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Clinical course of adolescents with type 2 diabetes mellitus: A nationwide cohort study in Taiwan

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ABSTRACT

Aims/Introduction: The global incidence of adolescents with type 2 diabetes mellitus is increasing. This cohort study was conducted aiming to describe the characteristics, drug-use condition, and long-term outcomes of adolescents with type 2 diabetes mellitus.

Materials and Methods: Two thousand seven hundred fifty-five newly diagnosed adolescents with type 2 diabetes mellitus (using ICD-9-CM: 250.x and having ≥3 clinic visits) were identified from the national health insurance dataset during 2000–2014. Treatments were classified into four groups: metformin, sulfonylurea (SU), metformin plus SU, and insulin with or without oral antidiabetic drugs. The multiple Cox regression model was used to compare the risks of mortality and hospitalization among these four groups.

Results: The mean follow-up period was 5.4 years. After 1 year of antidiabetic treatment, they gradually needed intensified therapy, and at 3 years, half of them showed treatment failure. The mortality rate was 2.08 per 1,000 person-years. Respiratory diseases (36.2%) and dysglycemia (16.4%) were the most common causes of hospitalization among these adolescents. Compared with persons taking metformin plus SU, metformin users were associated with a lower risk of all-cause hospitalization [0.82 (0.67–0.99)]; insulin users were associated with a higher risk of dysglycemia [4.38 (2.14–8.96)], cancer [3.76 (1.39–10.1)], and respiratory hospitalization [1.66 (1.14–2.41)]; and SU users were associated with a higher risk of hospitalization for respiratory diseases [1.91 (1.13–3.23)].

Conclusions: This nationwide cohort study demonstrated that adolescents with type 2 diabetes mellitus were prone to treatment failure. Furthermore, respiratory diseases and dysglycemia were the most common causes of hospitalization.

INTRODUCTION

Previously, diabetes in persons younger than 20 years of age was usually identified to be type 1 diabetes mellitus[1]. However, recently, the global incidence and prevalence of adolescents with type 2 diabetes mellitus have been increasing, possibly due to changes in dietary habits, reduced activities, and increased obesity[2]. The incidence of adolescents with type 2 diabetes mellitus increased from 9 cases per 100,000 in 2003 to 12.5 cases per 100,000 in 2012 in the United States[3]; from 5 adolescents per 100,000 in 2002 to 6.4 adolescents per 100,000 in 2012 in Australia[4]; from 7.3 junior high school children per 100,000 in 1976 to 13.9 children per 100,000 in 1995 in Japan[5]; and from 15 adolescents per 100,000 in 2005 to 19 adolescents per 100,000 in 2014 in Taiwan[6]. Furthermore, the prevalence of adolescent type 2 diabetes mellitus in Taiwan increased from 0.08% in 2005 to 0.14% of all type 2 diabetes mellitus cases in 2014[6]. In addition, Taiwan's 2003 report acknowledged that adolescents with type 2 diabetes mellitus were far more than those with type 1 diabetes mellitus (approximately 6:1 in

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ratio)[7]. Moreover, this phenomenon was seen in the adolescents of American Indian or Asian/Pacific islander in the Unites States[3].

Several studies have revealed that adolescents with type 2 diabetes mellitus were associated with higher risks of macro- and microvascular disease than those with type 1 diabetes mellitus[8,9]. The development of complications may be more rapid in adolescents with type 2 diabetes mellitus than in youths with type 1 diabetes mellitus. Furthermore, some adolescents with type 2 diabetes mellitus present a risk of cardiovascular disease[7,9], and many adolescents with type 2 diabetes mellitus belong to minority or disadvantaged populations[3,10]. The early onset of diabetes with an increased lifetime exposure to hyperglycemia, accelerated complication developments, and economic weakness make dealing with the disease difficult for adolescents with type 2 diabetes mellitus.

The treatment options for type 2 diabetes in adolescents and youth (TODAY) study compared metformin, metformin with lifestyle change, and metformin plus rosiglitazone therapies in adolescents with type 2 diabetes mellitus[11]. The results revealed that half of the adolescents taking metformin monotherapy failed therapy at 28 months, whereas those taking metformin plus rosiglitazone sustained treatment longer, with half of them needing additional medication at 5 years. Compared with adult type 2 diabetes mellitus persons, adolescents with type 2 diabetes mellitus display a rapidly progressive β-cell decline (annually 20–35% and 7% decline in adolescents and adults, respectively)[12]. Restoring insulin secretion (RISE) research used short-term aggressive insulin therapy in adolescents with early-stage type 2 diabetes mellitus to preserve β-cell function, but it failed[13]. The optimal management of adolescents with type 2 diabetes mellitus is challenging. In addition, most of the studies of adolescent patients with type 2 diabetes mellitus had a small sample size and were conducted in the West[14]. Therefore, this nationwide cohort study of adolescents with type 2 diabetes mellitus was performed aiming to provide a deeper understanding of this disease and its management.

