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Excess Burden of Mental Illness and Hospitalization in Young-Onset Type 2 Diabetes

A Population-Based Cohort Study

Calvin Ke, MD; Eric Lau, PhD; Baiju R. Shah, MD, PhD; Thérèse A. Stukel, PhD; Ronald C. Ma, MB BChir; Wing-Yee So, MBChB, MD; Alice P. Kong, MBChB, MD; Elaine Chow, MBChB, PhD; Philip Clarke, PhD; William Goggins, ScD; Juliana C.N. Chan, MBChB, MD; and Andrea Luk, MBChB, MD

Background: Type 2 diabetes (T2D) increases hospitalization risk. Young-onset T2D (YOD) (defined as onset before age 40 years) is associated with excess morbidity and mortality, but its effect on hospitalizations is unknown.

Objective: To determine hospitalization rates among persons with YOD and to examine the effect of age at onset on hospitalization risk.

Design: Prospective cohort study.

Setting: Hong Kong.

Participants: Adults aged 20 to 75 years in population-based (2002 to 2014; *n* = 422 908) and registry-based (2000 to 2014; *n* = 20 886) T2D cohorts.

Measurements: All-cause and cause-specific hospitalization rates. Negative binomial regression models estimated effect of age at onset on hospitalization rate and cumulative bed-days from onset to age 75 years for YOD.

Results: Patients with YOD had the highest hospitalization rates by attained age. In the registry cohort, 36.8% of YOD bed-days before age 40 years were due to mental illness. The adjusted rate ratios showed increased hospitalization in YOD versus usual-onset T2D (onset at age ≥40 years) (all-cause, 1.8 [95% CI, 1.7 to 2.0]; renal, 6.7 [CI, 4.2 to 10.6]; diabetes, 3.7 [CI, 3.0 to 4.6]; cardiovascular, 2.1 [CI, 1.8 to 2.5]; infection, 1.7 [CI, 1.4 to 2.1]; $P < 0.001$ for all). Models estimated that intensified risk factor control in YOD (hemoglobin A_{1c} level <6.2%, systolic blood pressure <120 mm Hg, low-density lipoprotein cholesterol level <2.0 mmol/L [<77.3 mg/dL], triglyceride level <1.3 mmol/L [<115.1 mg/dL], waist circumference of 85 cm [men] or 80 cm [women], and smoking cessation) was associated with a one-third reduction in cumulative bed-days from onset to age 75 years (97 to 65 bed-days).

Limitation: Possible residual confounding.

Conclusion: Adults with YOD have excess hospitalizations across their lifespan compared with persons with usual-onset T2D, including an unexpectedly large burden of mental illness in young adulthood. Efforts to prevent YOD and intensify cardiometabolic risk factor control while focusing on mental health are urgently needed.

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For author affiliations, see end of text.

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In the Emerging Risk Factors Collaboration, persons with usual-onset type 2 diabetes (T2D) (onset at age ≥40 years) died 6 years earlier than those without T2D (1). However, models estimate that persons with young-onset T2D (YOD) (defined here as onset before age 40 years) might lose 15 years of life (2). Young-onset T2D is a heterogeneous and aggressive phenotype associated with increased risk for death and complications compared with usual-onset T2D (3, 4). This finding was first described in Pima Indians and was later confirmed in other ethnic groups (5–8). The prevalence of YOD is increasing rapidly worldwide, especially in Asian populations, where 1 in 5 adults with T2D has YOD (9, 10).

Despite their high risk for long-term complications, persons with YOD tend to have worse risk factor control than those with usual-onset T2D (10). This may stem from an inadequate understanding of the burden and risk associated with YOD and the lack of evidence-based strategies to manage its decades-long course. The psychosocial effect of diabetes evolves across the lifespan, and young persons may be more vulnerable to maladaptive health behaviors (11). A U.S. study found that young patients with diabetes were more likely to be rehospitalized for severe dysglycemia (12). However, diabetes subtypes were not described, and the findings could have been driven by type 1 diabetes (T1D). Other studies of YOD used survival analyses that only examined time to the first event (4, 6, 13). Although hospitalization is a key driver of escalating health care costs, its burden in YOD is unknown. Given the long disease duration, increased glycemic burden, and suboptimal care quality and treatment adherence in YOD, comparative analysis of hospitalizations among persons with YOD and those with usual-onset T2D might reveal unmet needs and promote better care (14). By quantifying the real-world effect of poorly controlled risk factors on hospitalization, we might also be able to estimate the possible benefits of implementing and improving multifactorial intervention, which has been studied only in usual-onset T2D (15–17).

