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Persons with type 2 diabetes and high insulin persistence were associated with a lower risk of mortality: A nationwide retrospective cohort study

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ABSTRACT

Aims/Introduction: Studies assessing the long-term outcomes of insulin persistence are scant. We compared the risk of all-cause mortality among patients with different degrees of insulin persistence.

Materials and Methods: In total, 293,210 patients with type 2 diabetes mellitus undergoing insulin therapy were enrolled during 2002–2014. Insulin persistence was defined as continual insulin treatment without a 90-day gap of discontinuation in the 2-year observation period. Mortality rates were compared between 111,220 patients with ≥90% insulin persistence and 111,220 matched patients with <90% insulin persistence during the observational period.

Results: During the mean 5.37-year follow-up period, the mortality rates were 58.26 and 73.21 per 1,000 person-years for patients with ≥90% and <90% of insulin persistence. The adjusted hazard ratio for mortality was 0.80 (95% confidence interval 0.79–0.81, $P < 0.001$). Patients with high insulin persistence had significantly lower risks than did those with low insulin persistence of death due to hypertension, diabetes, cardiovascular disease, liver disease, kidney disease, respiratory disease, sepsis and cancer.

Conclusions: This study showed that patients with ≥90% insulin persistence were associated with lower risks of all-cause mortality than did patients with <90% insulin persistence.

INTRODUCTION

The global burden of type 2 diabetes mellitus has been rapidly increasing in recent decades. In 1994, 100 million people had type 2 diabetes mellitus; this number is approximately currently 425 million, but is expected to increase to 629 million in 2045[1]. According to a study of emerging risk factor collaboration, a 50-year-old person with type 2 diabetes mellitus might have a 6-year premature death than their counterpart without type 2 diabetes mellitus[2]. However, aggressive treatment of hyperglycemia could reduce all-cause mortality, as shown in a UK prospective diabetes study[3].

Type 2 diabetes mellitus is a progressive disease, in which the number of β-cells decreases at approximately 4% per year; eventually, most patients require insulin therapy[4]. Insulin is listed as an essential medicine by the World Health Organization[5], and can efficiently reduce blood glucose levels; however, in practice, it is difficult to encourage patients to receive insulin therapy. In the USA, only approximately 29% of patients with type 2 diabetes mellitus received insulin therapy[6]. Even after receiving insulin therapy, only approximately 50% of the

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patients attain their glycemic target[7]. The causes of this suboptimal treatment could be derived from poor adherence and lack of persistence of insulin treatment[8].

Encouraging patients with type 2 diabetes mellitus to receive insulin therapy is not easy. Therefore, we must hold the opportunity to titrate insulin doses, encourage patients to lead healthy lifestyles, and urge them to adhere to and be persistent with their treatments[9]. Globally, patients undergoing insulin treatment struggle with regimen adherence (the degree a patient acts in accordance with the prescribed interval and dosage of a regimen) and persistence. Studies have reported on the association between insulin persistence and hospitalization[10–12], but no known long-term outcomes have been reported. Therefore, we carried out this nationwide cohort study to assess the risk of all-cause mortality between patients with different degrees of insulin persistence.

METHODS

Data source

The National Health Insurance (NHI) program was implemented in Taiwan in 1995. It is a nationwide single-payer compulsory health insurance program, which has approximately 99% of Taiwan's 23 million residents enrolled[13]. The present study used the full population dataset from the NHI Research Database for analysis. The NHI Research Database is linked to the National Death Registry to certify mortality information. The dataset includes patients' registered location, sex, age, investigations, diagnoses, prescriptions and details of each instance of outpatient or inpatient care. Disease diagnoses were coded using the International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM). To ensure patient privacy, all information that could be used to identify patients or care providers is encrypted before release to the researchers; therefore, we were granted a waiver of informed consent. This study was approved by the institutional review board of the National Health Research Institutes (EC1060704-E).

Study population

This was a retrospective cohort study based on Taiwan's NHI Research Database administrative data collected from 1 January 2000 to 31 December 2015. We included data of patients who were newly diagnosed as having type 2 diabetes mellitus (ICD-9-CM: 250.x) in 2001–2014, with the age at diagnosis ≤90 years. To ensure diagnostic accuracy, we defined patients as having type 2 diabetes mellitus if they had a discharge diagnosis for three or more outpatient or one or more inpatient claims within 1 year. We selected patients who had received insulin treatment for at least 3 months after receiving a diagnosis of diabetes in our potential study population. The exclusion criteria were having type 1 diabetes mellitus (250.1) with a catastrophic illness card; undergoing dialysis; withdrawal from the NHI program within the first 2 years of observation; receipt of unclear insulin initiation; and having type 2 diabetes mellitus diagnosis, survival or follow-up duration data for <180 days after the index date.

