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Metformin and endometrial cancer risk in Chinese women with type 2 diabetes mellitus in Taiwan

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HIGHLIGHTS

- This study evaluated the effects of metformin use on endometrial cancer risk.
- The overall hazard ratio adjusted for propensity score was 0.675 (0.614–0.742).
- An inverse dose–response relationship was also observed.

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ABSTRACT

Objective. To evaluate metformin effects on endometrial cancer risk in Chinese female patients with type 2 diabetes mellitus (T2DM) in Taiwan.

Methods. This is a retrospective cohort analysis using the National Health Insurance database of Taiwan. Female patients with newly diagnosed T2DM and without endometrial cancer in 1998–2002 were followed to end of 2009 ($n = 478{,}921$). Among them, 285,916 were never-users and 193,005 were ever-users of metformin. A time-dependent approach was used to calculate endometrial cancer incidence and estimate hazard ratios by Cox regression for ever-users, never-users, and subgroups of metformin exposure (tertiles of cumulative duration and cumulative dose). Sensitivity analyses were conducted in various subgroups.

Results. During follow-up, 728 metformin ever-users and 2157 never-users developed endometrial cancer, representing an incidence of 60.00 and 121.69 per 100,000 person-years, respectively. The overall hazard ratio (95% confidence intervals) for ever- versus never-users after adjustment for propensity score (PS) was 0.675 (0.614–0.742). The PS-adjusted hazard ratios for the first, second, and third tertiles of cumulative duration of metformin therapy were 1.089 (0.966–1.228), 0.707 (0.616–0.812) and 0.313 (0.262–0.374), respectively (P-trend < 0.0001); and 1.062 (0.942–1.197), 0.620 (0.538–0.715) and 0.376 (0.317–0.447), respectively (P-trend < 0.0001), for cumulative dose of metformin. The dose–response relationship was demonstrated in various models and an overall reduced risk was consistently supported by sensitivity analyses.

Conclusions. The use of metformin in women with T2DM was associated with an overall significantly lower risk of endometrial cancer with dose–response relationship.

1. Introduction

The incidence of endometrial cancer is increasing worldwide [1,2], but it is more common in developed countries than in less developed countries, with respective age-standardized incidence of 12.9 and 5.9 per 100,000 population in 2008 [1].

Age and obesity are well recognized risk factors for endometrial cancer; while late menarche, early age at first birth, parity, the use of oral contraceptive and cigarette smoking are associated with a lower risk [3,4]. Studies suggest an increasing epidemic of obesity worldwide [5] and there is a linear relationship between body mass index and endometrial cancer risk [6]. Therefore the increasing epidemic of obesity may be responsible for the increasing incidence of endometrial cancer [4].

Whether metformin may reduce endometrial cancer risk in humans has rarely been studied. In a recent meta-analysis [7], the odds ratio (95% confidence interval) for endometrial cancer associated with metformin use was 0.90 (0.80–1.20) in one observational study [8] and was 0.87 (0.36–2.14) derived from two randomized controlled trials [9]. A case–control study using the UK-based General Practice

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Research Database suggested that ever- versus never-users of metformin had a lower but non-significant risk of endometrial cancer (odds ratio 0.86, 95% confidence interval = 0.63–1.18) [10]. Another recent retrospective cohort analysis using the US healthcare claims of the Truven Health Analytics' MarketScan® and Medicare supplemental databases showed a crude hazard ratio of 0.81 (95% confidence interval = 0.67–0.97) and an adjusted hazard ratio of 1.09 (95% confidence interval = 0.88–1.35) [11]. Therefore, the risk of endometrial cancer associated with metformin use is inconclusive.

The present study aimed at evaluating whether metformin use in the Chinese women with type 2 diabetes mellitus (T2DM) in Taiwan would affect the risk of endometrial cancer. Specifically, the reimbursement database of the National Health Insurance (NHI) was used and a new-user design and time-dependent approach for metformin use in data analyses were applied to minimize the potential "prevalent user bias" [12] and "immortal time bias" [13,14]. "Prevalent user bias" results from the inclusion of prevalent drug users, which may lead to biased estimates because prevalent users are survivors of early pharmacotherapy but risk may vary with time [12]. "Immortal time" refers to a period of follow-up during which the outcome could not occur [13,14]. This may result when the exposure is misclassified such that the person-times in the exposed and unexposed are miscalculated leading to biased estimates [13,14].

2. Methods

The planned analysis of the reimbursement database of all patients with a diagnosis of T2DM during the period from 1996 to 2009 was approved by the ethic review board of the National Health Research Institutes (approval number: 99274).