To fill these knowledge gaps, we examined 2 large cohorts of Chinese adults with T2D to determine the effects of age at onset and modifiable risk factors on

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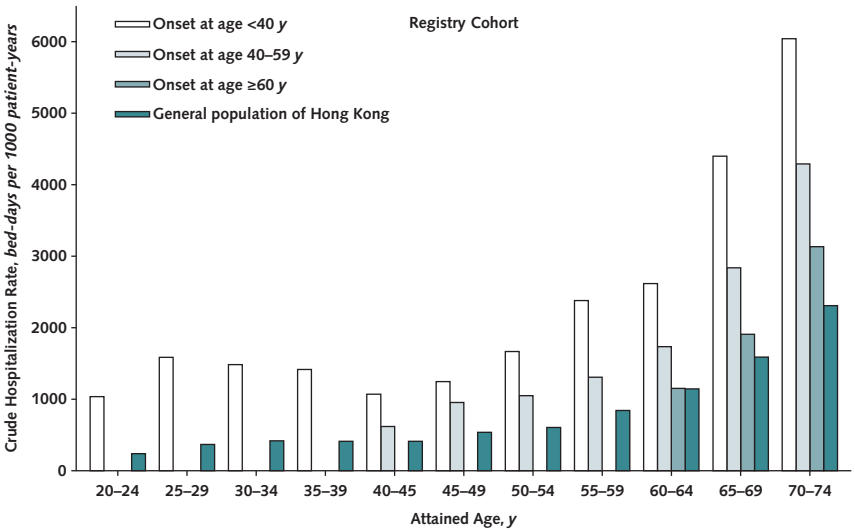
Table. Baseline Characteristics of Study Participants Within Each Cohort, by Age at Onset*

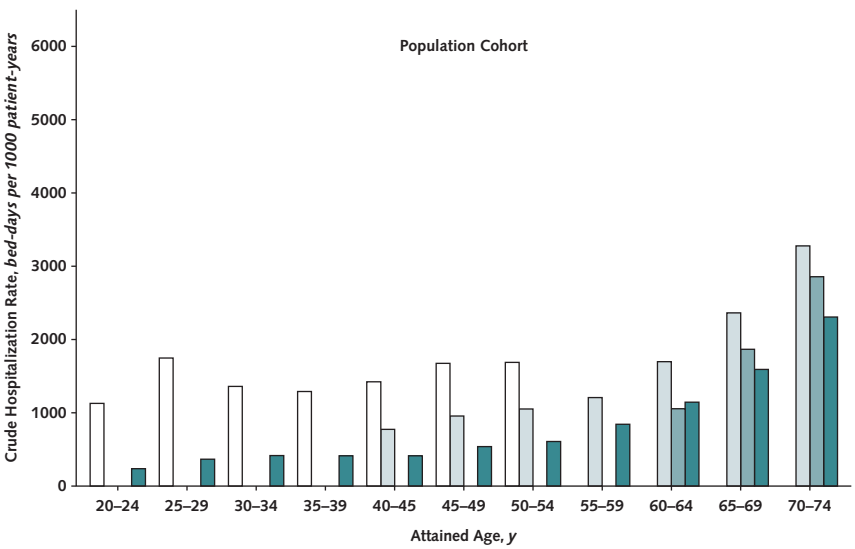
Characteristic	Age at Onset					
	Population Cohort			Registry Cohort		
	<40 y	40-59 y	≥60 y	<40 y	40-59 y	≥60 y
Total patients, *n*	21 032	208 557	193 319	3566	13 151	4169
Mean age at onset (SD), *y*	34.1 (5.5)	52.1 (5.2)	67.1 (4.3)	33.9 (5.3)	50.3 (5.5)	65.0 (3.5)
Mean age at index date (SD), *y*	–	–	–	41.4 (8.2)	53.8 (7.2)	66.4 (3.8)
Mean age at assessment (SD), *y*	–	–	–	44.6 (10.3)	57.7 (8.0)	69.8 (5.3)
Mean disease duration at assessment (SD), *y*	–	–	–	10.7 (9.4)	7.4 (6.7)	4.8 (4.5)
Women, %	42.1	45.0	48.3	49.8	46.3	48.1
Family history of diabetes, %†	–	–	–	64.7	54.6	31.8
Education, %‡						
Primary school or illiterate	–	–	–	27.0	41.5	61.0
Middle school	–	–	–	47.8	40.7	26.5
High school	–	–	–	9.9	6.8	4.3
College	–	–	–	15.0	10.8	8.0
Other	–	–	–	0.2	0.1	0.2
Employment, %						
Full-time	–	–	–	55.2	38.0	7.3
Part-time	–	–	–	5.1	5.5	2.7
Housewife	–	–	–	23.0	25.6	31.2
Retired	–	–	–	7.2	24.9	57.5
Unemployed	–	–	–	7.6	4.7	0.8
Other	–	–	–	2.1	1.2	0.6
Smoking status, %						
Current	–	–	–	16.5	12.4	9.9
Former	–	–	–	11.4	18.4	25.6
Never	–	–	–	72.1	69.3	64.5
Mean body mass index (SD), kg/m^2	–	–	–	26.1 (4.7)	25.7 (4.1)	25.4 (3.7)
Mean waist circumference (SD), *cm*						
Men	–	–	–	90.3 (11.6)	90.4 (10.2)	90.8 (9.7)
Women	–	–	–	83.9 (11.4)	85.2 (10.4)	86.3 (9.8)
Mean hemoglobin A_{1c} level (SD), %§	8.4 (2.5)	8.0 (2.1)	7.7 (1.9)	8.1 (2.0)	7.7 (1.9)	7.4 (1.8)