Insulin persistence

We identified newly diagnosed patients who received insulin treatment for ≥3 months, and we then observed them for 2 years (730 days) from the first insulin initiation date. A type 2 diabetes mellitus patient with a stable condition is usually given a continuous prescription for 2–3 months in Taiwan. If a patient does not return to the clinic 3 months after the last visit, they might have stopped the treatment. Therefore, we defined insulin persistence[14] as continual insulin treatment without a 90-day discontinuation gap in the 2-year observation period[15]. The days of insulin persistence was measured as the number of days of continuous insulin treatment before a 90-day discontinuation gap. The degree of insulin persistence was the number of persistent days divided by 730. We arbitrarily set ≥90% and <90% insulin persistence as high and low insulin persistence, respectively. The 731st day after insulin initiation was defined as the index date for both high and low insulin persistence cohorts.

Primary outcome

The primary outcome of the present study was all-cause mortality risk. The date and cause of mortality were identified from the National Death Registry records.

Basic characteristics and comorbidities

Comorbidities included hypertension (ICD-9-CM: 401–405 and A26), dyslipidemia (ICD-9-CM: 272, 278), chronic kidney disease (CKD; ICD-9-CM: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, V42.0, V45.1, V56.x and 790), coronary artery disease (CAD; ICD-9-CM: 410–414), congestive heart failure (ICD-9-CM: 428), atrial fibrillation (ICD-9-CM: 427.31), stroke (ICD-9-CM: 430–438), peripheral artery occlusive disease (ICD-9-CM: 440.2x, 443.9, 84.1x, 39.25, 39.29, 39.50 and 39.59), chronic obstructive pulmonary disease (COPD; ICD-9-CM: 491, 492 and 496), cirrhosis (ICD-9-CM: 571.5, 571.2 and 571.6), depression (ICD-9-CM: 311), psychotic disorders (ICD-9-CM: 290–299) and cancers (ICD-9-CM: 140–239). The Charlson Comorbidity Index (CCI)[16] and Diabetes Complications Severity Index (DCSI)[17] scores were also considered. The comorbidities, CCI and DCSI scores were calculated according to participants' NHI records 1 year before the index date. To increase the validity of diagnoses of comorbidities in the administrative dataset, we only included patients who received two or more outpatient diagnoses or at least one inpatient claim.

We examined the frequency of outpatient department visits per year and the use of antidiabetic drugs other than insulin within 2 years before the index date. These drugs included biguanides, sulfonylureas, meglitinides, alpha glucosidase

