in the baseline year (one year before diagnosis date).

** No. of cases with event refers to the number of patients who had incident events after type 1 diabetes was confirmed.

† Cumulative follow-up time (person-years) was calculated as the sum of follow-up years during observation period.

Note: Patients with type 1 diabetes were retrieved from incidence cases from 2000 to 2012. Follow-up time started from the first diagnosis date to the time the event occurred, death, discontinued enrollment from Taiwan's National Health Insurance Program, or the end of 2013, whichever came first.

Abbreviations: STDR: sight-threatening diabetic retinopathy, CVD: cardiovascular disease, DKA: diabetic ketoacidosis, CI: confidence interval. ‡ $p < 0.05$

Figure 1. Flowchart of study cohort selection

Figure 2: Cumulative incidences of diabetic ketoacidosis, mild hypoglycemia according to the duration of diabetes in patients with type 1 diabetes (shadow area indicates 95 % confidence interval)

Figure 3: Cumulative incidences of retinopathy, sight-threatening diabetic retinopathy, neuropathy, nephropathy, renal failure, and cardiovascular diseases according to the duration of diabetes in patients with type 1 diabetes (shadow area indicates 95 % confidence interval)

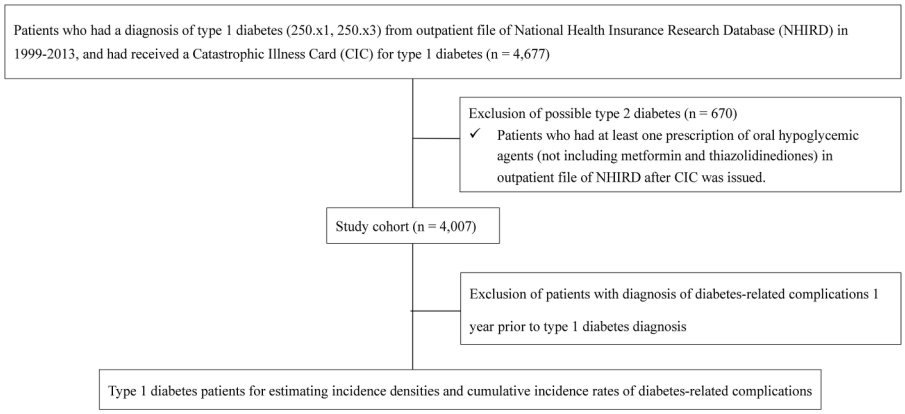

Figure 1. Flowchart of study cohort selection

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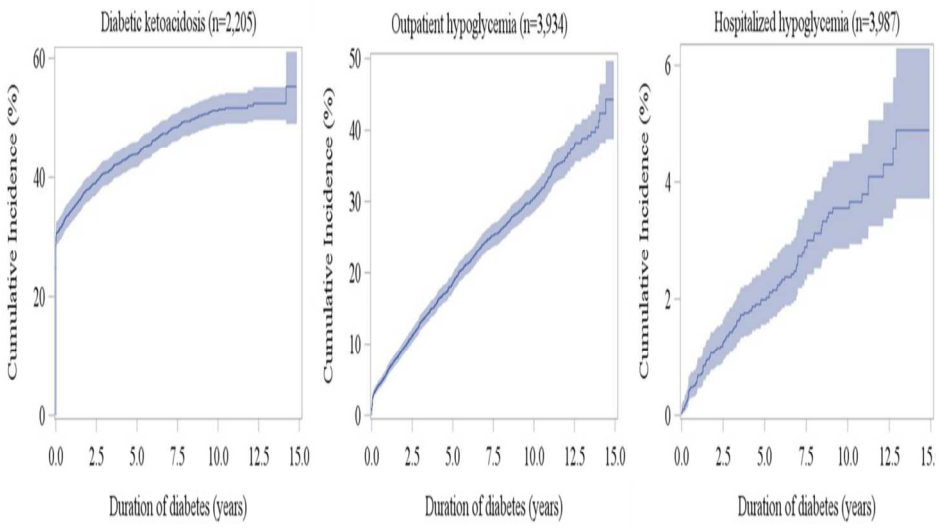


Figure 2: Cumulative incidences of diabetic ketoacidosis, mild hypoglycemia according to the duration of diabetes in patients with type 1 diabetes (shadow area indicates 95 % confidence interval)

209x148mm (300 x 300 DPI)

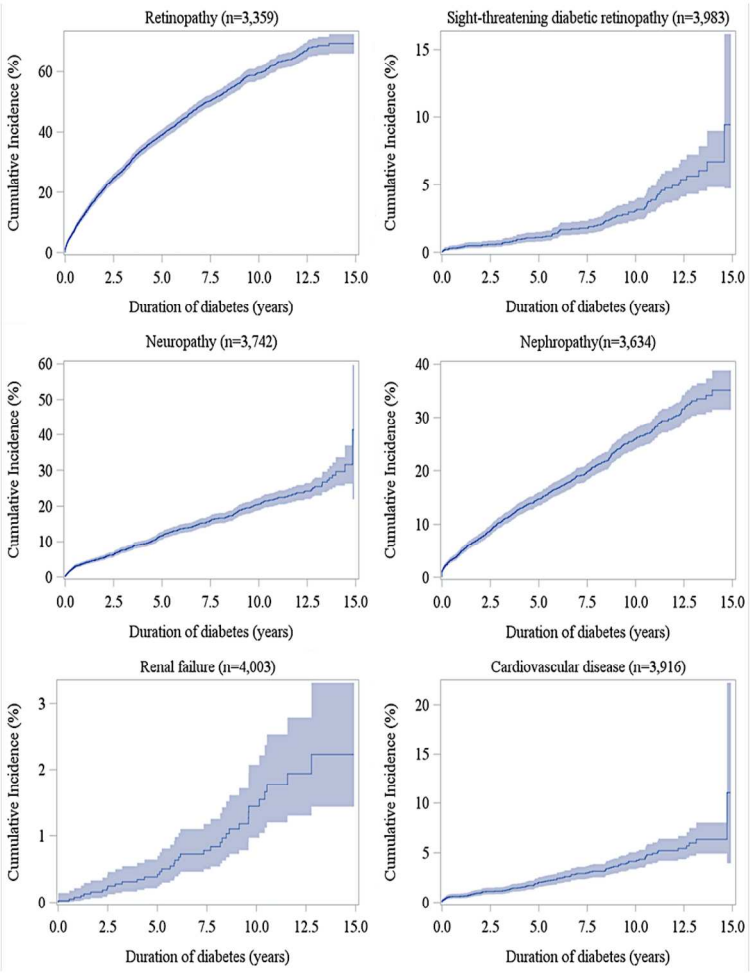


Figure 3: Cumulative incidences of retinopathy, sight-threatening diabetic retinopathy, neuropathy, nephropathy, renal failure, and cardiovascular diseases according to the duration of diabetes in patients with type 1 diabetes (shadow area indicates 95 % confidence interval)

297x420mm (300 x 300 DPI)