Mean systolic blood pressure (SD), *mm Hg*	–	–	–	128.8 (16.6)	134.3 (17.8)	139.4 (18.8)
Mean LDL-C level (SD)§						
mmol/L	3.0 (1.0)	3.2 (1.0)	3.1 (1.0)	3.0 (1.0)	3.0 (1.0)	3.0 (1.0)
mg/dL	118.3 (38.2)	122.8 (38.3)	120.5 (38.1)	116.0 (36.8)	115.4 (37.2)	113.0 (37.7)
Mean HDL-C level (SD)§						
mmol/L	1.1 (0.3)	1.2 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
mg/dL	43.9 (12.5)	47.4 (15.2)	48.8 (15.5)	49.3 (14.4)	50.7 (14.1)	51.4 (14.2)
Median triglyceride level (IQR)§						
mmol/L	1.7 (1.5)	1.5 (1.2)	1.5 (1.0)	1.4 (1.3)	1.4 (1.2)	1.5 (1.1)
mg/dL	149.7 (132.9)	136.4 (106.3)	129.3 (91.2)	127.5 (114.3)	128.4 (101.9)	130.2 (96.5)
Mean eGFR (SD), $mL/min/1.73\ m^2$‖	105.6 (19.8)	89.8 (17.6)	73.8 (18.4)	95.8 (23.1)	82.7 (21.3)	69.1 (19.9)
Median urinary ACR (IQR)						
mg/mmol	–	–	–	1.6 (7.1)	1.6 (6.3)	2.3 (8.6)
µg/mg	–	–	–	14.2 (62.6)	14.1 (56.1)	20.3 (76.3)
Comorbidities, %						
Albuminuria	–	–	–	38.3	37.7	44.7
Coronary heart disease	–	–	–	4.5	10.4	15.7
Stroke	–	–	–	3.1	5.3	9.5
Peripheral vascular disease	–	–	–	3.1	3.2	5.6
Congestive heart failure	–	–	–	1.2	2.1	4.4
Chronic kidney disease	–	–	–	9.6	16.3	31.2
End-stage renal disease	–	–	–	1.4	1.4	1.3
Cancer	–	–	–	1.9	4.2	6.9
Peripheral sensory neuropathy	–	–	–	11.0	10.2	12.6
Diabetic retinopathy	–	–	–	27.6	25.2	24.6
Medication use, %¶						
Noninsulin medications	71.4	73.7	69.8	69.2	80.5	77.9
Insulin	14.0	7.8	8.7	25.5	17.2	11.9
Renin-angiotensin system inhibitors	32.4	44.5	51.9	25.8	33.5	37.9
Antihypertensive medications	–	–	–	38.0	56.0	70.8
Lipid-lowering medications	21.8	36.6	40.7	24.8	38.8	45.1
Median assessments (IQR), *n*	–	–	–	2.0 (2.0)	1.0 (1.0)	1.0 (1.0)
Median assessment interval (IQR), *y***	–	–	–	2.6 (3.1)	1.8 (1.8)	1.4 (1.5)