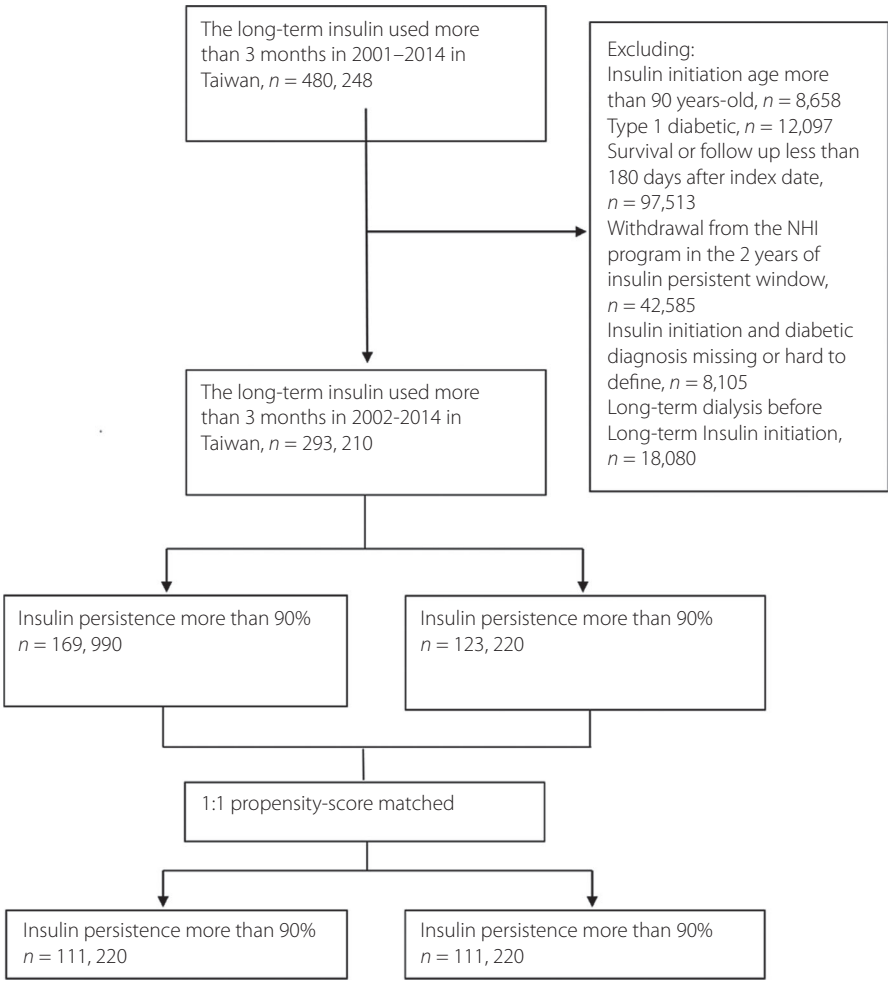

Figure 1 | Flow of selection of cohorts with different insulin persistence from the National Health Insurance Research Database. NHI, National Health Insurance.

inhibitors, thiazolidinedione and dipeptidyl peptidase-4 inhibitors. Antihypertension drug, statin and aspirin use were also considered.

Statistical analysis

Baseline characteristics, comorbidities, DCSI scores, outpatient department visit frequency, and drug use were compared between high- and low insulin persistence cohorts. We used multiple logistic regression analysis to calculate propensity scores, and selected the 1:1 comparison pairs matched by age, sex, comorbidities, DCSI score, outpatient department visits per year and drug use[18]. For categorical variables, the χ^2-test was used to determine the statistical difference between the two groups, whereas for continuous variables, the Student's *t*-test was used. Hazard ratios (HRs) and 95% confidence intervals were estimated using the Cox proportional hazards model. Kaplan–Meier and log–rank tests were used to assess the differences between cumulative incidence rates. A *P*-value of <0.05 was considered statistically significant. We used *E*-value analysis to estimate the relative risk of an unmeasured confounder to account for the association of insulin persistence with mortality in our study[19]. SAS (version 9.4; SAS Institute, Cary, NC, USA) and Stata (version 15.1; StataCorp, College Station, TX, USA) were used for statistical analysis.

RESULTS

We recruited 222,440 matched patients with type 2 diabetes mellitus (111,220 in each cohort; Figure 1). Table 1 presents the basic characteristics of the study population. After propensity score matching was carried out, the difference in all variables between patients with ≥90 and <90% of insulin persistence remained non-significant. In the present study, the number of men exceeded that of women; the mean age was 62.8 and 62.6 years in patients with high and low insulin persistence, respectively. Furthermore, the mean follow-up duration was

Table 1 | Basic characteristics of patients with <90% and ≥90% insulin persistence