Supplementary Table 1: Diabetes-related acute and chronic complications

Complications	ICD-9-CM disease codes	ICD-9-CM procedure codes	NHI procedure codes
CVD (cardiovascular disease and cerebrovascular disease)[a,b]			
Acute myocardial infarction	410, 412*	---	---
Ischemic heart disease	411, 413, 414, V45.81, V45.82	00.66, 36.0, 36.1, 36.2, 36.3, 36.9, 88.5	---
Heart failure	428		---
Stroke	430-437, 438*, V12.54	00.61, 00.63, 38.11, 38.12	---
Cardiogenic shock	785.51	---	---
Sudden cardiac arrest	V12.53	---	---
Arteriosclerotic cardiovascular disease	429.2	---	---
Arrhythmia	426, 427	---	---
Microvascular complications[a,c]			
Nephropathy	250.4, 403, 404, 580, 581, 582, 583, 584, 585, 586, 587, 588, 593, 791.0, V13.03, V42.0, V45.1, V56	38.95, 39.27, 39.42, 39.95, 54.98, 55.4, 55.5, 55.6	---
Renal failure (dialysis or transplantation)[d]	V45.1, V56	39.95, 54.98 55.6	---
Retinopathy	250.5, 361, 362, 364, 365, 366, 368, 369, 377, 379.2	12.41, 12.73, 14.23, 14.24, 14.25, 14.33, 14.34, 14.35, 14.53, 14.54, 14.55, 16.92, 16.99	86206B, 86207B, 60001C, 60002C*, 60003C, 60004C*
Proliferative retinopathy[d]	362.02	---	60001C, 60002C*, 60003C, 60004C*
Sight-threatening diabetic retinopathy[e]	---	---	86206B, 86207B, 60001C, 60002C*, 60003C, 60004C*
Neuropathy	250.6, 302.72, 337.1, 354, 355, 357.2, 358.1, 607.84, 713.5, 729.2	---	---
Metabolic complications			
Diabetic ketoacidosis[a]	250.1	---	---
Hypoglycemia[a,f]	251.0, 251.1, 251.2, 270.3, 775.0, 775.6	---	---

*For identifying prevalent cases only. a: Nutr Metab Cardiovasc Dis. 2014;24(1):10-7. b: Pharmacoepidemiol Drug Saf. 2009;18(6):497-503. c: Diabetes Care. 2008;31(3):596-615. d: Diabetes. 2006;55(5):1463-9. e: JAMA Ophthalmol. 2014;132(8):922-928. f: BMC Endocr Disord. 2008;8:4. Abbreviations: ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification, NHI: Taiwan National Health Insurance.

Supplementary Table 2: Incidence density of hospitalized hypoglycemia among patients with incident type 1 diabetes diagnosed between 1999 and 2013 (using primary diagnosis to define hospitalization for hypoglycemia)

	Overall patients	Male subgroup			Female subgroup		
		Overall male‡	Male early-onset (0-12 years)‡	Male late-onset (≥13 years)	Overall female	Female early-onset (0-12 years)‡	Female late-onset (≥13 years)
No. of cases*	4,001	1,903	719	1,184	2,098	777	1,321
No. of cases with event	36	12	4	8	24	6	18
Follow-up time (person-years)†	27,374	13,205	5,327	7,878	14,169	5,890	8,280
Incidence density (1,000 person-years) (95% CI)	1.32 (0.9-1.8)	0.91 (0.5-1.6)	0.75 (0.2-1.9)	1.02 (0.4-2.0)	1.69 (1.1-2.5)	1.02 (0.4-2.2)	2.17 (1.3-3.4)

* No. of cases refers to the number of patients who had no complication event of interest before type 1 diabetes was confirmed.

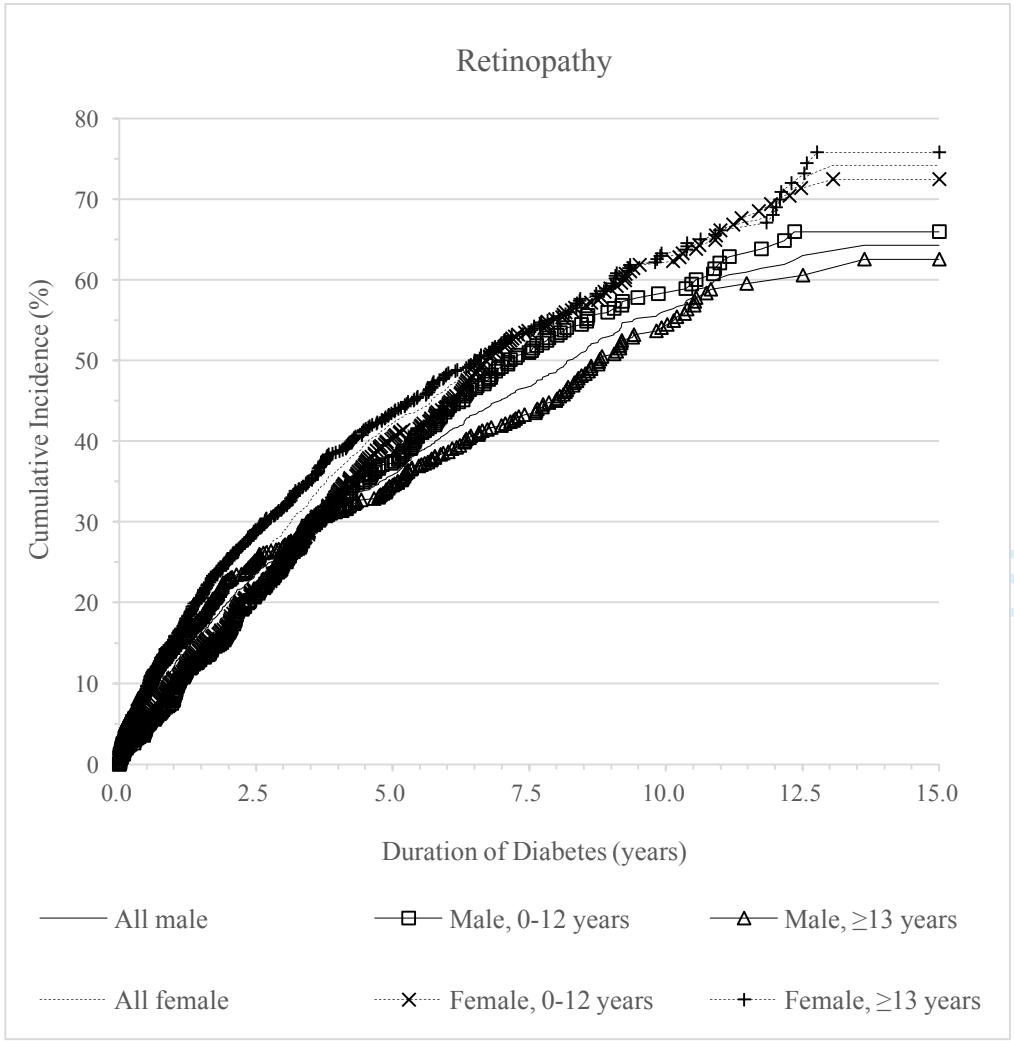
† Cumulative follow-up time (person-years) was calculated as the sum of follow-up years during observation period.