MATERIALS AND METHODS

Data source

Taiwan's National Health Insurance (NHI) program was established in 1995. It is a compulsory single-payer nationwide health insurance program, with approximately 99% of Taiwan's 23 million residents from 2000 onward[15]. Our study used the full-population NHI Research Database (NHIRD), and this database is linked to the National Death Registry to confirm mortality information. This dataset involves the patients' residence area, age, sex, diagnoses, prescriptions, procedures, and details of outpatient or inpatient care. Disease diagnoses were recorded using the International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM). Patient and care provider details were deidentified before release to ensure individual privacy; therefore, informed consent for our study was waived. This study was approved by the Institutional Review Board of the National Health Research Institutes (EC1060704-E).

Study population

We conducted this retrospective cohort study by consecutively retrieving data between January 1, 2000, and December 31, 2015, from the Taiwan's NHIRD. Persons with newly diagnosed type 2 diabetes mellitus (*ICD-9-CM*: 250.x) in 2000–2014 were identified from the NHIRD, and their age at diagnosis was ≥10 and <20 years. To ensure diagnostic accuracy, we defined persons as having type 2 diabetes mellitus if they had a discharge diagnosis for ≥3 outpatient visits or ≥1 inpatient admission within 1 year. This algorithm of using ICD-9 to define type 2 diabetes mellitus has been validated by Taiwan's medical surveys with an accuracy of 74.6%[16]. In order to compare the long-term outcomes of different antidiabetic treatments, few adolescents with diet control (to exclude patients whose diabetes diagnoses were not so certain) and very few persons taking thiazolidinedione, dipeptidyl peptidase-4 inhibitors, or glucagon-like peptide-1 agonists were excluded from this study (the results of too few cases cannot be retrieved from the NHI administration). Sodium glucose cotransporter-2 inhibitors were not marketed in Taiwan until 2016. Furthermore, persons with type 1 diabetes mellitus (*ICD-9-CM*: 250.1) with a catastrophic illness card (Patients diagnosed by a physician as having a condition classified as a catastrophic illness by the Ministry of Health and Welfare can submit relevant information and apply for a catastrophic illness card to reduce their co-payment for outpatient or inpatient care) were excluded from this study. Patients with maturity-onset diabetes of the young (MODY; ICD-10: E13) or mitochondrial diabetes (ICD 10: E88.40, E13.8) were also excluded from the study.

Basic characteristics, comorbidities, and medications

On the basis of the age at diagnosis of type 2 diabetes mellitus, we divided our adolescents into four age groups: 10–12, 13–15, 16–17, and 18–19 years. On the basis of declared insured salary of the children's parents, they were classified into the following groups: poor (who were recognized by the local municipal authorities to live below the lowest living index and were exempted from NHI premiums), <733 US Dollars (USD, Taiwan's minimum wage level in 2018 was 733 USD), 733–1,499 USD, and 1,500 USD. We classified the urbanization of cities as highly urbanized, median urbanized, township, and rural areas. The comorbidities considered were hypertension (ICD-9-CM: 401–405 and A26), dyslipidemia (ICD-9-CM: 272 and 278), and chronic kidney disease (CKD; ICD-9-CM: 250.4, 585, 581.8, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, V42.0, V45.1, V56.x). Moreover, Charlson comorbidity index (CCI)[17] and Diabetes Complications Severity Index (DCSI)[18] scores were considered. Data on the comorbidities and CCI and DCSI scores were retrieved from a persons' NHI records 1 year before the index date. At least two outpatient visits or one inpatient diagnosis were considered to

increase the diagnosis validity of comorbidities. Furthermore, antihypertension drugs, such as angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers, and diuretics, and statins were analyzed in this study.

Main outcomes

To investigate a person's drug use and its long-term outcomes, we divided our adolescents into four groups: metformin (used metformin only), sulfonylurea (SU, used SU only), metformin plus SU, and insulin (used insulin with or without other oral antidiabetic drugs). The treatments were recognized within 3 months after the diagnosis of type 2 diabetes mellitus. The diagnosis date of type 2 diabetes mellitus was set as the index date. We assessed the risks of all-cause mortality, all-cause hospitalization, and cause-specific hospitalization. The date and incidence of mortality were identified from the National Death Registry records. In this study, we calculated the incidence of hospitalization due to all-cause, sight-threatening retinopathy (ICD-9-CM: 362.01, 362.02, 362.03–362.06, 362.0, 362.07, 362.53, 362.83, 364.42, 379.23, and 369; procedure codes: 86206B, 86207B, 86407B, 86408B, 60001C, 60002C, 6005C, 6006C, 6003C, and 6004C), dysglycemia [hypoglycemia: 251.0, 251.1, and 251.2; diabetic ketoacidosis (DKA): 250.1; and hyperglycemic hyperosmolar syndrome: 250.2], cancer (140–208), mental disorders (290–316), respiratory diseases (460.xx–466.xx, 470.xx–478.xx, 490.xx–496.xx, 487.xx–488.xx, 500.xx–508.xx, and 510.xx–519.xx), and cardiovascular diseases (heart: 398.91, 402.xx, 404.xx, 410.xx, 414.xx, 428.xx, 00.66, 36.xx, 36.01, 36.02, 36.05, 36.06, 36.07, and 36.1x and stroke: 430–438).