	Pre-propensity score matched				Post-propensity score matched			
	Persistence ≥90%	Persistence <90%	*P*-value	SID	Persistence ≥90%	Persistence <90%	*P*-value	SID
n	169,990	123,220			111,220	111,220		
Age group (years)								
00–17	193 (0.1)	204 (0.2)	<0.001	0.077	178 (0.2)	172 (0.2)	0.75	0.038
18–39	6,828 (4.0)	8,149 (6.6)	<0.001	0.241	6,178 (5.6)	6,197 (5.6)	0.86	0.003
40–64	80,081 (47.1)	57,968 (47.0)	<0.001	0.470	53,075 (47.7)	53,238 (47.9)	0.49	0.003
65–74	46,044 (27.1)	29,730 (24.1)	<0.001	0.636	27,651 (24.9)	27,555 (24.8)	0.64	0.004
75–100	36,844 (21.7)	27,169 (22.0)	<0.001	0.443	24,138 (21.7)	24,058 (21.6)	0.68	0.004
Mean (SD)	63.5 (12.9)	62.4 (14.2)	<0.001	0.086	62.8 (13.6)	62.6 (13.8)	0.003	0.013
Sex								
Male	84,042 (49.4)	65,083 (52.8)	<0.001	0.371	57,518 (51.7)	57,743 (51.9)	0.34	0.004
Female	85,948 (50.6)	58,137 (47.2)		0.569	53,702 (48.3)	53,477 (48.1)		0.005
Comorbidity								
Hypertension	121,714 (71.6)	84,922 (68.9)	<0.001	0.524	77,259 (69.5)	77,221 (69.4)	0.86	0.001
Dyslipidemia	55,497 (32.6)	41,776 (33.9)	<0.001	0.412	37,195 (33.4)	37,303 (33.5)	0.63	0.003
CKD	61,723 (36.3)	44,713 (36.3)	<0.001	0.469	40,232 (36.2)	40,233 (36.2)	0.99	0.001
CAD	46,148 (27.1)	32,289 (26.2)	<0.001	0.519	29,271 (26.3)	29,227 (26.3)	0.83	0.002
CHF	19,395 (11.4)	15,741 (12.8)	<0.001	0.302	13,578 (12.2)	13,585 (12.2)	0.96	0.001
AF	4,419 (2.6)	3,953 (3.2)	<0.001	0.160	3,224 (2.9)	3,239 (2.9)	0.85	0.005
Stroke	35,350 (20.8)	28,130 (22.8)	<0.001	0.331	24,661 (22.2)	24,598 (22.1)	0.75	0.003
PAOD	11,436 (6.7)	8,453 (6.9)	<0.001	0.439	7,605 (6.8)	7,618 (6.8)	0.91	0.002
COPD	28,000 (16.5)	23,025 (18.7)	<0.001	0.282	19,899 (17.9)	19,851 (17.8)	0.79	0.003
Cirrhosis	7,218 (4.2)	6,730 (5.5)	<0.001	0.100	5,414 (4.9)	5,414 (4.9)	0.99	0.001
Depression	3,118 (1.8)	2,689 (2.2)	<0.001	0.213	2,251 (2.0)	2,251 (2.0)	0.99	0.001
Psychotic disorders	14,596 (8.6)	138,39 (11.2)	<0.001	0.076	11,360 (10.2)	11,349 (10.2)	0.94	0.001
Cancer	12,937 (7.6)	105,95 (8.6)		0.288	9,224 (8.3)	9,245 (8.3)	0.87	0.003
CCI scores								
≤1	41,161 (24.2)	28,665 (23.3)	<0.001	0.526	26,301 (23.6)	26,416 (23.8)	0.57	0.005
2	33,347 (19.6)	21,549 (17.5)	<0.001	0.635	20,051 (18.0)	20,098 (18.1)	0.80	0.003
3	27,237 (16.0)	18,667 (15.1)	<0.001	0.550	17,227 (15.5)	17,200 (15.5)	0.87	0.002
4	68,245 (40.1)	54,339 (44.1)	<0.001	0.330	47,641 (42.8)	47,506 (42.7)	0.56	0.003
Mean (SD)	3.4 (2.3)	3.7 (2.5)	<0.001	0.103	3.5 (2.4)	3.6 (2.5)	<0.001	0.030
DCSI score								
0	34,892 (20.5)	27,167 (22.0)	<0.001	0.363	24,333 (21.9)	24,350 (21.9)	0.93	0.001
1	34,266 (20.2)	22,848 (18.5)	<0.001	0.590	21,301 (19.2)	21,234 (19.1)	0.72	0.004
2	33,345 (19.6)	23,728 (19.3)	<0.001	0.495	21,567 (19.4)	21,580 (19.4)	0.94	0.001
3	67,487 (39.7)	49,477 (40.2)	<0.001	0.451	44,019 (39.6)	44,056 (39.6)	0.87	0.001
Mean (SD)	2.3 (2.0)	2.4 (2.1)	<0.001	0.021	2.3 (2.0)	2.3 (2.1)	0.50	0.014
Frequency of OPD visits/year	4.3 (2.5)	4 (2.6)	<0.001	0.094	4.1 (2.4)	4.1 (2.6)	0.50	0.016
Prescription								
Metformin	139,226 (81.9)	102,160 (82.9)	<0.001	0.450	91,482 (82.3)	91,530 (82.3)	0.79	0.001
Sulfonylurea	139,350 (82.0)	100,169 (81.3)	<0.001	0.480	90,497 (81.4)	90,442 (81.3)	0.76	0.001
Meglitinide	34,202 (20.1)	26,295 (21.3)	<0.001	0.381	23,326 (21.0)	23,273 (20.9)	0.78	0.003
AGI	61,278 (36.0)	40,692 (33.0)	<0.001	0.596	37,634 (33.8)	37,506 (33.7)	0.57	0.004
TZD	65,709 (38.7)	40,998 (33.3)	<0.001	0.685	38,700 (34.8)	38,383 (34.5)	0.16	0.009
DPP-4i	39,081 (23.0)	39,374 (32.0)	<0.001	0.011	33,186 (29.8)	33,181 (29.8)	0.98	0.001
Insulin								
Basal	112,981 (66.5)	88,303 (71.7)	<0.001	0.357	78,726 (70.8)	78,486 (70.6)	0.26	0.003
Premixed	69,218 (40.7)	44,914 (36.5)	0.001	0.629	41,300 (37.1)	41,446 (37.3)	0.52	0.004
Fast-acting	33,940 (20.0)	31,763 (25.8)	<0.001	0.094	26,494 (23.8)	26,502 (23.8)	0.97	0.001
Insulin initiation year	6.5 (4.1)	6.2 (4.6)	<0.001	0.078	6.4 (4.2)	6.4 (4.6)	0.35	0.004
ACEi/ARBs	113,140 (66.6)	75,805 (61.5)	<0.001	0.583	69,737 (62.7)	69,679 (62.6)	0.80	0.001
Beta-blocker	59,092 (34.8)	39,813 (32.3)	<0.001	0.574	36,601 (32.9)	36,555 (32.9)	0.84	0.001