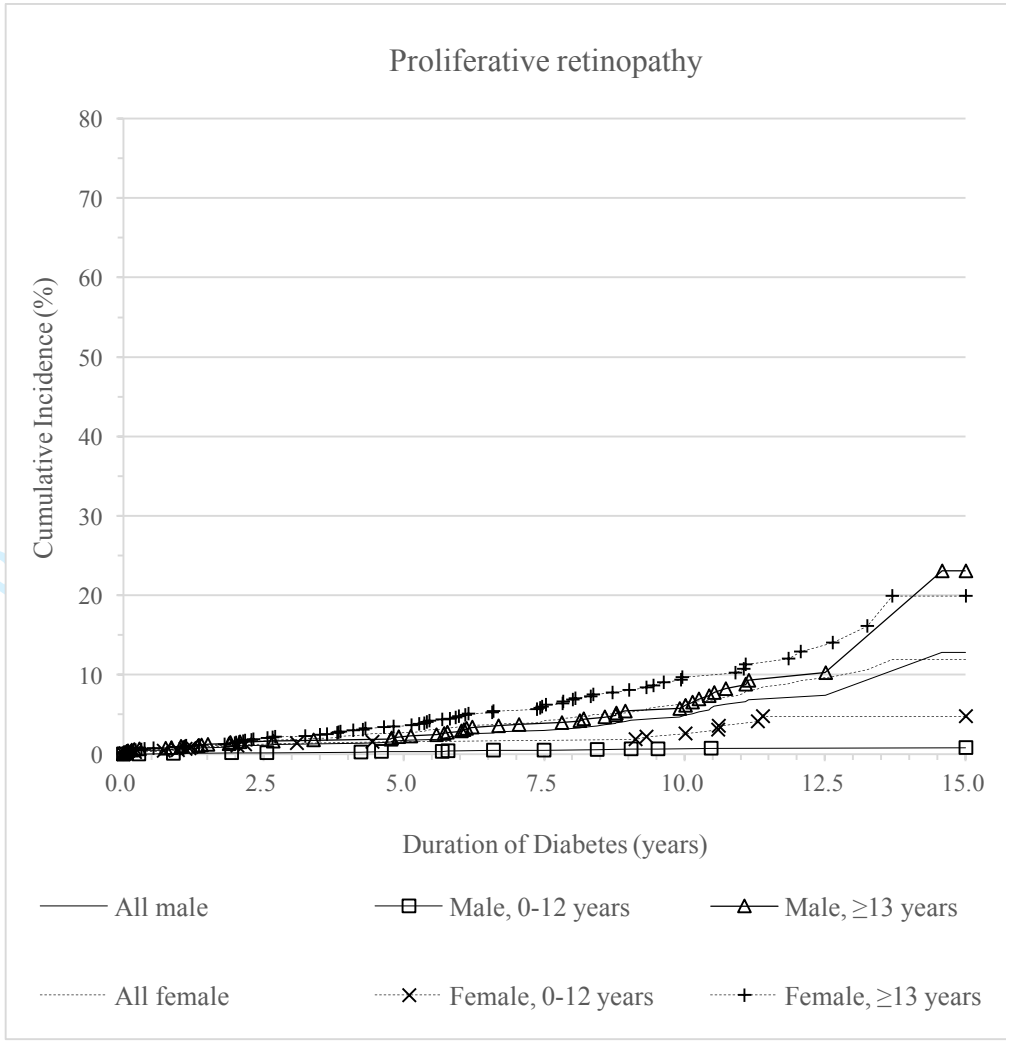
Note: Patients with type 1 diabetes were retrieved from incidence cases from 2000 to 2012. Follow-up time started from the first diagnosis date to the time the event occurred, death, discontinued enrollment from Taiwan's National Health Insurance Program, or the end of 2013, whichever came first.

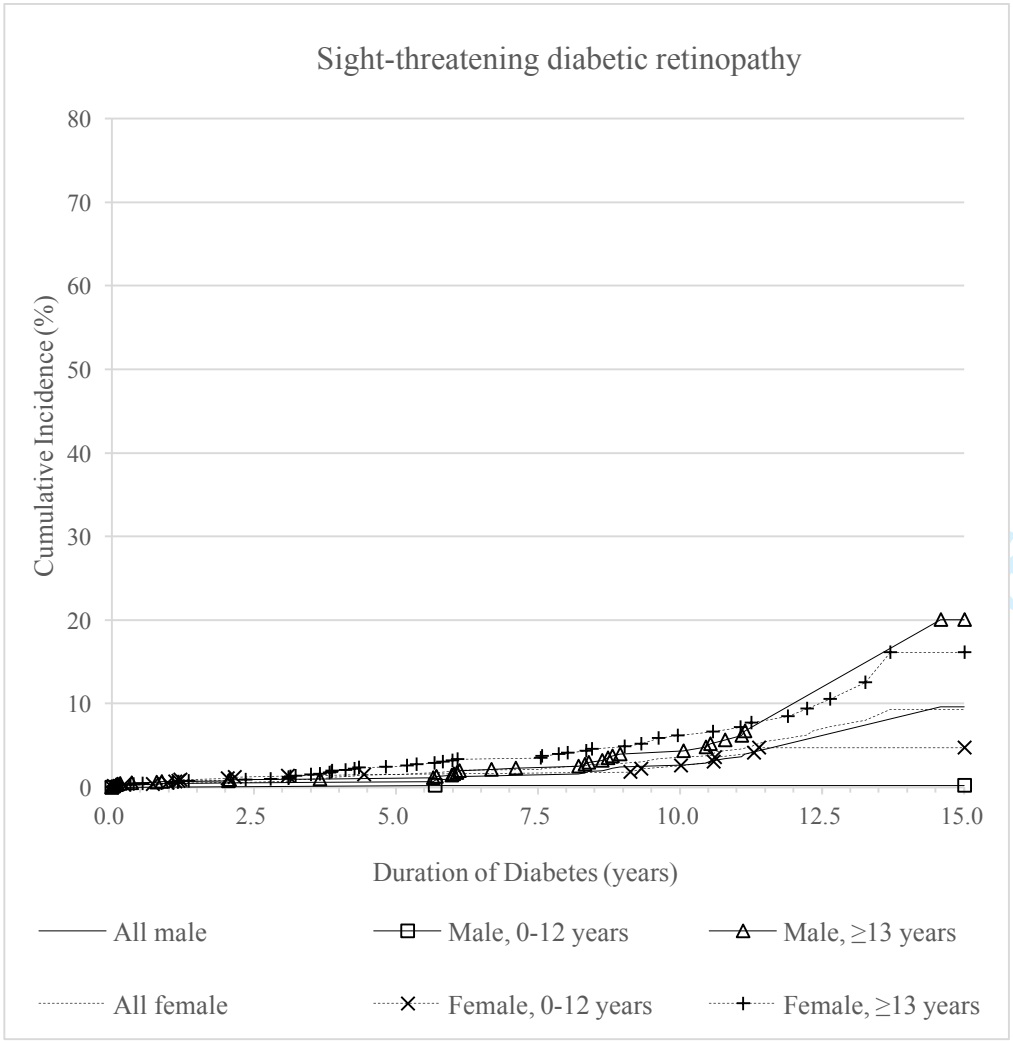
‡ 95% CI of incidence density difference for male vs. female was [-1.6 to 0.1]; in male subgroup, early vs. late-onset was [-1.3 to 0.8]; and in female subgroup, early vs. late-onset was [-2.5 to 0.2].