Statistical analysis

Age, sex, premium level (our people pay health insurance premiums based on their monthly salary level, the premium level reflects their salary level), urbanization, hypertension, dyslipidemia, CKD, CCI scores, DCSI scores, and drug use were compared in this study. The chi-square and Student's *t*-tests were used to determine the statistical differences among categorical variables and continuous variables, respectively. A multiple Cox regression model was used to estimate the hazard ratios and 95% confidence intervals (95% CIs). The Kaplan–Meier method was used to compare the cumulative incidences of all-cause and respiratory hospitalization among different groups of antidiabetic treatments. A P value of <0.05 was considered statistically significant. SAS (version 9.4; SAS Institute, Cary, NC, USA) and STATA (version 15.1; Stata Corp, College Station, TX, USA) were used for statistical analyses.

RESULTS

From 2000 to 2014, we recruited 2,755 adolescents with type 2 diabetes mellitus who underwent antidiabetic treatments (Table 1). Of them, 1,611(58.5%) were >15 years old [the mean (standard deviation, SD) age of diagnosis was 15.9 (2.2) years]; 1,405 (51%) were boys; 174 (6.3%) of them were poor, 913 (33.1%) of them resided in rural areas; 106 (3.8%), 201 (7.3%), and 87 (3.2%) of them had hypertension, dyslipidemia, and CKD, respectively; 257 (9.3%) had a CCI score of >1; 323 (11.7%) had a DCSI score of ≥1; and 199 (7.2%) and 269 (9.8%) of them received ACEi/ARB and statin, respectively. The mean (SD) follow-up time in this study was 5.4 (3.1) years.

In total, 1,313, 138, 772, and 532 adolescents with type 2 diabetes mellitus were included in the metformin, SU, metformin plus SU, and insulin groups, respectively (Table 1). Adolescents taking metformin plus SU were older; the metformin group had more girls than boys; a smaller proportion of patients in the SU group had a premium level of ≥1,500 USD; a higher proportion of patients in the insulin group resided in rural areas; a higher proportion of patients in the insulin group had more comorbidities and higher CCI and DCSI scores; a higher proportion of patients in the metformin plus SU group took ACEi/ARB; more SU users received β-blockers; a higher proportion of patients in the metformin plus SU and insulin groups used statins; and the insulin group had the shortest follow-up time. The NHIRD has a lack of the information of blood hemoglobin A1C (HbA1c) levels, but the Diabetes Mellitus Pay-for-Performance (P4P) database, a NHIRD subsample, was used to calculate the maximum, average and minimum HbA1c levels during the study period. The mean (±SD), minimum, and maximum HbA1c levels of all adolescents, metformin, sulfonylurea (SU), metformin + SU, and insulin users were (8 ± 2, 3.7–15%), (7.3 ± 1.7, 4.2–14.1%), (8 ± 1.7, 5.9–10.9%), (8.1 ± 2, 4.7–14.7%), and (7.9 ± 1.9, 3.7–15%), respectively.

Figure 1 displays the prescription details of this cohort. Most of the adolescents had taken medications consistently within 3 months of diagnosis, and approximately 50% of them were receiving metformin alone. After the first year, antidiabetic medication use gradually changed. In the third year, the proportion of metformin plus SU users and insulin users slowly increased and exceeded that of the metformin users. After the ninth year, insulin users accounted for the highest proportion in this cohort. Furthermore, the percentages of patients using metformin, metformin +SU, SU, insulin as their initial remedy, respectively, changed their treatment regimen in the end of follow-up were 29.98, 43.27, 72.37, and 3.78%.