ACR = albumin–creatinine ratio; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol.
* The population cohort was followed during 2002 to 2016, and characteristics were derived from electronic health records. The registry cohort was followed during 2000 to 2015, and all data were collected at the time of the first comprehensive assessment unless otherwise indicated. Rates of missing data were <10% and ≤5% in the population and registry cohorts, respectively, unless otherwise indicated.
† Registry cohort: First-degree relative (parent or sibling).
‡ Registry cohort: Available after 2007 (*n* = 14 384).
§ Registry cohort: First available value on or after index date.
‖ Population cohort: 21% missing.
¶ Population cohort: Defined as any prescription of ≥90 days' duration within 3 y of diabetes onset.
** Register cohort: Among patients with >1 comprehensive assessment recorded.

Figure 1. Crude annual age-specific hospitalization rates (bed-days per 1000 patient-years), stratified by age at onset, for the registry cohort (*top*) and the population cohort (*bottom*) compared with the general population of Hong Kong.



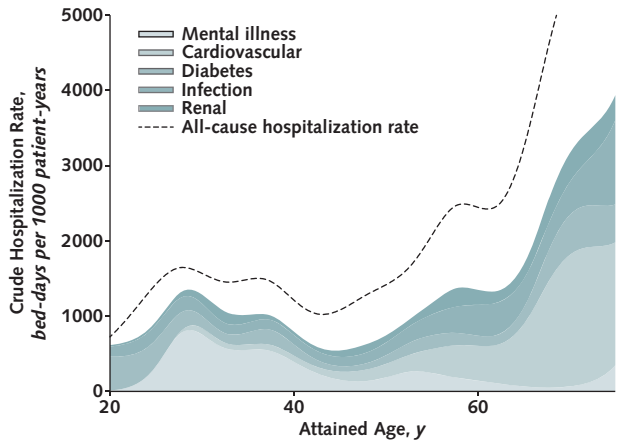
Bed-days	20–24	25–29	30–34	35–39	40–45	45–49	50–54	55–59	60–64	65–69	70–74
<40 y	266	983	2358	6417	9953	12 528	14 874	13 962	8275	6362	3583
40–59 y	–	–	–	–	1253	10 320	24 150	40 740	52 032	56 573	53 320
≥60 y	–	–	–	–	–	–	–	–	3116	17 299	39 664
Follow-up (person-years)											
<40 y	257	620	1590	4529	9294	10 058	8920	5868	3163	1447	593
40–59 y	–	–	–	–	2030	10 820	23 005	31 143	29 983	19 943	12 426
≥60 y	–	–	–	–	–	–	–	–	2702	9065	12 658



Bed-days (thousands)	20–24	25–29	30–34	35–39	40–45	45–49	50–54	55–59	60–64	65–69	70–74
<40 y	5.2	15.8	28.8	64.1	78.1	38.9	7.0	–	–	–	–
40–59 y	–	–	–	–	42.4	187.4	389.7	601.0	628.1	304.2	50.7
≥60 y	–	–	–	–	–	–	–	–	180.3	723.2	1299.5
Follow-up (thousand person-years)											
<40 y	4.6	9.0	21.2	49.7	54.9	23.3	4.2	–	–	–	–
40–59 y	–	–	–	–	54.7	195.7	371.0	497.3	369.8	128.7	15.5
≥60 y	–	–	–	–	–	–	–	–	171.0	387.5	455.1

Bed-days and follow-up are shown for patients in the study cohorts only. Each patient could contribute bed-days and patient-years to >1 age interval. Age-specific hospitalization rates for the general population of Hong Kong are based on data from the Hong Kong Hospital Authority (rates are averages from 2006 and 2012 [27, 28]).

Figure 2. Crude hospitalization rates (bed-days per 1000 patient-years) for selected principal diagnoses, by attained age, among persons with young-onset type 2 diabetes in the registry cohort.



hospitalization during the working lifespan (defined here as 20 to 75 years). We hypothesized that YOD and poor risk factor control would be associated with increased hospitalization.

METHODS

Study Setting and Data Sources

Hong Kong is a special administrative region of China. It is the world's most densely populated high-income area, with a population of 7.3 million and an estimated diabetes prevalence of 10.3% (18). The Hong Kong Hospital Authority (HA) operates the region's universal public health care system, which is modeled after the U.K. National Health Service. Because of the large public–private cost differential, about 95% of all inpatient bed-days occur in HA hospitals (19).

The Hong Kong Diabetes Surveillance Database (HKDSD) uses electronic health records from the HA to identify diabetes on the basis of the date of the first occurrence of a hemoglobin A_{1c} level of 6.5% or greater, an outpatient fasting plasma glucose level of 7.0 mmol/L (126 mg/dL) or greater, or prescription of any noninsulin antihyperglycemic medication or long-term insulin (≥28 days). Women with gestational diabetes are excluded from the database on the basis of diagnoses occurring 9 months before or 6 months after delivery (International Classification of Diseases, Ninth Revision [ICD-9], codes 72 to 75) or within 9 months of any pregnancy-related encounter (ICD-9 codes 630 to 676) outside these periods.

The Hong Kong Diabetes Registry (HKDR) is a research-driven quality improvement program established in 1995 at the Diabetes and Endocrine Centre at Prince of Wales Hospital, a public tertiary care hospital with a catchment of 1.3 million residents (20–22) (**Supplement Tables 1** and **2**, available at Annals.org). The HKDR enrolls 30 to 50 persons each week who are referred from community clinics, general practitioners, and hospital-based specialty clinics for comprehensive metabolic and complications assessment, including eye and foot examinations, blood tests, and urine tests. These are performed every 2 to 3 years by trained nurses using a modified European DiabCare protocol (20). There was a time lag between T2D onset and comprehensive assessment because most patients were managed by primary care or hospital physicians before enrollment in the registry. We extracted all HA hospitalization records and outpatient laboratory results for persons in the registry and linked the data using the unique Hong Kong Identity Card number, which is mandatory for all residents. The research was approved by the Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee.

Study Population

Population Cohort (HKDSD)

We included persons in the HKDSD with incident diabetes from 1 January 2002 to 31 December 2014 and excluded those with onset before age 10 years or any hospital or clinic visit for T1D (ICD-9 code 250.x1 or 250.x3). We defined the index date as the date of onset or the person's 20th birthday (if onset occurred before age 20 years) and followed persons until 31 December 2016 (**Supplement Figures 1** and **2**, available at Annals.org).

Registry Cohort (HKDR)

We included ethnic Chinese residents of Hong Kong in the HKDR who were aged 20 years or older and had prevalent or incident T2D from 1 June 2000 to 31 May 2014. We defined the index date as the earliest date in this period in which all of these criteria were met, and we followed persons until 31 May 2015. We excluded persons with T1D or diabetes onset before age 10 years.