Table 1 (*Continued*)

	Pre-propensity score matched				Post-propensity score matched			
	Persistence ≥90%	Persistence <90%	*P*-value	SID	Persistence ≥90%	Persistence <90%	*P*-value	SID
CCB	91,063 (53.6)	61,118 (49.6)	<0.001	0.580	56,112 (50.5)	56,008 (50.4)	0.66	0.002
Diuretics	80,975 (47.6)	53,320 (43.3)	<0.001	0.608	48,844 (43.9)	48,601 (43.7)	0.30	0.006
Statin	89,056 (52.4)	63,054 (51.2)	<0.001	0.502	57,315 (51.5)	57,314 (51.5)	0.99	0.001
Aspirin	72,163 (42.5)	48,545 (39.4)	<0.001	0.577	44,730 (40.2)	44,520 (40.0)	0.36	0.005
Propensity score	0.597 (0.096)	0.554 (0.104)	<0.001	0.426	0.565 (0.095)	0.564 (0.095)	0.05	0.008

ACEi, angiotension-converting enzyme inhibitor; AF, atrial fibrillation; AGI, alpha-glucosidase inhibitor; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; CCB, calcium channel blocker; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DCSI, Diabetes Complications Severity Index; DPP-4i, dipeptidyl peptidase-4 inhibitor; OPD, outpatient department; PAOD, peripheral artery occlusive disease; SD, standard deviation; SID, standardized differences; TZD, thiazolidinedione.

5.96 and 4.39 years in patients with ≥90 and <90% of insulin persistence, respectively. In the 2-year observation period, the mean and median insulin persistence durations were 548 and 730 days, respectively. Furthermore, at 6, 12 and 24 months, the rates of insulin persistence were 91.3, 88.3 and 80.8%, respectively.

Mortality rates were 58.26 and 73.21 per 1,000 person-years for patients with ≥90 and <90% of insulin persistence, respectively (Table 2). The HR for mortality was 0.80 (95% confidence interval 0.79–0.81, $P < 0.001$) for patients with ≥90% insulin persistence against those with <90% insulin persistence. The difference in survival probability among the different proportions of insulin persistence is shown through a Kaplan–Meier plot in Figure S1, which demonstrates a higher survival probability in patients with ≥90% of insulin persistence than in patients with <50, 50–69, and 70–89% insulin persistence (log–rank test, $P < 0.001$). Table 3 shows that compared with those with ≥90% insulin persistence, patients with <50, 50–69 and 70–89% insulin persistence had a 22–29% higher mortality risk.

Figure 2 describes the number and adjusted HR (aHR) for mortality risks in patients with ≥90% versus <90% insulin persistence, stratified by various basic characteristics, comorbidities and medications. It shows that the survival benefit of insulin persistence was more significant in patients who were aged <40 years, were male, did not have dyslipidemia, had CKD, had stroke, had COPD, had CCI ≥4, had DCSI ≥3, used metformin and used sulfonylureas (*P* for interaction <0.05).

Table 2 also lists the incidence rates of and aHRs for death due to cancer, CAD, stroke, diabetes, liver disease, hypertension, kidney disease, general accidents, suicide, sepsis, pneumonia, respiratory disease, and other causes between patients with ≥90 and <90% insulin persistence. Patients with high insulin persistence had significantly lower all-cause mortality than did those with low insulin persistence.

To assess the strength of association of unmeasured confounders, we identified *E*-values (relative risks) of insulin persistence on all-cause mortality; the estimated and upper confidence intervals were 1.81 and 1.77, respectively.

DISCUSSION

The present study showed that patients with ≥90% insulin persistence in 2 years had significantly lower all-cause and cause-specific mortality risks than did patients with <90% insulin persistence. The subgroup analysis showed that the survival benefit of insulin persistence was more significant in patients who were aged <40 years, were male, had CKD, had stroke, had COPD, had high CCI, had high DCSI and used metformin or sulfonylureas, compared with their counterparts.