In the metformin, SU, metformin plus SU, and insulin groups, 11, 2, 8, and 10 persons, respectively, died during follow-up (Table 2). The incidence rates of all-cause mortality were 1.40, 1.72, 1.50, and 3.57 per 1,000 person-years, respectively. The overall mortality rate was 2.08 per 1,000 person-years. The mean diabetes duration for the mortality cases was 4.96 (±3.69) years. No significant difference was noted in mortality risk among these four treatment groups. Our health insurance database stipulates that if the number of people is <3, the data cannot be carried out. The number of different cause of deaths in our adolescents with type 2 diabetes mellitus

Table 1 | Basic characteristics of adolescents aged 10–19 years with type 2 diabetes

	Total	Metformin only	Sulfonylurea only	Metformin and sulfonylurea	Insulin	*P* value
N	2,755	1,313	138	772	532	
Age group (year)						
10–12	193 (7.0)	104 (7.9)	10 (7.2)	34 (4.4)	45 (8.5)	0.01
13–15	951 (34.5)	422 (32.1)	45 (32.6)	261 (33.8)	223 (41.9)	0.001
16–17	788 (28.6)	375 (28.6)	48 (34.8)	229 (29.7)	136 (25.6)	0.14
18–19	823 (29.9)	412 (31.4)	35 (25.4)	248 (32.1)	128 (24.1)	0.004
Mean (SD)	15.9 (2.3)	15.9 (2.3)	15.9 (2.1)	16.1 (2.2)	15.5 (2.3)	0.009
Sex						
Male	1,405 (51.0)	601 (45.8)	78 (56.5)	439 (56.9)	287 (53.9)	<0.001
Female	1,350 (49.0)	712 (54.2)	60 (43.5)	333 (43.1)	245 (46.1)	
Premium level (USD)						
Poor	174 (6.3)	90 (6.9)	7 (5.1)	46 (6)	31 (5.8)	0.71
<733	1,161 (42.1)	512 (39)	78 (56.5)	363 (47)	208 (39.1)	<0.001
733–1,499	1,157 (42.0)	567 (43.2)	49 (35.5)	300 (38.9)	241 (45.3)	0.034
≥1,500	263 (9.6)	144 (11)	4 (2.9)	63 (8.2)	52 (9.8)	0.008
Urbanization						
High	606 (22.0)	292 (22.2)	32 (23.2)	160 (20.7)	122 (22.9)	0.76
Median	937 (34.0)	440 (33.5)	48 (34.8)	294 (38.1)	155 (29.1)	0.009
Township	299 (10.9)	140 (10.7)	17 (12.3)	85 (11)	57 (10.7)	0.94
Rural area	913 (33.1)	441 (33.6)	41 (29.7)	233 (30.2)	198 (37.2)	0.048
Comorbidity						
Hypertension	106 (3.8)	15 (1.1)	4 (2.9)	44 (5.7)	43 (8.1)	<0.001
Dyslipidemia	201 (7.3)	28 (2.1)	11 (8)	65 (8.4)	97 (18.2)	<0.001
CKD	87 (3.2)	19 (1.4)	7 (5.1)	31 (4)	30 (5.6)	<0.001
CCI scores						
≤1	2,498 (90.7)	1,272 (96.9)	124 (89.9)	708 (91.7)	394 (74.1)	<0.001
2	162 (5.9)	26 (2)	6 (4.3)	40 (5.2)	90 (16.9)	<0.001
≥3	95 (3.4)	15 (1.1)	8 (5.8)	24 (3.1)	48 (9)	<0.001
Mean (SD)	1.6 (1.1)	1.6 (1.1)	1.7 (1)	1.5 (1)	1.5 (1.1)	<0.001
DCSI scores						
0	2,432 (88.3)	1,276 (97.2)	124 (89.9)	702 (90.9)	330 (62)	<0.001
1	92 (3.3)	16 (1.2)	8 (5.8)	32 (4.1)	36 (6.8)	<0.001
≥2	231 (8.4)	21 (1.6)	6 (4.3)	38 (4.9)	166 (31.2)	<0.001
Mean (SD)	1.9 (1.1)	1.9 (1.2)	1.6 (0.9)	1.9 (1.1)	2 (0.8)	<0.001
Prescription						
ACEi/ARBs	199 (7.2)	73 (5.6)	10 (7.2)	75 (9.7)	41 (7.7)	0.005
Beta blocker	45 (1.6)	17 (1.3)	7 (5.1)	14 (1.8)	7 (1.3)	0.009
CCB	101 (3.7)	44 (3.4)	5 (3.6)	35 (4.5)	17 (3.2)	0.50
Diuretics	90 (3.2)	46 (3.5)	8 (5.8)	18 (2.3)	18 (3.4)	0.16
Statin	269 (9.8)	94 (7.2)	12 (8.7)	96 (12.4)	67 (12.6)	<0.001
Follow-up time (year)	5.4 (3.1)	5.2 (3.1)	6.7 (3.5)	5.7 (3.2)	4 (2.6)	<0.001
Death	31 (1.1)	11 (0.8)	2 (1.4)	8 (1)	10 (1.9)	0.27

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker; CCI, Charlson comorbidity index; CKD, chronic kidney disease; DCSI, Diabetes Complications Severity Index; SD, standard deviation.

is too small to carry out; therefore, we cannot list the cause of death in this study.