Baseline Covariates and Outcomes

We retrieved all hemoglobin A_{1c}, low-density lipoprotein cholesterol (LDL-C), and triglyceride values from the HA for both cohorts. In the registry cohort, we also obtained information on employment, education, age at onset, systolic blood pressure (SBP), waist circumference, diet and exercise patterns, and baseline comorbidities during the first assessment. We included updated SBP measurements from repeated comprehensive assessments.

The primary outcome was the rate of all-cause hospitalizations during follow-up for each person. We excluded same-day emergency visits, pregnancy-related admissions, and events within 1 year of diabetes onset. For the registry cohort, we extracted and classified the principal diagnosis for each admission (23) (**Supplement Table 3**, available at Annals.org). Hospitalization rates for diabetes, cardiovascular disease, infections, and renal complications were considered as secondary outcomes. Patients with any hospitalization lasting more than 365 days were excluded because these were

likely long-term convalescent placements. We censored patients at death or age 75 years.

Statistical Analysis

Both Cohorts

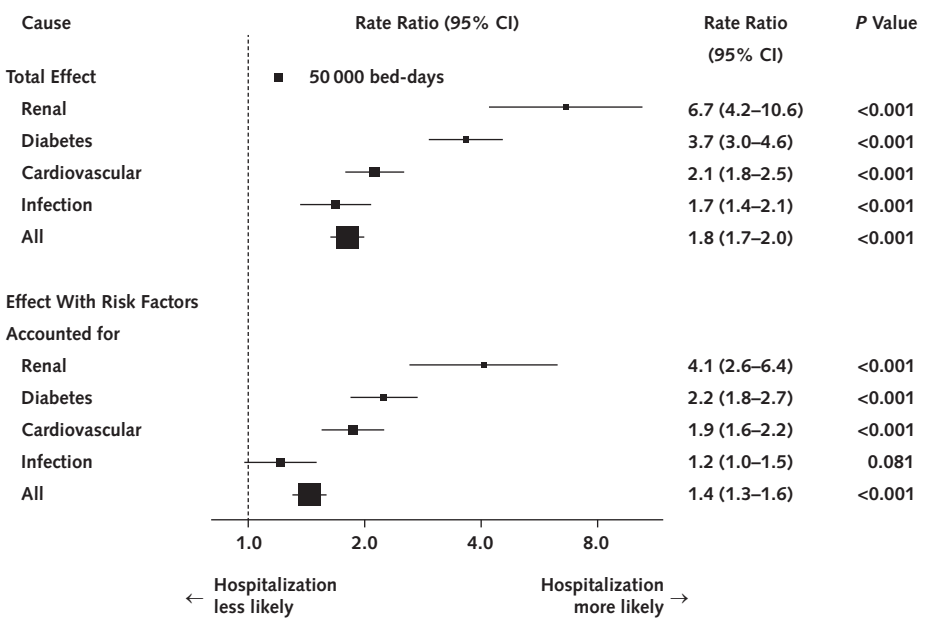
We computed crude hospitalization rates by dividing the total number of bed-days by the total follow-up time within 5-year categories of attained age. We characterized hospitalizations by age at onset (<40, 40 to 59, or ≥60 years) and expressed the rate as bed-days per 1000 patient-years.

Registry Cohort

Subsequent analyses were done in the registry cohort because it had more comprehensive data and patients across all ages at onset and attained ages. We examined the effect of age at onset on hospitalization rate using negative binomial regression instead of Poisson regression because the variance in hospitalization rates exceeded the mean. We included an offset term to account for follow-up duration. In all models, the unit of analysis was the individual patient, the dependent variable was the total number of days in the hospital, and the offset term was total follow-up time. Although YOD has been practically defined using an age cutoff, we modeled age at onset as a continuous variable because younger onset occurs along a continuous spectrum. Because variation in the rate of hospitalizations by attained age differed on the basis of age at onset, we included an interaction term for attained age and age at onset in all models. We computed rate ratios (RRs) describing the effect of age at onset on hospitalization rate at an attained age of 60 years, using a 20-year increment in age at onset to match the observed mean difference between YOD (33.9 years) and usual-onset T2D (53.8 years). We first adjusted for prespecified confounding variables, including attained age, sex, smoking, and employment (**Supplement Figure 3**, available at Annals.org). We did not adjust for disease duration because it was accounted for by age at onset and attained age. In the second model, we also adjusted for time-updated SBP, hemoglobin A_{1c} level, LDL-C level, and triglyceride level (24); waist circumference; and an interaction term for waist circumference and sex because of the sex-specific effect of waist circumference (25).