The UK Prospective Diabetes Study Group showed that aggressive treatment of type 2 diabetes mellitus could reduce all-cause mortality risk[3], regardless of whether the treatment was sulfonylurea- or insulin-based. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study on patients with type 1 diabetes mellitus[20] showed that intensive insulin therapy could reduce the risks of non-fatal myocardial infarction, stroke or death due to cardiovascular disease. The Kumamoto study of Japanese patients with type 2 diabetes mellitus[21] also showed that aggressive insulin treatment could alleviate microvascular complications, but not produce satisfactory results regarding macrovascular complications or survival. Evidence supports the efficacy and safety of early insulin treatment of type 2 diabetes mellitus, which can mitigate the prolonged glycemic burden and possibly alter the progressive course of the disease[22]. Studies have shown that high insulin persistence could reduce the related hospitalization and medical service use[10–12]. However, no study has explored the related mortality risks. The present study showed that high insulin persistence can lower all-cause mortality. A possible explanation for the survival benefit for patients with high insulin persistence might be that a high persistence of insulin treatment is accompanied by effective glucose control and few harmful effects that potentially cause organ damage and death (e.g., advanced glycation end-product accumulation, reactive oxidative stress and atherosclerosis)[3,23]. Second, insulin treatments provides anti-inflammatory and anti-oxidant benefits to protect against endothelial dysfunction and vascular diseases[24]. Third, patients

Table 2 | Incident all-cause and cause-specific mortality rates in <90 and ≥90% insulin persistence cohorts after propensity score matching

Outcome	Persistence ≥90%		Persistence <90%		Crude model		Adjusted model		After propensity score matched adjusted model‡	
	Event	IR†	Event	IR	Hazard ratio (95% confidence interval)	*P*-value	Hazard ratio (95% confidence interval)	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
All-cause	58,980	58.26	39,602	73.21	0.79 (0.78–0.80)	<0.001	0.80 (0.79–0.81)	<0.001	0.80 (0.79–0.81)	<0.001
Cause of death										
Cancer	9,556	9.44	5,979	11.05	0.86 (0.83–0.88)	<0.001	0.88 (0.85–0.91)	<0.001	0.88 (0.85–0.92)	<0.001
CAD	6,704	6.62	4,076	7.54	0.86 (0.83–0.90)	<0.001	0.84 (0.80–0.87)	<0.001	0.83 (0.79–0.86)	<0.001
Stroke	3,766	3.72	2,874	5.31	0.70 (0.66–0.73)	<0.001	0.72 (0.69–0.76)	<0.001	0.72 (0.69–0.76)	<0.001
Diabetes	16,277	16.08	10,660	19.71	0.81 (0.79–0.83)	<0.001	0.82 (0.80–0.84)	<0.001	0.82 (0.80–0.84)	<0.001
Liver disease	2,152	2.13	1,699	3.14	0.69 (0.65–0.73)	<0.001	0.85 (0.80–0.91)	<0.001	0.86 (0.80–0.92)	<0.001
Hypertension	1,273	1.26	859	1.59	0.78 (0.71–0.85)	<0.001	0.74 (0.68–0.81)	<0.001	0.71 (0.65–0.79)	<0.001
Kidney	3,808	3.76	2,310	4.27	0.86 (0.81–0.90)	<0.001	0.82 (0.78–0.86)	<0.001	0.82 (0.77–0.87)	<0.001
Accidence	1,038	1.03	786	1.45	0.70 (0.64–0.77)	<0.001	0.72 (0.65–0.79)	<0.001	0.73 (0.66–0.81)	<0.001
Suicide	453	0.45	350	0.65	0.70 (0.61–0.80)	<0.001	0.76 (0.66–0.88)	<0.001	0.75 (0.64–0.88)	<0.001
Sepsis	1,565	1.55	1,010	1.87	0.81 (0.75–0.88)	<0.001	0.81 (0.75–0.88)	<0.001	0.84 (0.77–0.91)	<0.001
Pneumonia	3,353	3.31	2,412	4.46	0.73 (0.69–0.77)	<0.001	0.74 (0.70–0.78)	<0.001	0.74 (0.70–0.78)	<0.001
Respiratory disease	1,006	0.99	779	1.44	0.68 (0.62–0.75)	<0.001	0.73 (0.67–0.81)	<0.001	0.75 (0.67–0.83)	<0.001
Other	8,029	7.93	5,808	10.74	0.73 (0.71–0.76)	<0.001	0.74 (0.72–0.77)	<0.001	0.74 (0.71–0.76)	<0.001

†Incidence rate (IR; per 1,000 people per year). ‡Adjusted for variables, including: age, sex, comorbidities, Charlson comorbidity index, Diabetes Complications Severity Index scores, outpatient department visits per year, anti-diabetic and anti-hypertensive drugs, statin and aspirin.