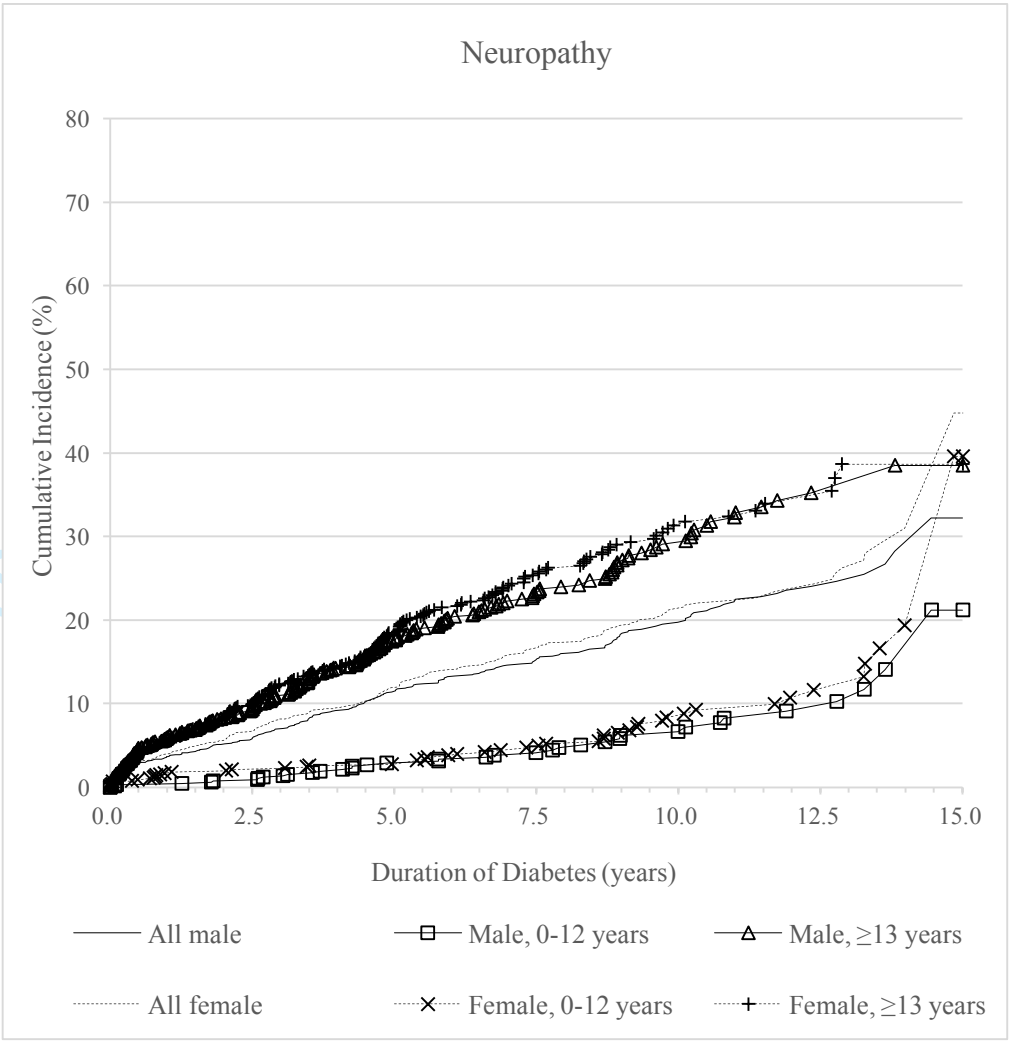
Abbreviations: STDR: sight-threatening diabetic retinopathy, CVD: cardiovascular disease, DKA: diabetic ketoacidosis, CI: confidence interval.

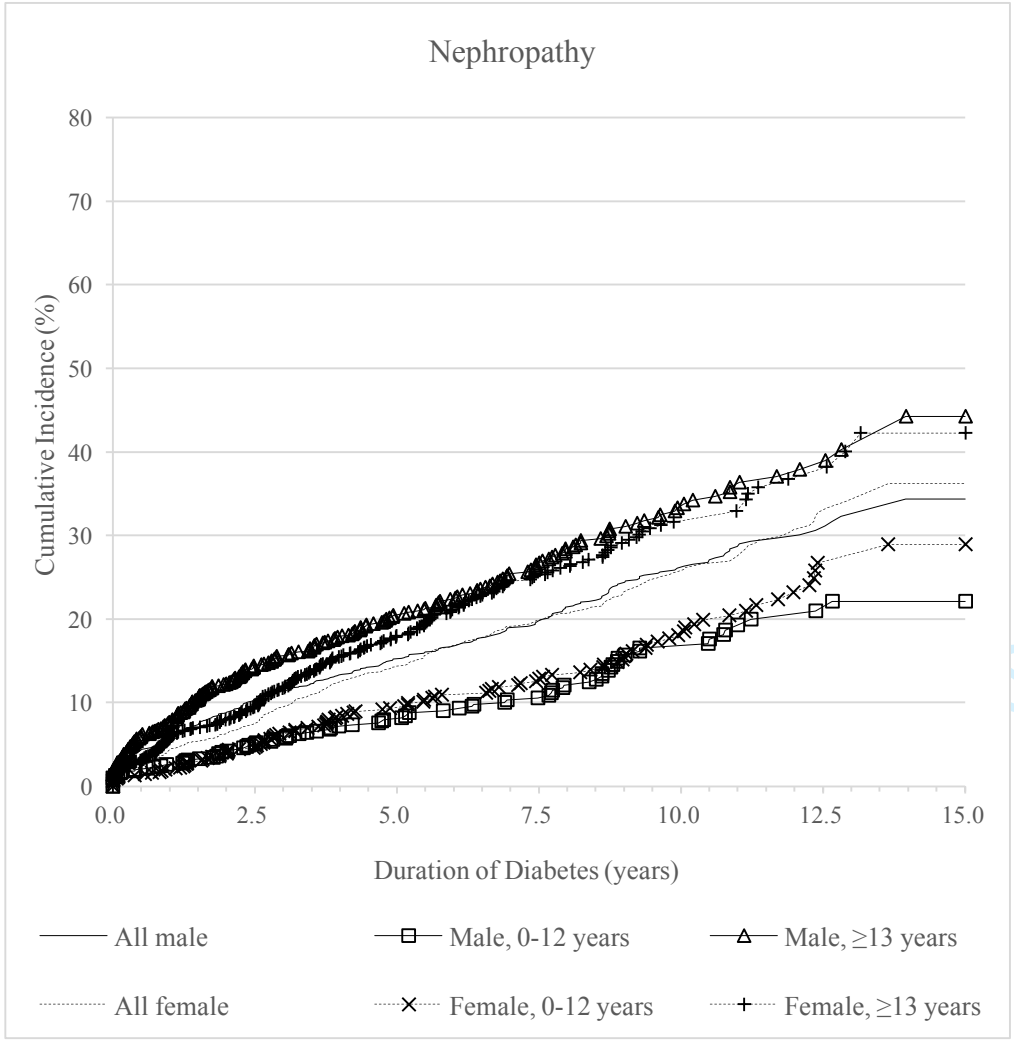
Supplementary Figure 1: Age-sex-specific cumulative incidences of diabetes complications according to duration of diabetes in patients with type 1 diabetes (early-onset: 0-12 years, late-onset: ≥13 years)