According to local regulations, the NHI database can be used for academic research after the approval by an ethic review board. For the protection of personal privacy, the identification information of the individuals was scrambled before the release of the database. The *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) has been used during the study period and diabetes was coded as 250.XX and endometrial cancer as 182.

In Taiwan, physicians always follow the recommendation of the American Diabetes Association for the diagnosis of diabetes mellitus. Because major changes in the diagnostic criteria have been recommended in 1997 [15], the recruitment of patients into the study started after 1998 to minimize the impact of changes in diagnostic criteria. According to the 1997 recommendations, diabetes is diagnosed based on one of the following criteria: 1) symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dL; 2) fasting plasma glucose ≥126 mg/dL; or 3) 2-hour plasma glucose ≥200 mg/dL during a 75-g oral glucose tolerance test [15].

Fig. 1 shows the procedures in creating a cohort of female patients with newly-onset T2DM at entry during 1998–2002 for the study. Male patients and patients with a diagnosis of diabetes at outpatient clinics during 1996 and 1997 were first excluded. This yielded 494,481 female patients. After further excluding patients with type 1 diabetes mellitus (n = 1189), those with a diagnosis of endometrial cancer before the diagnosis of diabetes (n = 1669), those with a duplicated identification number (n = 35), unclear information on date of birth or sex (n = 7366), or a follow-up duration of less than 180 days (n = 11,095), 478,921 patients with a diagnosis of newly-onset T2DM during 1998–2002 were identified.

The age-standardized (to the 2000 World Health Organization population) incidence of endometrial cancer among the diabetic

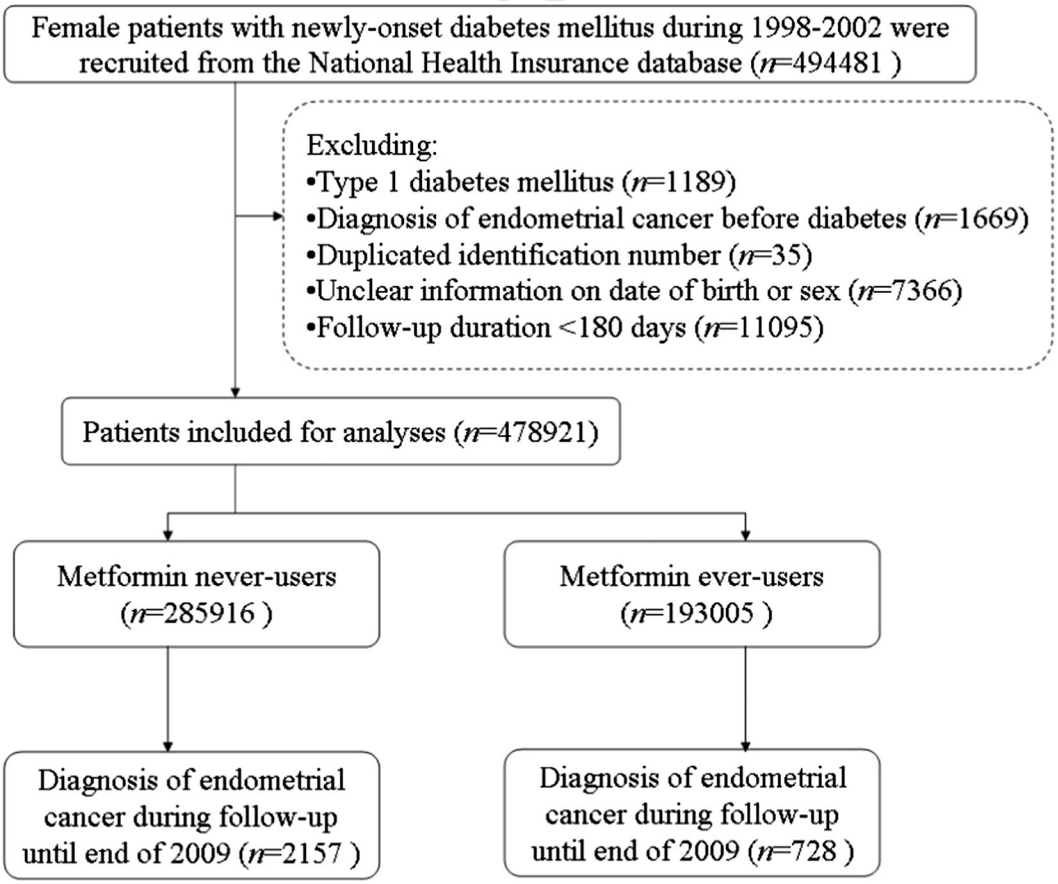

Fig. 1. Flowchart showing the procedures followed in creating a cohort of female patients with newly-onset type 2 diabetes mellitus during 1998–2002.