Table 3 | Hazard ratios for all-cause mortality rates versus different proportions of insulin persistence

Insulin persistence (%)	*n*	Crude model		Adjusted model†	
		Hazard ratio (95% confidence interval)	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
<50	73,284	1.24 (1.22–1.26)	<0.001	1.22 (1.20–1.24)	<0.001
50–69	27,262	1.29 (1.27–1.32)	<0.001	1.29 (1.26–1.32)	<0.001
70–89	22,674	1.34 (1.31–1.38)	<0.001	1.29 (1.25–1.32)	<0.001
>90	169,990	Reference		Reference	

†Adjusted for variables, including: age, sex, comorbidities, Charlson comorbidity index, Diabetes Complications Severity Index scores, outpatient department visits per year, anti-diabetic and anti-hypertensive drugs, statin and aspirin.

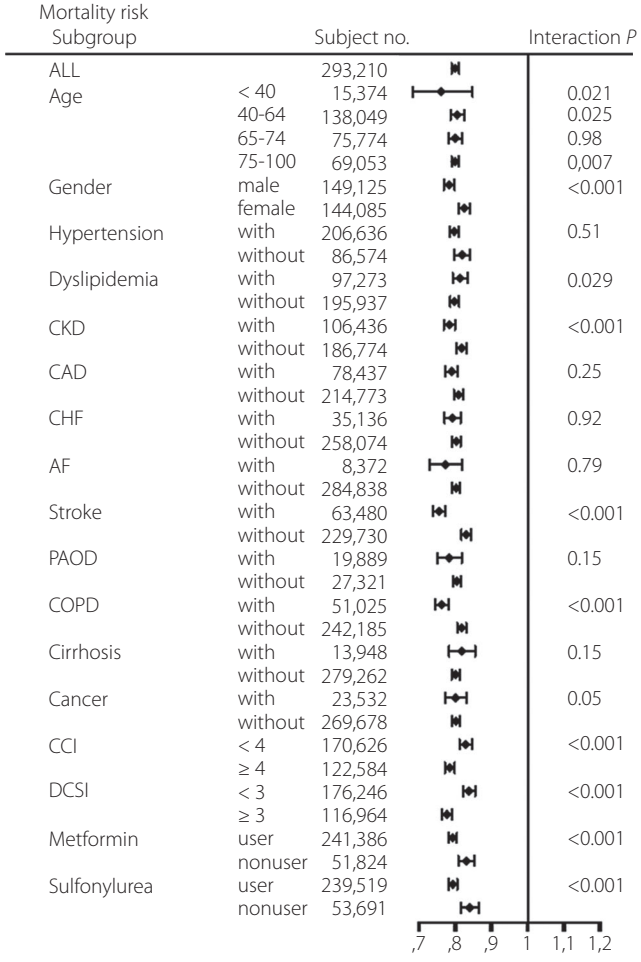

Figure 2 | Subgroup analysis. Effects of ≥90% versus <90% insulin persistence on all-cause mortality risks in patients with type 2 diabetes mellitus. AF, atrial fibrillation; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CHD, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DCSI, Diabetes Complications Severity Index; PAOD, peripheral artery occlusive disease.

with high insulin persistence are also more likely to adhere to other essential treatments[25], which might lead to effective disease control and survival[26].

The present study showed that patients with high insulin persistence had lower risks of CV and non-CV, macrovascular and microvascular, and diabetic and non-diabetic mortality than did those with low insulin persistence. Patients with high insulin persistence might have had an increased risk of severe hypoglycemia and accidents, but the present study did not find any such significant difference (incident rate of hospitalized hypoglycemia of patients with high vs low insulin persistence: 3.32 vs 3.58 per 1,000 person-years; aHR 0.98, 95% confidence interval 0.93–1.04; $P = 0.53$). Overall, patients with high insulin persistence had lower all-cause mortality risk than did patients with low insulin persistence.

Studies have shown that young persons with type 2 diabetes mellitus are more likely to have suboptimal glycemic control, be required for insulin treatment, have poorer medication adherence[26], and suffer from higher risks of cardiovascular diseases and mortality[27]. Whereas, the present study disclosed that younger patients with high insulin persistence were associated with a lower risk of mortality. Our results provide empirical evidence to encourage young patients requiring insulin therapy to remain on the treatment. The subgroup analysis also showed that sulfonylurea or metformin users with high insulin persistence had significantly lower risks of mortality than did non-users. More than 60% of the patients used basal insulin, and approximately 20% used fast-acting insulin. Continual sulfonylurea or metformin use with basal insulin might have reduced the fluctuation in blood glucose levels and provided a survival benefit. Patients with multiple comorbidities were suggested to receive less stringent treatment of type 2 diabetes mellitus[28], but the present study reported that for patients with CKD, stroke, COPD, high CCI and high DCSI, high insulin persistence was associated with a significantly lower mortality risk than for patients without such comorbidities. The patients with comorbidities who had high insulin persistence might have developed effective self-care behaviors to manage their diseases.