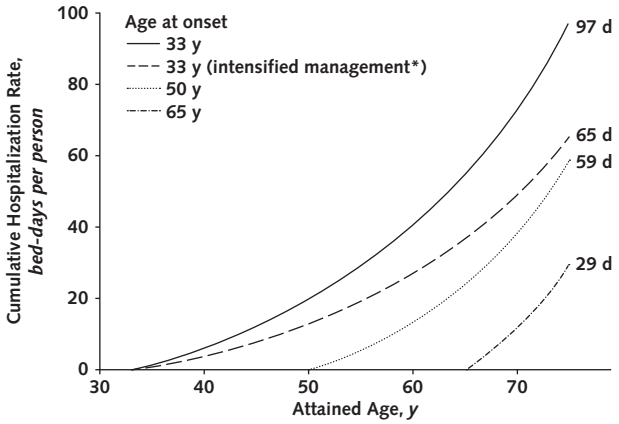
We then estimated the number of bed-days that an average person in each age-at-onset group would accumulate from onset to age 75 years, using the procedure described on page 9 of the **Supplement** (available at Annals.org). To estimate the difference in cumulative bed-days associated with intensified risk factor control in YOD, we repeated this procedure for YOD and substituted intensified target values for risk factor covariates (hemoglobin A_{1c} level of 6.2%, SBP of 120 mm Hg, LDL-C level of 2.0 mmol/L [77.3 mg/dL], triglyceride level of 1.3 mmol/L [115.1 mg/dL], waist circumference of 85 cm [men] or 80 cm [women], and smoking cessation). These targets were investigated in J-DOIT3 (Japan Diabetes Optimal Integrated Treatment Study for 3 Major Risk Factors of Cardiovascular Diseases), which

Figure 3. Effect of age at onset of type 2 diabetes (34 vs. 54 y) on hospitalization rate at age 60 y, by principal diagnosis in the registry cohort.



Both models were adjusted for attained age, sex, smoking, employment, and interaction between age at onset and attained age. The area of each square is proportional to the number of bed-days. Crude hospitalization rates are shown in **Supplement Table 4**. **Top.** Total effect of younger onset on hospitalization rates. **Bottom.** Effect of younger onset on hospitalization rates after modifiable risk factors (hemoglobin A_{1c} level, systolic blood pressure, low-density lipoprotein cholesterol level, triglyceride level, and waist circumference), which partially mediate the effect, are accounted for.

Figure 4. Estimated cumulative hospitalization rate (bed-days per person) up to age 75 y for persons with type 2 diabetes onset at ages 33, 50, and 65 y.



The dashed line shows the estimated rate if risk factor control were improved to meet intensified targets. Based on model estimates that accounted for age at onset, attained age, sex, employment, smoking, and modifiable risk factors (hemoglobin A_{1c} level, systolic blood pressure, low-density lipoprotein cholesterol level, triglyceride level, and waist circumference).
* Targets include hemoglobin A_{1c} level of 6.2%, systolic blood pressure of 120 mm Hg, low-density lipoprotein cholesterol level of 2.0 mmol/L (77.3 mg/dL), triglyceride level of 1.3 mmol/L (115.1 mg/dL), waist circumference of 85 cm (men) or 80 cm (women), and smoking cessation.

showed a 40% to 60% reduction in cardiorenal disease among Japanese persons older than 50 years with T2D (26). We conducted several sensitivity analyses, which are described on page 13 of the **Supplement**. Missing data were minimal (≤5%) and were handled by censoring. We used the GENMOD procedure in SAS, version 9.4 (SAS Institute), for all analyses.

Role of the Funding Source

The funding source had no role in the design or conduct of the study; collection, analysis, or interpretation of the data; or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit the manuscript for publication.

RESULTS

We followed 422 908 persons (46.3% women) for 2.8 million person-years (median, 6.1 years) in the population cohort and 20 886 persons (47.2% women) for 0.2 million person-years (median, 10.6 years) in the registry cohort (**Table**). In the registry cohort, those with YOD were more likely to have a family history of diabetes (64.7%, 54.6%, and 31.8% for those with onset at age <40, 40 to 59, and ≥60 years, respectively). At the time of comprehensive assessment, the mean ages were 44.6, 57.7, and 69.8 years, respectively, in each age group. The lag between the index and assessment dates was similar in each age group (3.2, 3.9, and 3.4 years, respectively). Patients with YOD were more likely to be unemployed at the time of assessment despite being better educated as well as to be current smokers. Although patients with YOD had smaller waist circumferences, body mass index (BMI), hemoglobin A_{1c}, LDL-C, and triglyceride values were higher than in those with usual-onset T2D. Chronic kidney disease and other comorbidities were common in patients with YOD despite their relatively young age at assessment. Insulin use was more frequent in YOD than in usual-onset T2D, whereas use of other medications, including statins and renin–angiotensin system inhibitors, was less frequent.