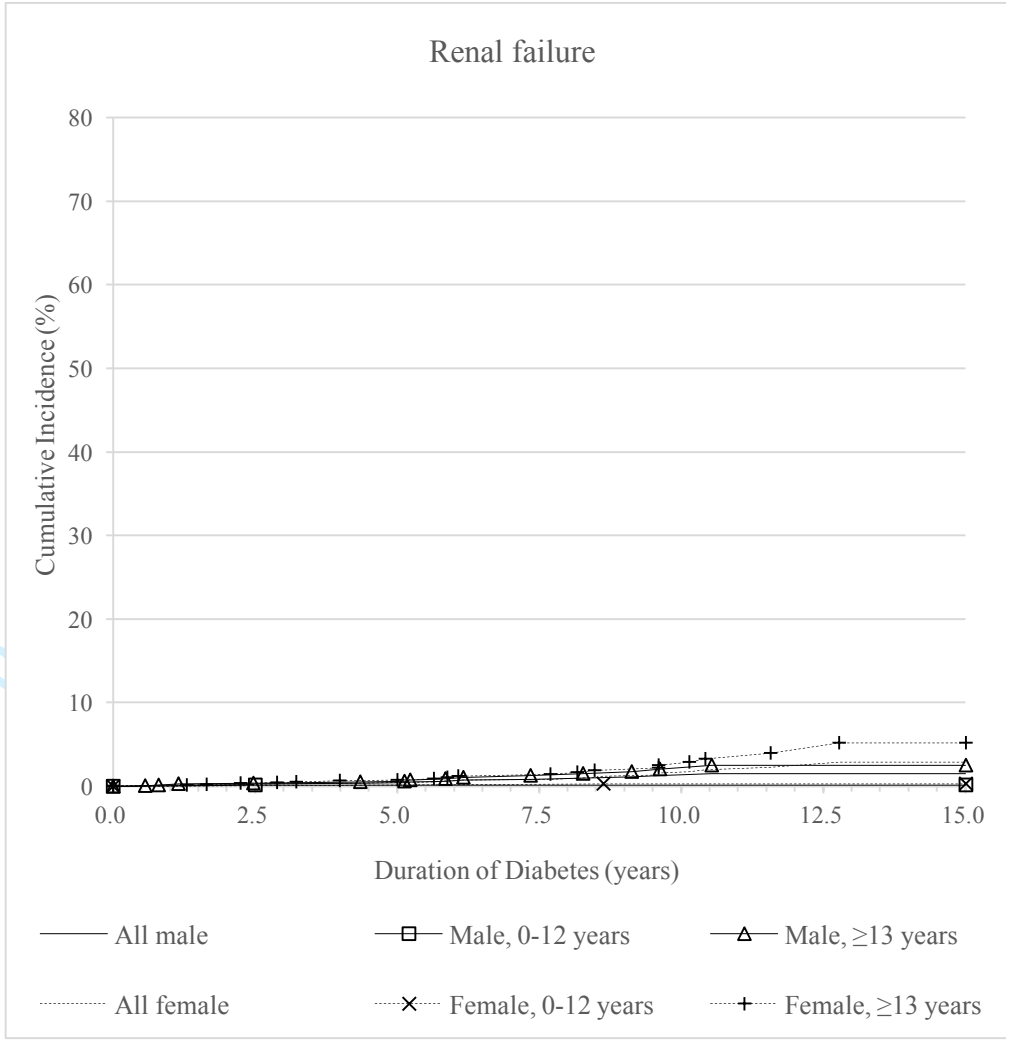


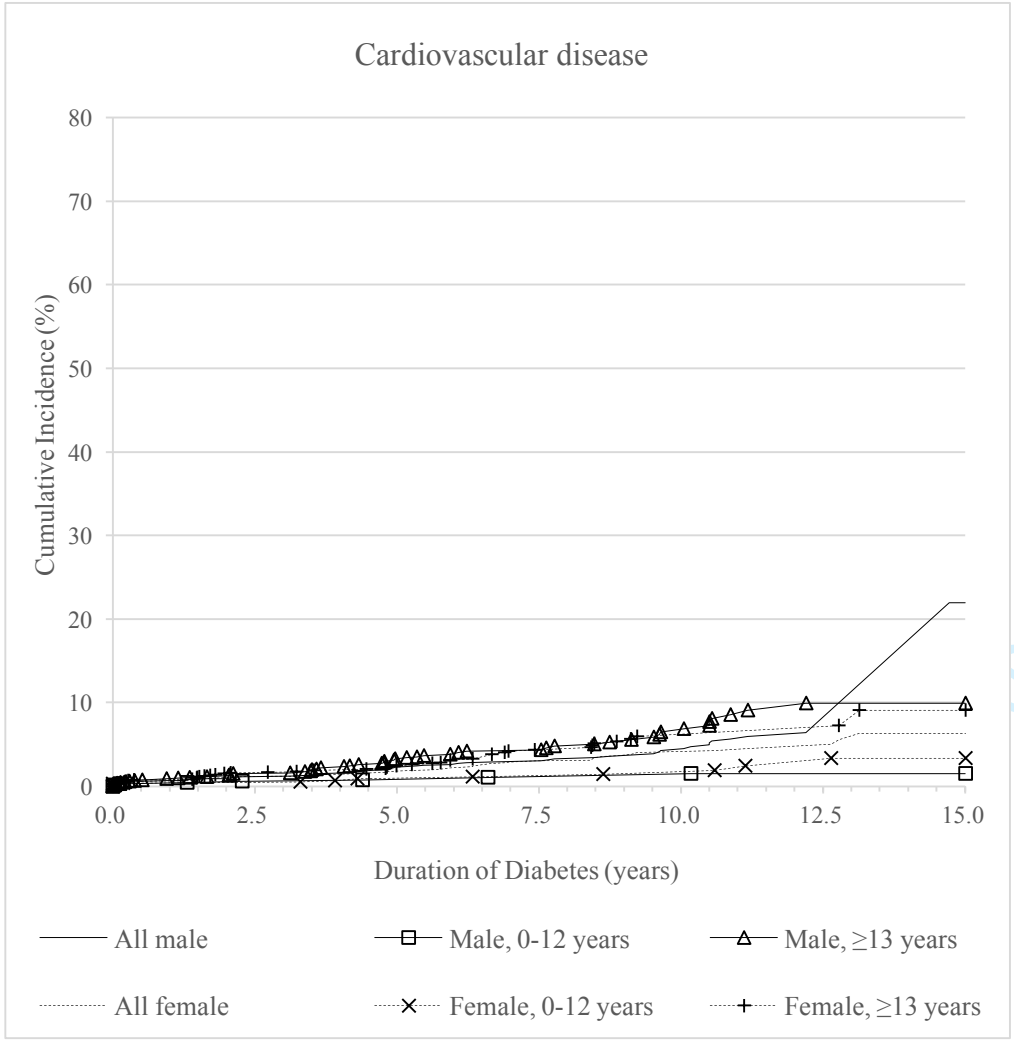


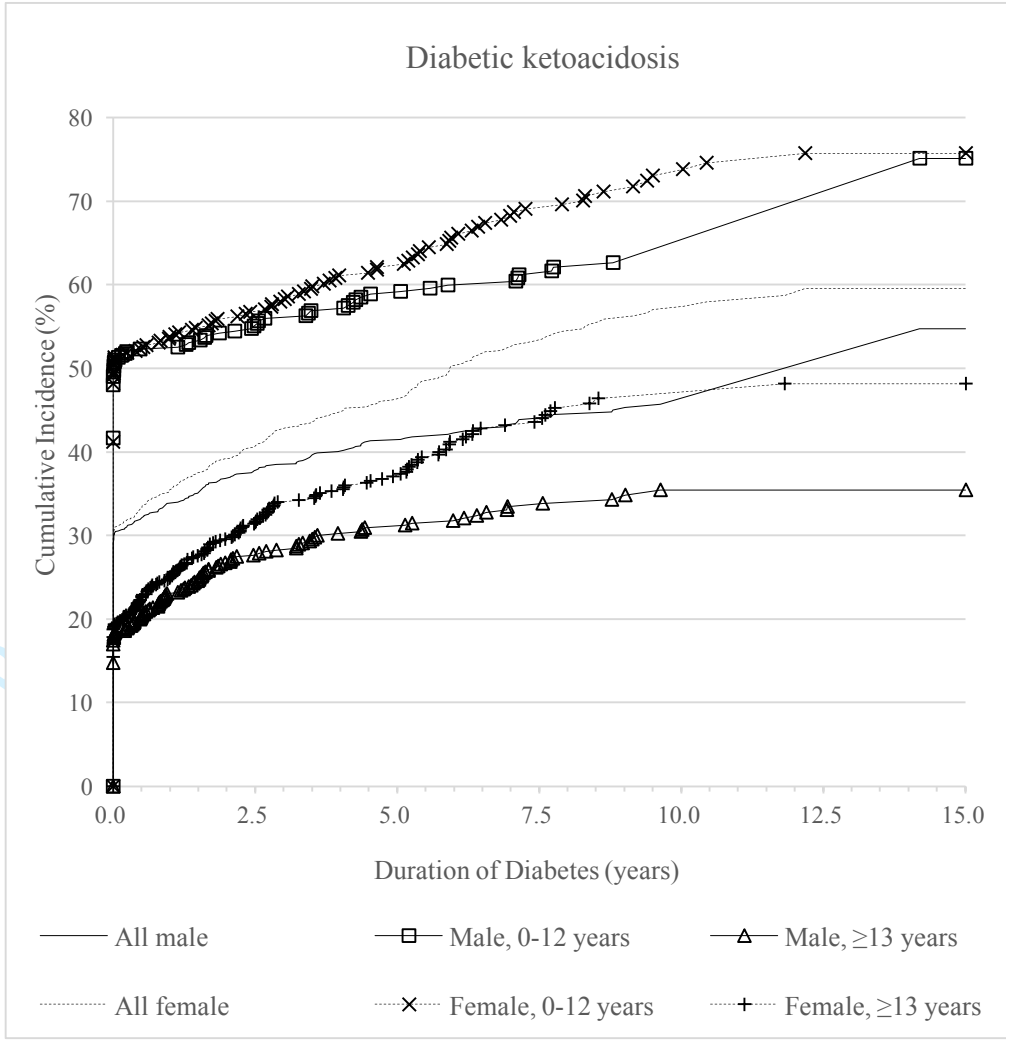

Sight-threatening diabetic retinopathy
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years