In total, 641 hospitalization events were recorded in this study (Table 2); 232 (36.2%), 105 (16.4%), 60 (9.4%), 39 (6.1%), 27 (4.2%), and 22 (3.4%) of admissions were due to respiratory diseases, dysglycemia, mental disorders, cancers, cardiovascular diseases, and sight-threatening retinopathy, respectively. The incidences of hospitalized severe hypoglycemia in metformin, SU, metformin plus SU, and insulin groups were 4.94, 3.46, 2.21, and 3.29 per 1,000 per-years, respectively. Compared with metformin plus SU, adolescents receiving metformin monotherapy were associated with a lower risk of all-cause hospitalization [adjusted hazard ratio, aHR (95% CI): 0.82 (0.67–0.99)]; adolescents taking insulin with or without

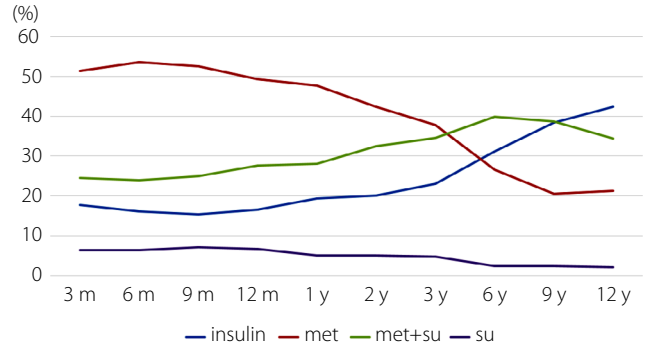

Figure 1 | Prescription of antidiabetic medications in adolescents aged 10–19 years with type 2 diabetes. The unit of the *y* axis is percentage (%).

oral antidiabetic drugs (OADs) were associated with a higher risk of respiratory hospitalization [aHR 1.66 (1.14–2.41)], dysglycemic hospitalization [aHR 4.38 (2.14–8.96)], and cancer hospitalization [aHR 3.76 (1.39–10.1)]; and adolescents using SU monotherapy were associated with a higher risk of respiratory hospitalization [aHR 1.91 (1.13–3.23)].

The cumulative incidence of all-cause hospitalizations per Kaplan–Meier analysis indicated significantly lower risks of all-cause hospitalization in adolescents taking metformin alone, SU alone, or metformin plus SU than in those taking insulin with or without OADs (log-rank test, $P < 0.05$; Figure 2). Similarly, the cumulative incidence of respiratory hospitalizations showed significantly lower risks of respiratory hospitalization in adolescents using metformin alone, SU alone, or metformin plus SU than in those using insulin with or without OADs (log-rank test, $P < 0.05$; Figure 3).

DISCUSSION

Although the global incidence and prevalence of adolescents with type 2 diabetes mellitus are increasing, the number of patients in each country is still small. Few studies have reported the clinical course of adolescent type 2 diabetes mellitus with a large series[14]. We conducted a nationwide cohort study of adolescents with type 2 diabetes mellitus and described their demographics, antidiabetic medications, and long-term outcomes. Initially, approximately half of the adolescents received metformin monotherapy and were gradually shifted to other treatments after 1 year. Respiratory diseases and dysglycemia were the most common causes of hospitalization for these adolescents. Compared with metformin plus SU users, metformin users were associated with a lower risk of all-cause hospitalization; insulin users were associated with higher risks of dysglycemia, cancer, and respiratory hospitalization; and SU users were associated with a higher risk of hospitalization for respiratory diseases.

Some reports have demonstrated that girls[3] and people with a disadvantaged socio-economic background[10] are more likely to be associated with adolescent type 2 diabetes mellitus. However, in our study, girls, poor people, or persons living in rural areas were not found to have an increased incidence of adolescents with type 2 diabetes mellitus. Approximately 3.8%, 7.3%, and 3.2% of our adolescents had hypertension, dyslipidemia, and chronic kidney disease, respectively, which is consistent with the findings of other studies[11,19]. These comorbidities may increase the cardiovascular disease risk in these teenagers.

Studies have revealed that β-cell-function decline is particularly rapid in adolescents with type 2 diabetes mellitus[12]. Furthermore, our study showed that approximately 50% of the persons taking metformin monotherapy needed intensified treatment after 3 years, which is similar to the results of the TODAY trial[11]. However, our study was real-world research, and hence, the antidiabetic treatments were not aggressive and intensified as in a randomized trial. Therefore, the antidiabetic treatment failure for adolescents with type 2 diabetes mellitus in Asia may be sooner than for those in the West. The rapid treatment failure with most of them requiring insulin therapy in our study may imply a rapid decline in β-cell function[12].