Patients with YOD had the highest hospitalization rates by attained age in both cohorts (**Figure 1**; **Supplement Table 4**, available at Annals.org), far exceeding age-specific rates for the general population in 2006 and 2012 (27, 28). Hospitalization rates increased across the age range in the registry cohort, with the steepest increases among patients with YOD. In these patients, 36.8% of bed-days before age 40 years were due to mental illness (**Figure 2**), primarily psychotic and mood disorders (55.1% and 31.4%, respectively). This could not be explained by antipsychotic medications, miscoding, or secular effects (page 16 of the **Supplement**). When we restricted the analysis to the first and second halves of the study (**Supplement Figure 8**, available at Annals.org), the proportion of mental illness hospitalizations for patients aged 20 to 39 years with YOD was 42.7% for 2000 to 2007 versus 28.0% for 2008 to 2015. These differences were largely due to variation in the rate of all-cause hospitalizations. After age 60 years, cardiovascular disease was the most common cause of hospitalization among patients with YOD and usual-onset T2D (25.8% and 20.0% of bed-days, respectively).

By age 60 years, patients with YOD had double the rate of all-cause hospitalizations versus those with usual-onset T2D (RR, 1.8 [95% CI, 1.7 to 2.0]) after multivariable adjustment (**Figure 3**), and the effect was greater at younger attained ages (P for interaction <0.001). Compared with usual-onset T2D, YOD was associated with 6.7 (CI, 4.2 to 10.6) times the hospitalization rate for renal causes, 3.7 (CI, 3.0 to 4.6) times the rate for diabetes, and 2.1 (CI, 1.8 to 2.5) times the rate for cardiovascular causes. Although the YOD group had worse control of modifiable risk factors, such as hemoglobin A_{1c} level, LDL-C level, and BMI, these associations remained significant even after these differences were accounted for. The hospitalization rate for infection was 1.7-fold (CI, 1.4- to 2.1-fold) higher in YOD, but this was attenuated after modifiable risk factors were accounted for. Sensitivity analyses showed similar findings (**Supplement Tables 5** to **7**, available at Annals.org).

On the basis of the observed hospitalization rates, we estimated that a patient diagnosed with YOD would spend nearly 100 days in the hospital by his or her 75th birthday (**Figure 4**; **Supplement Figure 4**, available at Annals.org). Intensified control of modifiable risk factors was associated with a one-third decrease to 65 estimated bed-days. A delay in onset until age 40 years further reduced this to 47 bed-days (data not shown). Patients with usual-onset T2D had substantially fewer

cumulative bed-days than those with YOD (59 and 29 days for those with onset at ages 50 and 65 years, respectively).

DISCUSSION

In our large population- and registry-based study, the burden of hospitalization in patients with YOD showed a striking evolution across the lifespan. We found a previously unknown burden of serious mental illness before age 40 years, and understanding its causes is imperative to improving mental health care in young adults. Compared with patients with usual-onset T2D, those with YOD had, on average, double the hospitalization rate by age 60 years for any cause, including cardiovascular events, renal complications (for which the rate was 7 times higher), diabetes, and infections. These increased rates reveal the disproportionate effects of increased disease duration and glycemic burden in YOD and challenge the perception that youth protects against hospitalization. These associations were partially mediated by control of modifiable risk factors, demonstrating the importance of early intervention to reduce the adverse effects of cumulative exposure to cardiometabolic risk factors (29, 30). Hospitalization rates in patients with YOD were reduced by one third with intensified management and by more than half if onset was delayed until age 40 years.

Although a bidirectional association between T2D and depression has been reported previously (31, 32), the burden of serious mental illness early in the course of YOD has never been described. The multinational DAWN (Diabetes Attitudes, Wishes and Needs) Study found that 24.9% of persons with diabetes have depression or high diabetes-related distress (33). Our study suggests that this association may be particularly severe in YOD during young adulthood. Although the underlying mechanisms are unknown, atypical antipsychotics—which are known to increase T2D risk among persons with schizophrenia (34)—could not explain the association we observed. Hyperglycemia, which is worse in YOD, may cause neuroinflammation, which in turn increases risk for depression, schizophrenia, and other psychiatric disorders (35–37). Diabetes may alter brain connectivity and cause cognitive dysfunction (35), which may worsen schizophrenia (37). Mental illness may also affect risk for complications given that our group has previously reported increased cardiovascular risk in persons with T2D and depression (38) and given that depression is associated with poor glycemic control, which is partially attributable to poor self-care and nonadherence (39). Improving outcomes in this vulnerable population will require team-based, holistic, and integrated care approaches that are shown to improve health, increase patient satisfaction, and reduce hospitalizations (40, 41). To this end, we have reported the positive effects of peer support in reducing hospitalization by enhancing self-efficacy and reducing negative emotions and nonadherence (42).

In addition to mental illness, persons with YOD had especially high rates of hospitalization for renal disease and other complications. Although the high risk for complications in YOD is well known (6, 13), we found that the hospitalization burden is 7 times higher for renal events, 4 times higher for diabetes admissions, and 2 times higher for cardiovascular causes compared with usual-onset T2D. These differences are much higher than previously known because earlier analyses did not capture multiple admissions. Care providers must recognize the high risk for hospitalization for dysglycemia, especially given the frequent need for insulin in YOD. Some young adults may also have atypical causes of diabetes that require specialized investigation and individualized treatment (43). After modifiable risk factors were accounted for, the effect of YOD remained significant for diabetes, cardiovascular, and renal hospitalizations, but not for infections. These findings confirm the importance of disease duration and glycemic burden—which are inherently increased in YOD—in driving diabetes complications (13, 16), whereas infection risk is driven primarily by poor glycemic control (44).