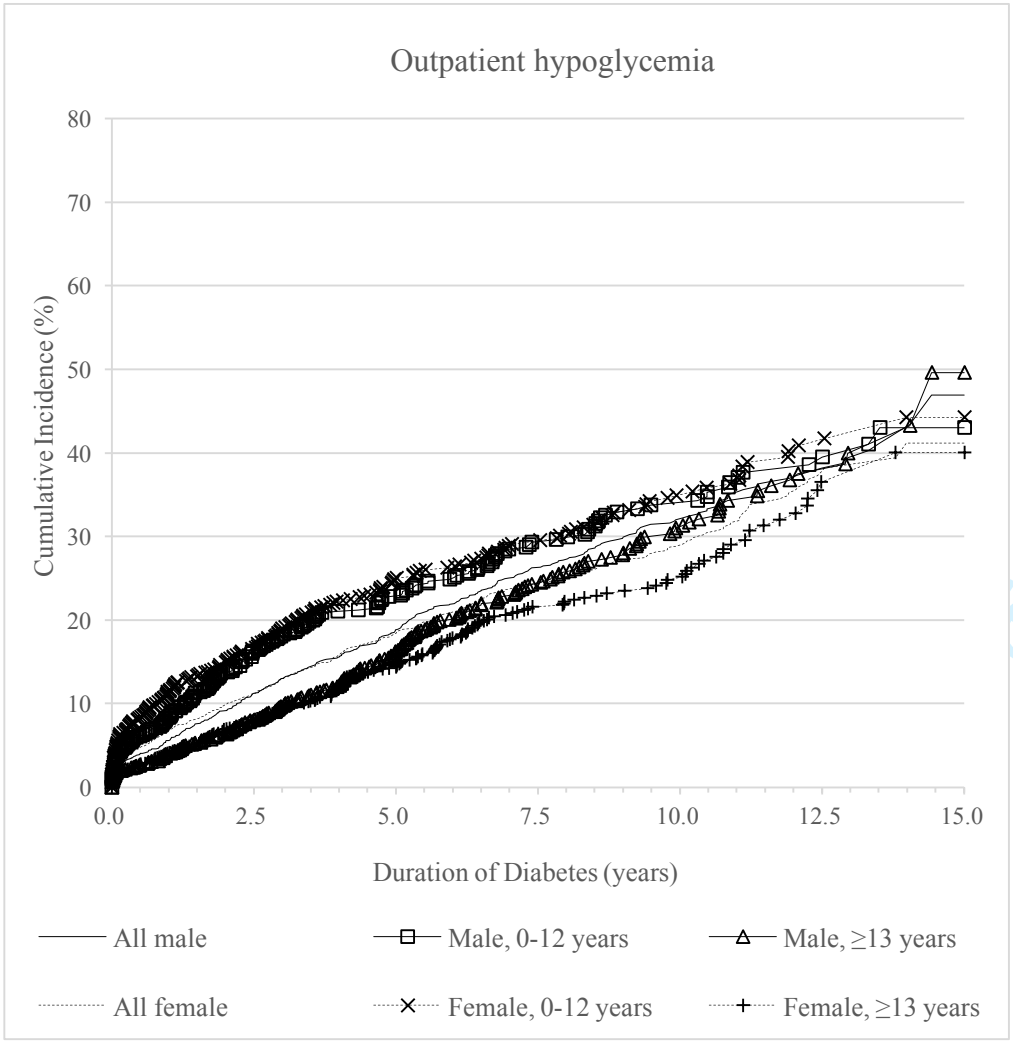

Neuropathy
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years

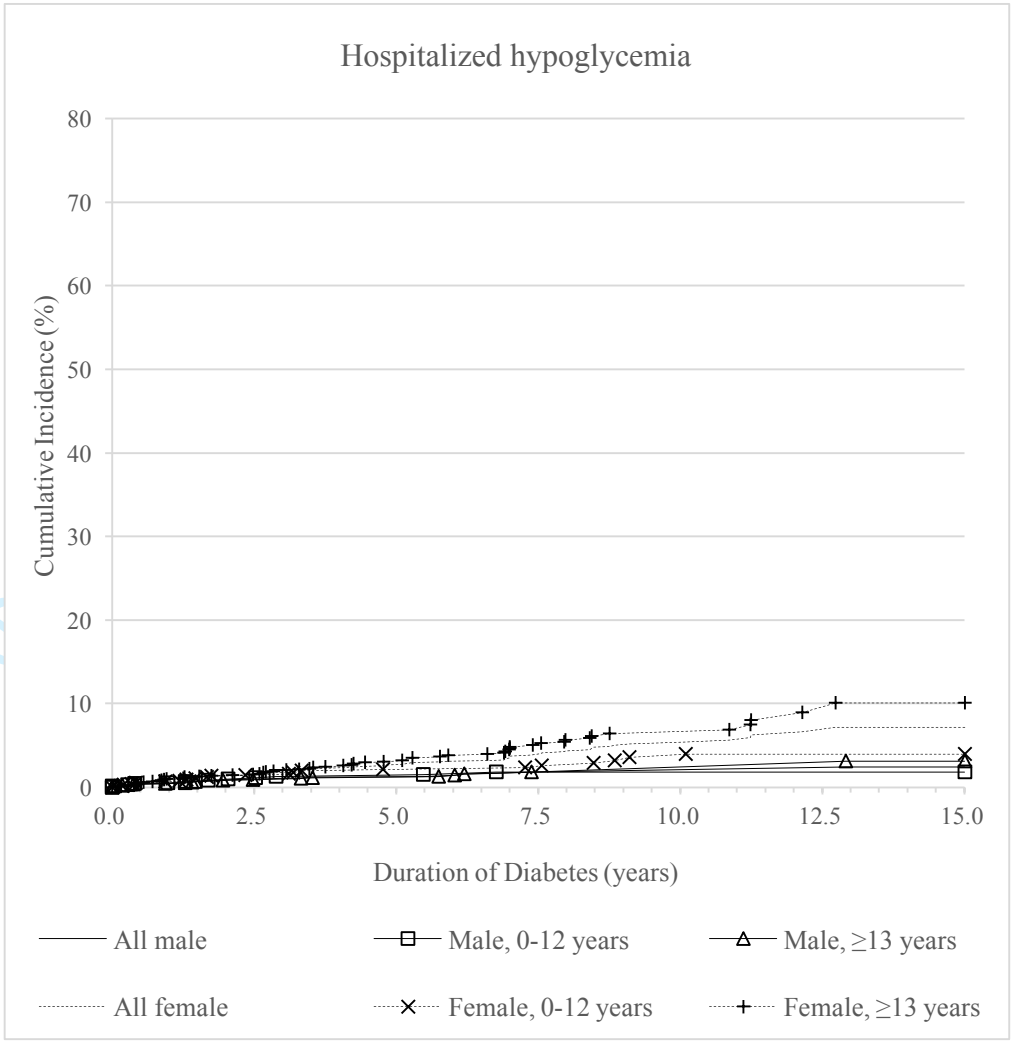

Nephropathy
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Renal failure
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Cardiovascular disease
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years


Diabetic ketoacidosis
Cumulative Incidence (%)
0
10
20
30
40
50
60
70
80
0.0
2.5
5.0
7.5
10.0
12.5
15.0
Duration of Diabetes (years)
All male
Male, 0-12 years
Male, ≥13 years
All female
Female, 0-12 years
Female, ≥13 years





Note:

p value for comparison of cumulative incidence of retinopathy for male vs. female was 0.0006, for male, early vs. late-onset was 0.4553, for female, early vs. late-onset was 0.0908.