Mortality data for adolescents with type 2 diabetes mellitus are limited. Even if our adolescents are followed up for 15 years, they will be <35 years old. Because they are young, their mortality rate (2.08 per 1,000 person-years) is lower than that of persons with adult-onset type 2 diabetes mellitus (32.8–38.2 per 1,000 person-years)[20]. Similarly, because our study population is young, hospitalization due to cardiovascular disease or cancer was relatively low. This is different from hospitalization causes in persons with adult-onset type 2 diabetes mellitus[21].

Our study population was more often hospitalized for respiratory diseases or suboptimal sugar control. Furthermore, they were commonly hospitalized for mental illness. Because hospitalization due to respiratory disease was noted in persons with adult-onset type 2 diabetes mellitus[21], adolescents must be encouraged to avoid smoking and to receive influenza and pneumococcus vaccination to decrease the occurrence or progression of respiratory diseases. Adolescents with type 2 diabetes mellitus have been reported to have diabetic ketoacidosis[19,22]. In these young persons, diet control is difficult, treatment adherence is suboptimal[19], β-cell-function decline is rapid[12], and blood glucose fluctuation may be more frequent. Therefore, we shall recommend that our adolescents frequently monitor their blood glucose levels and stabilize them.

A retrospective study in the United States disclosed that 19.4% of the children with type 2 diabetes mellitus had neuropsychiatric disease at presentation[23]. Our study also demonstrated that approximately 10% of adolescents were hospitalized due to mental disorders.

Our study further demonstrated that adolescents taking metformin monotherapy were associated with a lower risk of all-cause hospitalization compared with those taking metformin plus SU. This result was similar to a report of a UK cohort study that metformin users were associated with a lower risk of complication and mortality than metformin plus SU users[24]. However, notably, the different outcome risks between these two groups of

Table 2 | Mortality and hospitalization results of adolescents aged 10–19 years with type 2 diabetes

	Event	Incidence rate, per 1,000 person-years	Crude model		Adjusted model†	
			Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)	*P* value
All-cause mortality						
Insulin	10	3.57	2.34 (0.92–5.95)	0.07	1.84 (0.66–5.08)	0.24
Metformin and sulfonylurea	8	1.50	1.0 (reference)		1.0 (reference)	
Metformin only	11	1.40	0.92 (0.37–2.29)	0.86	1.05 (0.42–2.66)	0.92
Sulfonylurea only	2	1.72	1.16 (0.25–5.49)	0.85	1.22 (0.26–5.75)	0.81
All-cause hospitalization						
Insulin	149	69.64	1.53 (1.24–1.90)	<0.001	1.16 (0.92–1.46)	0.21
Metformin and sulfonylurea	205	46.43	1.0 (reference)		1.0 (reference)	
Metformin only	243	35.45	0.77 (0.64–0.92)	0.005	0.82 (0.67–0.99)	0.035
Sulfonylurea only	44	47.76	1.04 (0.75–1.44)	0.81	1.02 (0.73–1.41)	0.91
Sight-threatening hospitalization						
Insulin	11	4.00	4.01 (1.47–11.0)	0.007	2.20 (0.74–6.53)	0.16
Metformin and sulfonylurea	6	1.13	1.0 (reference)		1.0 (reference)	
Metformin only	5	0.64	0.61 (0.19–2.00)	0.41	0.66 (0.19–2.25)	0.51
Sulfonylurea only	–	–	–		–	
Dysglycemic hospitalization						
Insulin	84	35.35	16.0 (8.02–31.9)	<0.001	4.38 (2.14–8.96)	<0.001
Metformin and sulfonylurea	9	1.7	1.0 (reference)		1.0 (reference)	
Metformin only	9	1.15	0.62 (0.25–1.56)	0.31	1.19 (0.46–3.08)	0.72
Sulfonylurea only	3	2.62	1.71 (0.46–6.33)	0.42	1.91 (0.51–7.08)	0.33
Cancer hospitalization						
Insulin	16	5.9	4.16 (1.63–10.7)	0.002	3.76 (1.39–10.1)	0.009
Metformin and sulfonylurea	6	1.13	1.0 (reference)		1.0 (reference)	
Metformin only	14	1.79	1.41 (0.54–3.68)	0.48	1.37 (0.52–3.59)	0.53
Sulfonylurea only	3	2.62	2.73 (0.68–10.9)	0.16	2.91 (0.73–11.7)	0.13
Mental hospitalization						
Insulin	18	6.65	1.90 (0.96–3.73)	0.06	1.26 (0.61–2.63)	0.53
Metformin and sulfonylurea	16	3.05	1.0 (reference)		1.0 (reference)	
Metformin only	23	2.97	0.91 (0.48–1.73)	0.78	1.06 (0.55–2.03)	0.87
Sulfonylurea only	3	2.62	0.94 (0.27–3.24)	0.93	0.98 (0.29–3.38)	0.98
Respiratory hospitalization						
Insulin	77	31.74	2.49 (1.76–3.53)	<0.001	1.66 (1.14–2.41)	0.008
Metformin and sulfonylurea	54	10.7	1.0 (reference)		1.0 (reference)	
Metformin only	82	10.96	0.95 (0.68–1.34)	0.78	1.07 (0.76–1.52)	0.69
Sulfonylurea only	19	18.45	1.87 (1.11–3.16)	0.018	1.91 (1.13–3.23)	0.015
Cardiovascular hospitalization						
Insulin	7	2.52	1.90 (0.66–5.46)	0.23	1.18 (0.38–3.65)	0.78
Metformin and sulfonylurea	7	1.31	1.0 (reference)		1.0 (reference)	
Metformin only	10	1.28	0.97 (0.37–2.56)	0.95	1.39 (0.50–3.83)	0.52
Sulfonylurea only	3	2.63	1.91 (0.49–7.41)	0.35	2.35 (0.60–9.26)	0.22