Because young persons are more likely to experience costly work disruptions due to hospitalization, our findings arguably call for a paradigm shift to reduce the effect of YOD by intensifying risk factor control. Large international surveys have found that young persons with YOD have consistently poor risk factor control and decreased use of organ-protective drugs (10, 45). Our projections suggest that aggressive risk factor management might reduce hospitalizations by one third, although randomized cardiovascular outcome trials have not yet been done to confirm these benefits in YOD. However, the J-DOIT3 study found that 8 years of intensified risk factor control led to an annual mortality rate less than 1% among high-risk middle-aged Japanese persons with T2D (46). Increased uptake of integrated, team-based care models may further strengthen management in this population (47). Our models also suggest that delaying onset could further reduce hospitalizations, especially if efforts are targeted to high-risk persons with a family history of T2D (48).

Strengths of our study include the complementary cohorts, with the registry cohort corroborating evidence from the large population cohort, which allowed us to characterize distinctive hospitalization patterns across the lifespan in more granular detail. The comprehensive assessments of all registered persons enabled us to account for many variables that are typically unavailable in administrative databases. Other strengths include our standardized outcome definitions and our use of a territory-wide hospitalization database, which accounted for 95% of bed-days in Hong Kong and enabled near-complete outcome capture with virtually no loss to follow-up (19). However, our analysis and interpretation have limitations. First, the registry cohort may have preferentially selected healthier YOD survivors, thus conservatively biasing the results toward older attained ages. Second, because the HKDR is a real-world registry, there was a lag between the index date and the comprehensive assessment. Although we

retrieved laboratory data from 2000 onward, it was impossible to estimate prior risk factor control, and SBP and BMI were measured only during structured assessments. Although we cannot exclude the possibility of residual confounding, our sensitivity analysis that was limited to prospective events after initial assessment showed similar findings.

In summary, this large study highlights the evolution of hospitalization during the long course of YOD, with an excess burden of serious mental illness in early adulthood and cardiorenal complications later in life. This costly burden is an urgent call for policymakers, payers, patients, and health care providers to take action and address this unmet need. An integrated system is needed to identify patients with YOD for comprehensive assessment of physical and psychological health, followed by optimization of cardiometabolic risk factors and individualized care to improve quality of life and reduce the effects of long-term complications on patients, their families, employers, and the health care system.

From The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong (C.K., E.L., R.C.M., W.S., A.P.K., E.C., W.G., J.C.C., A.L.), and University of Toronto, Toronto, Ontario, Canada (C.K.); University of Toronto, Institute for Clinical Evaluative Sciences, and Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (B.R.S.); University of Toronto and Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (T.A.S.); and University of Oxford, United Kingdom (P.C.).

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Corresponding Author: Juliana C.N. Chan, MD, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Lui Che Woo Clinical Sciences Building, 9th Floor, Room 114025, Shatin, New Territories, Hong Kong; e-mail, jchan@cuhk.edu.hk.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Drs. Ke, Shah, and Stukel: Institute for Clinical Evaluative Sciences, 2075 Bayview Avenue, Suite G106, Toronto, Ontario M4N 3M5, Canada.
Dr. Lau: Asia Diabetes Foundation, Unit 3, 17th Floor, Metropole Square, 2 On Yiu Street, Shatin, New Territories, Hong Kong.
Drs. Ma, So, Kong, Chan, Chow, and Luk: Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Lui Che Woo Clinical Sciences Building, 9th Floor, Shatin, New Territories, Hong Kong.
Dr. Clarke: Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom.
Dr. Goggins: The Jockey Club School of Public Health and Primary Care, Prince of Wales Hospital, Shatin, New Territories, Hong Kong.

Author Contributions: Conception and design: C. Ke, T.A. Stukel, W.Y. So, J.C.N. Chan, A. Luk.
Analysis and interpretation of the data: C. Ke, E. Lau, B.R. Shah, P. Clarke, W. Goggins, J.C.N. Chan.
Drafting of the article: C. Ke.
Critical revision of the article for important intellectual content: C. Ke, B.R. Shah, T.A. Stukel, R.C. Ma, W.Y. So, E. Chow, W. Goggins, J.C.N. Chan, A. Luk.
Final approval of the article: C. Ke, E. Lau, B.R. Shah, T.A. Stukel, R.C. Ma, W.Y. So, A.P. Kong, E. Chow, P. Clarke, W. Goggins, J.C.N. Chan, A. Luk.
Provision of study materials or patients: R.C. Ma, A.P. Kong, J.C.N. Chan.
Statistical expertise: T.A. Stukel.
Obtaining of funding: J.C.N. Chan.
Administrative, technical, or logistic support: R.C. Ma, W.Y. So, J.C.N. Chan, A. Luk.
Collection and assembly of data: W.Y. So, A.P. Kong, J.C.N. Chan, A. Luk.