p value for comparison of cumulative incidence of proliferative retinopathy for male vs. female was 0.0567, for male, early vs. late-onset was 0.0013, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of sight-threatening diabetic retinopathy for male vs. female was 0.0405, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of neuropathy for male vs. female was 0.4050, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of nephropathy for male vs. female was 0.6191, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of renal failure for male vs. female was 0.4222, for male, early vs. late-onset was 0.0078, for female, early vs. late-onset was 0.0003.

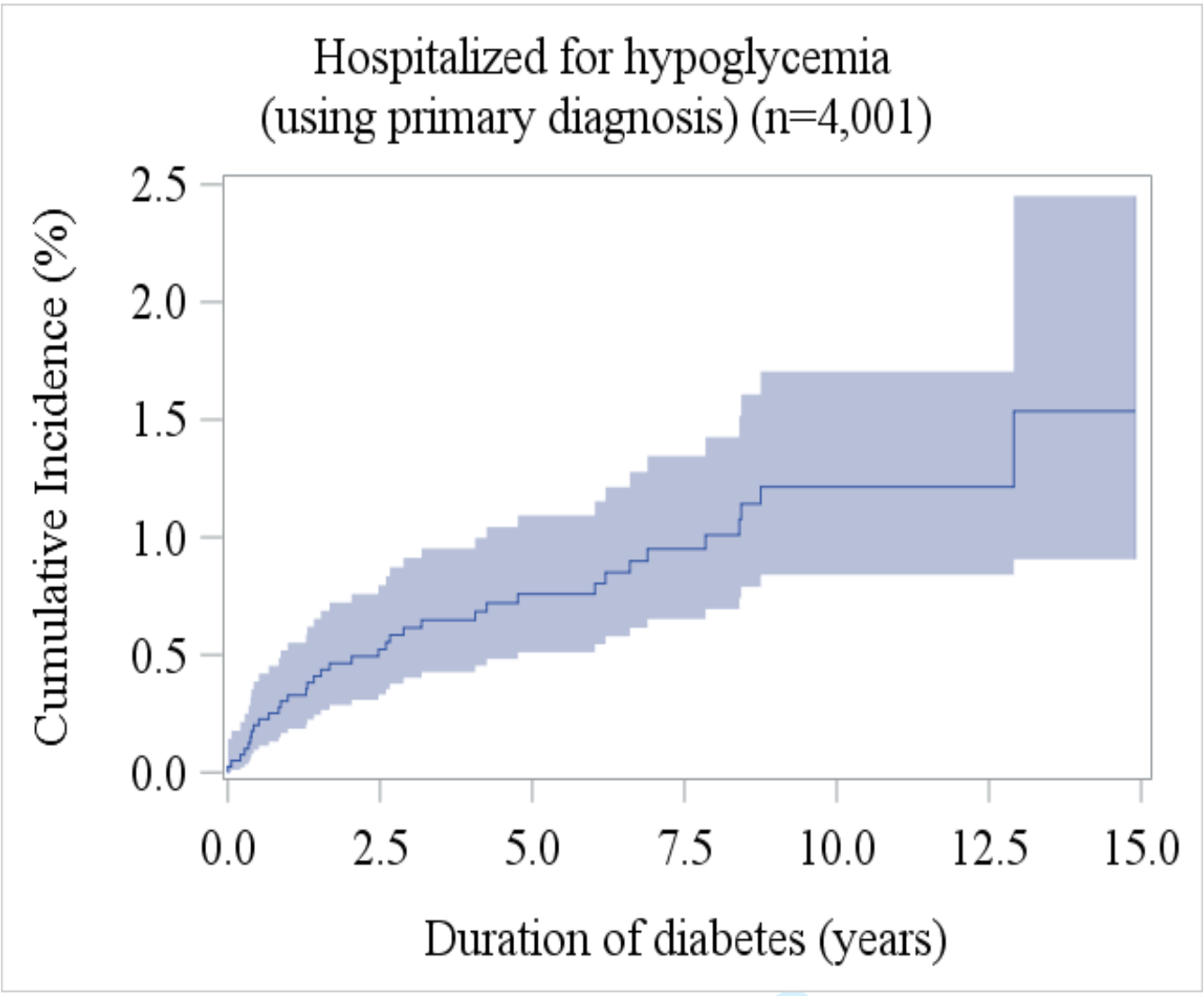
p value for comparison of cumulative incidence of cardiovascular disease for male vs. female was 0.4655, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was 0.0004.