†Adjusted for all variables in Table 1, including age, sex, premium levels, urbanization, comorbidities, Charlson comorbidity index scores, Diabetes Complications Severity Index scores, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, β blocker, calcium channel blocker, diuretics, and statin use.

patients may also be caused by the difference in their basic characteristics and response to antidiabetic treatments.

In our study, adolescents taking insulin were associated with a higher hospitalization risk due to dysglycemia, cancer, and respiratory diseases than those using metformin plus SU. The registered study of the Pediatric Diabetes Consortium in the United States demonstrated that adolescents receiving insulin therapy had a ratio of hemoglobin A1C ≥9%[14]. Moreover, insulin has been reported to be associated with a higher risk of cancer[25] and asthma attack[26]. Adolescents who received insulin had increased suboptimal glycemic control[14], which may lead to higher risks of cancer and respiratory disease.

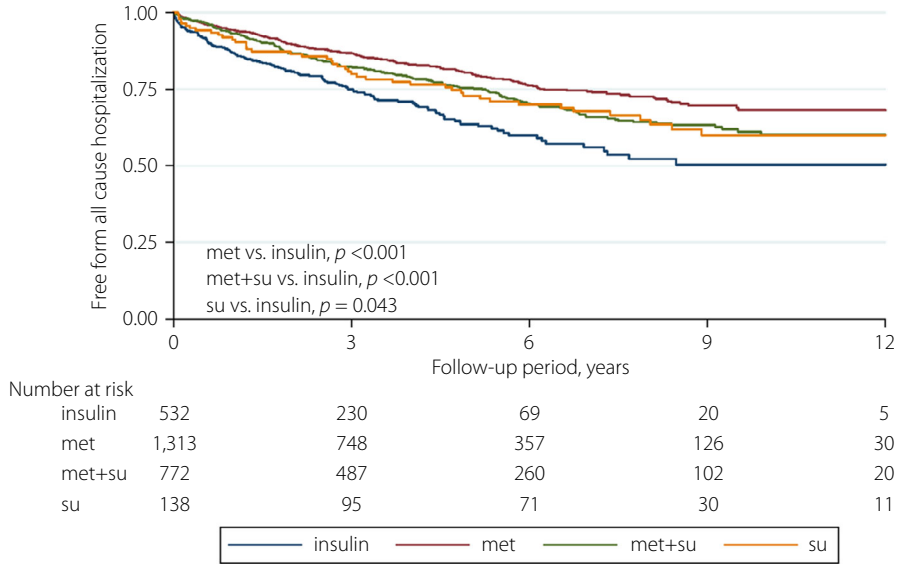

Figure 2 | Kaplan–Meier curves for all-cause hospitalization according to different groups of antidiabetic treatments.