Within a 2-year period, 42% and 58% of patients had <90, and ≥90% insulin persistence, respectively. Therefore, we arbitrarily considered 90% insulin persistence as the demarcation point to see the difference in the mortality between patients with low and high insulin persistence. Unlike that for high drug adherence (i.e., 80% of the medicine possession ratio)[29], no recognized standard for high insulin persistence exists. Stolpe[15]

reviewed 15 studies that used the same method to measure insulin persistence. Of these, 11 also marked 90% insulin persistence as the cut-off to analyze high and low insulin persistence. In the present study, we compared all-cause mortality risks in patients with <50, 50–69, 70–89 and ≥90% insulin persistence. The mortality risk was 22–29% higher in patients with <90% insulin persistence than in those with ≥90% insulin persistence. This study suggested that all patients with low insulin persistence had higher mortality risks than did those with high insulin persistence, but without a dose relationship. Previous studies disclosed that patients with higher risk of insulin non-persistence would take more oral antidiabetic drugs[10,30]. This phenomenon might bring some beneficial effects for glycemic control although they stop insulin injection; mortality risk could therefore be attenuated to some extent. We believed the preference of taking more oral antidiabetic drugs could influence insulin persistence and also change mortality risk, leading our results to no dose–response relationship.

The present study had several clinical implications. First, the problem of non-persistence of medication has long been a predicament for chronic disease care. This study showed that high insulin persistence can provide survival benefits. This finding of the association between insulin persistence and mortality expands the literature on persistence issues and emphasizes the importance of insulin persistence in clinical practice. Second, lack of recognition or under-recognition of insulin non-persistence can have adverse consequences. Patients might experience poor glycemic control related to insulin non-persistence, but physicians might attribute this poor glycemic control to therapeutic ineffectiveness and increase the dosage of insulin or add medications. This could lead to hypoglycemia or other adverse consequences. Third, the condition of insulin injection must be considered to solve related difficulties and encourage patients to continue insulin treatment. Patients must not stop insulin injection unless they are advised by doctors to do so. Finally, if patients with the comorbidities of CKD, stroke or COPD continue insulin treatment, their mortality risks can decrease. These patients require more dedicated care, and thus, we recommend continuing insulin injections to prolong their survival.

The present study, however, had several limitations. First, the administrative database was lacking information about patients' lifestyles, including smoking or drinking habits, bodyweight and height, or blood pressure, that might influence mortality risk. Second, the dataset did not include blood test results, such as glycated hemoglobin, renal function, glucose or cholesterol levels. It also did not have the results of eye fundus or neurological examination. Third, lack of insulin persistence does not always indicate poor adherence to the recommended treatment. Patients might be advised by their doctors to stop insulin treatment due to improved glycemic control, although we excluded patients with insulin use <3 months (some of them might receive temporary [short-term] intensive insulin treatment). Some patients might stop insulin treatment after using glucagon-like peptide-1 receptor agonists, although only a few patients received glucagon-like peptide-1 receptor agonists in Taiwan during the study period (glucagon-like peptide-1 receptor agonists have been marketed in Taiwan since 2011, and constituted only 0.01% of all antidiabetic drugs prescribed in 2011, and 0.19% in 2014)[31]. Additionally, the insulin persistence of prescription did not really represent injection persistence. Patients might persistently receive the prescription of insulin, but they might not inject insulin persistently[29]. Fourth, the insulin treatment outcomes were affected by not only insulin persistence, but also insulin adherence. From the administrative claims, examining the timing, dosage and frequency of insulin injection was difficult, and thus the influence of insulin adherence on mortality risk could not be evaluated. Fifth, observational studies are always subject to indication bias, implying that treatments might have been selected by the preference of clinicians or patients. We attempted to balance variables between the two comparison groups by applying propensity score matching. Finally, several inevitable biases might have existed in the cohort study, and randomized control studies are warranted to verify our results.

Owing to the progressive nature of type 2 diabetes mellitus, insulin typically becomes necessary for patients to achieve and maintain their glycemic targets. After engaging patients in the decision to receive insulin, providers might encourage them to inject insulin persistently to lower all-cause mortality risks.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Kaplan–Meier survival curves according to different insulin persistence.