p value for comparison of cumulative incidence of diabetic ketoacidosis for male vs. female was 0.0015, for male, early vs. late-onset was <.0001, for female, early vs. late-onset was <.0001.

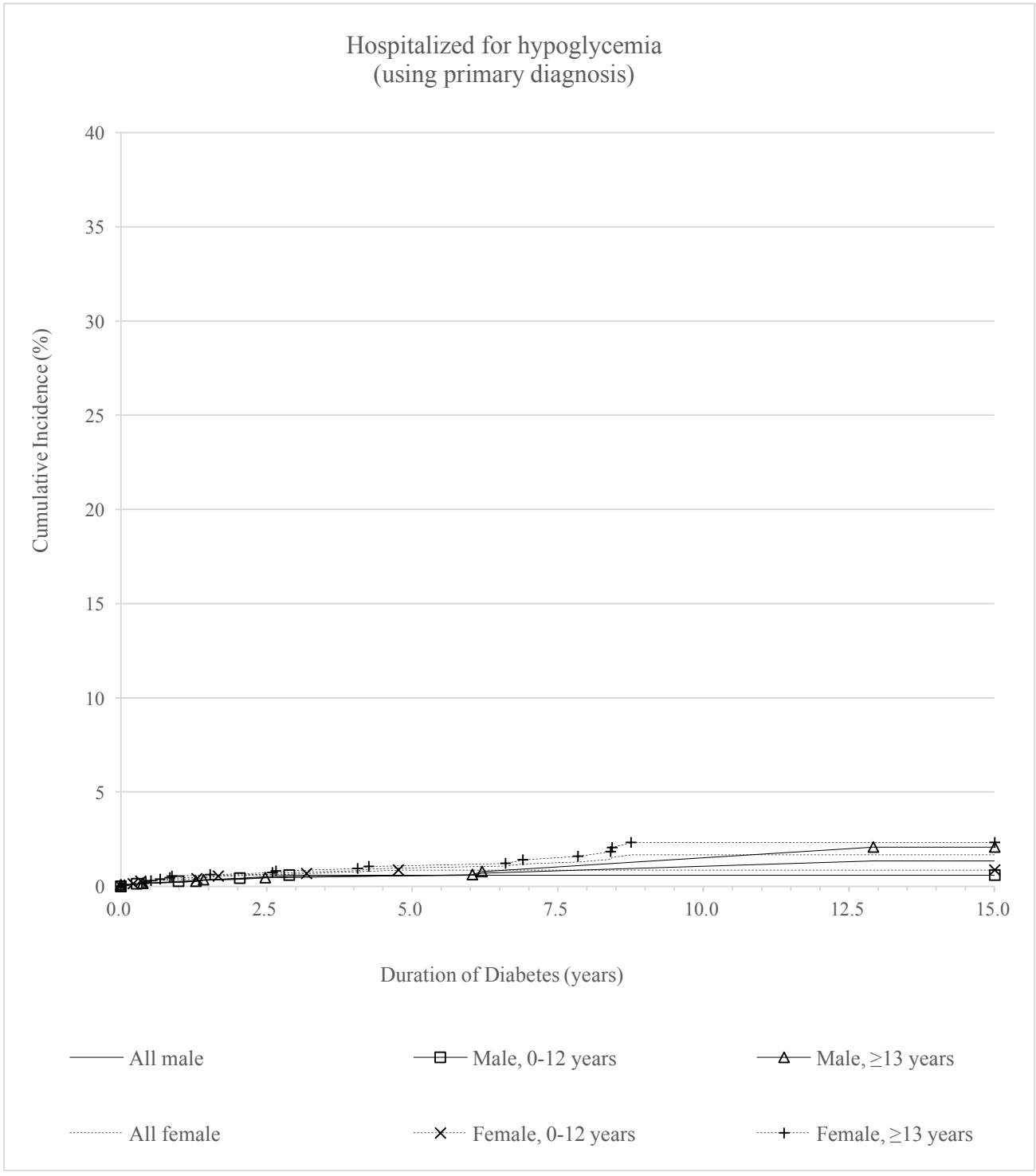
p value for comparison of cumulative incidence of outpatient hypoglycemia for male vs. female was 0.4095 for male, early vs. late-onset was 0.0097, for female, early vs. late-onset was <.0001.

p value for comparison of cumulative incidence of hospitalized hypoglycemia for male vs. female was <.0001, for male, early vs. late-onset was 0.9600, for female, early vs. late-onset was 0.0113.

Supplementary Figure 2: Cumulative incidence of hospitalized for hypoglycemia according to the duration of diabetes in patients with type 1 diabetes (shadow area indicates 95 % confidence interval)



Supplementary Figure 3: Age-sex-specific cumulative incidences of hospitalized for hypoglycemia according to duration of diabetes in patients with type 1 diabetes (early-onset: 0-12 years, late-onset: ≥13 years)



Note:

p value for comparison of cumulative incidence for male vs. female was 0.0782, for male, early vs. late-onset was 0.6272, for female, early vs. late-onset was 0.1326.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7, 8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7, 8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, 9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9, 10
		(*c*) Explain how missing data were addressed	9, 10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9, 10

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 11
		(*b*) Report category boundaries when continuous variables were categorized	10, 11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21
Generalisability	21	Discuss the generalisability (external validity) of the study results	21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.