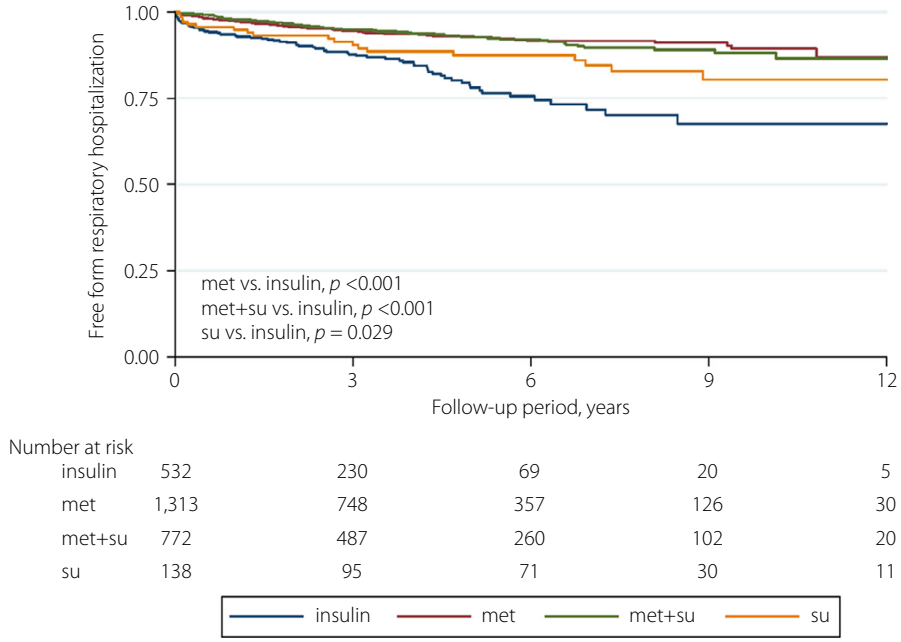

Figure 3 | Kaplan–Meier curves for respiratory hospitalization according to different groups of antidiabetic treatments.

Moreover, our study revealed that adolescents taking sulfonylurea monotherapy were associated with a higher risk of respiratory hospitalization than those taking metformin plus SU. Clinical studies have demonstrated that potassium channel openers can modulate the response of airway smooth muscle and may play a role in respiratory disease treatment[27]. However, our study disclosed that adolescents with sulfonylurea monotherapy were associated with a higher risk of respiratory hospitalization. Persons taking SU or insulin therapy will tend to have high serum insulin levels, which may increase the risk of respiratory disease[26]; these adolescents also may have suboptimal glycemic control with the risk of respiratory complications[28]. In addition, sulfonylureas are not generally recommended for the glycemic management of adolescents with type 2 diabetes mellitus in most

clinical practice guidelines[29], due to the increased risk of hypoglycemia and more rapid loss of β-cell function. However, sulfonylurea use was not uncommon in our study. It may be that physicians did not notice the different treatment recommendations for adolescents with type 2 diabetes mellitus and they prescribed medications in accordance with the guidelines for adults with type 2 diabetes mellitus. This is a caveat of which we must remind our physicians.

This study has some clinical implications. First, we obtained our data from a nationwide database that spans 15 years. The study provided a large series of adolescents with type 2 diabetes mellitus diabetes and their baseline characteristics, medications, and long-term outcomes. Second, physiological and psychological changes normally occur at adolescence, and glucose control in adolescents requires a high degree of family involvement. For this group of people, achieving a stringent treatment goal is difficult. Furthermore, our research found that the drug durability of adolescents was short, and their treatments failed easily. In addition, their hospitalization risk due to extreme blood glucose levels was high. We must empower them to closely monitor and optimally control their glucose levels.

This study also has some disadvantages. First, we used ICD-9 codes to identify type 2 diabetes mellitus patients from the NHIRD, and the accuracy of this diagnostic criterion was 74.6%, therefore, approximately 15.4% of this cohort may not have had type 2 diabetes mellitus. Additionally, this dataset lacked information regarding insulin antibody, islet cell antibody, glutamic acid decarboxylase antibody, insulin levels, and genetic tests and some adolescents with type 1 diabetes mellitus, latent autoimmune diabetes in adults, and monogenic diabetes may be misclassified as having adolescent type 2 diabetes mellitus. Second, blood test results, such as glucose, hemoglobin A1C, cholesterol levels, and renal function, were unavailable. Blood tests could not be used to diagnose diabetes mellitus and to assess sugar control and disease severity in this study. Third, although we classified our adolescents into four treatment groups, physicians may choose different treatments based on different clinical conditions of the patients. Moreover, adolescents may choose their treatment based on their personal knowledge. Fourth, thiazolidinediones and dipeptidyl peptidase-4 inhibitors do not have the Taiwan FDA approval as an indication for diabetes treatment in adolescents under the age of 18. Therefore, few adolescents with type 2 diabetes mellitus in Taiwan were prescribed these two medications. Fifth, this administrative database lacked information regarding dietary patterns, physical activity, dinking or smoking habits, and body weight, which may have influenced our assessed outcomes. However, we adjusted for age, sex, premium levels, urbanization, comorbidities, diabetes complication scores, and medications to maximally decrease the confounding known variables. Sixth, the ethnic group of this study is entirely Chinese, and the study results may not be applicable to other ethnicities. Finally, observational studies are always subject to some inevitable biases, and randomized control studies are warranted to confirm our results.

Our study demonstrated that adolescents with type 2 diabetes mellitus gradually needed intensified treatment after 1 year of antidiabetic therapy, and most of them finally required insulin therapy. Moreover, these adolescents were readily hospitalized for suboptimal blood glucose levels and respiratory diseases. This observation extends our current knowledge, although it falls short of a strong case for diagnostic utility.

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DISCLOSURE

The authors declare no conflict of interest in this study.
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Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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