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cohort was calculated in order to compare with those reported for the general population in the literature.

Patients who had ever been prescribed metformin after entry were defined as ever-users (n = 193,005, 40.3%); never-users (n = 285,916, 59.7%) were defined as those who had never been prescribed metformin. Cumulative duration (months) and cumulative dose (mg) of metformin use were calculated from the database. Cumulative duration was measured by accumulating the days of metformin prescriptions in all visits within the study period and was expressed in months of exposure by dividing the accumulated number of days of metformin prescriptions by 30. Cumulative dose was calculated by summating the total doses of metformin in mg prescribed during the study period. To evaluate a potential dose–response relationship, tertiles of cumulative metformin duration and dose were used for analyses. Exposure to other oral antidiabetic drugs (sulfonylurea, acarbose, pioglitazone, and rosiglitazone) and insulin was also similarly defined for ever-users and never-users.

A number of comorbidities and covariates were determined as a status/diagnosis at the time of entry. These have been described in detail previously [16–18] and included nephropathy, hypertension, chronic obstructive pulmonary disease (a surrogate for smoking), stroke, ischemic heart disease, peripheral arterial disease, eye disease, obesity, dyslipidemia, urinary tract disease, and other cancers. Other medications included statin, fibrate, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, calcium channel blocker, aspirin, ticlopidine, clopidogrel, dipyridamole and non-steroidal anti-inflammatory drugs (excluding aspirin).

Follow-up started on the first day of diabetes diagnosis and ended on 31 December 2009, at the time of a new diagnosis of endometrial cancer, or at the date of the last reimbursement record. In the lack of information on the vital status of the patients, the last reimbursement record may serve as a surrogate for interval death because patients who die should be withdrawn from the NHI in Taiwan. Exposure to metformin was treated as a time-dependent variable. Therefore, the metformin ever-users contributed person-years to the non-metformin group until they started using metformin, and after starting metformin, to the metformin group.

The baseline characteristics of metformin never-users and ever-users were compared by Student's t test for age and by Chi-square test for others. The crude incidence density of endometrial cancer was calculated for metformin ever-users and never-users and for the different exposure subgroups (primary analyses). The numerator for the incidence was the number of patients with incident endometrial cancer during follow-up, and the denominator was the person-years of follow-up. To examine whether short term use of metformin or short duration of follow-up might affect the estimation of the incidence of endometrial cancer, the incidences for the various metformin exposure subgroups were recalculated after excluding patients who had a cumulative duration of metformin use <180 days, and after excluding patients who had a follow-up duration <2 years in either the use or the non-use period of metformin, respectively (sensitivity analyses).

Time-dependent Cox proportional hazards regression was performed to estimate the hazard ratios for endometrial cancer among metformin ever-users versus never-users, and for the various dose–response parameter subgroups. The following models I to IV were created.

Model I considered the adjustment for all variables compared previously as baseline characteristics between ever-users and never-users (fully adjusted).

Model II were adjusted for propensity score (PS-adjusted) derived from the baseline characteristics, to reduce the potential biased estimates resulting from the systematic differences between treatment groups in nonrandomized studies [19].

Model III were adjusted for PS after excluding patients who used antidiabetic drugs other than metformin, in order to create a "cleaner" comparison for metformin only versus diabetic patients without the use of antidiabetic drugs. The exclusion of patients using the other antidiabetic drugs was based on the following considerations. First, metformin is always considered as the first-line treatment, therefore the uses of other antidiabetic drugs were not independent of prior use of metformin. Second, the uses of other antidiabetic drugs were also time-dependent and biased estimates may result from time-dependent confounders which are themselves affected by prior exposure to the drug under investigation [20]. Therefore, it would be too simple to treat the other antidiabetic drugs as simple yes/no covariates [20]. Third, in prior analyses, models were created to estimate hazard ratios for metformin ever-users versus never-users either unadjusted or adjusted for one variable at a time. It was noted that hazard ratios for adjusted variables other than antidiabetic drugs ranged from 0.41 to 0.42, which was very similar to the unadjusted hazard ratio of 0.41. However, the hazard ratios after adjustment for other antidiabetic drugs ranged from 0.47 to 0.51, suggesting that the use of other antidiabetic drugs might pose a confounding effect.

Models IV were adjusted for PS after excluding patients who had been followed for <2 years during the non-use or the use period of metformin, to allow a 2-year "washout" period because detection time bias might occur during the transition of diabetes from diet or lifestyle modification or non-metformin antidiabetic treatment (most of these drugs may cause body weight gain) to commencement with metformin (which can cause weight reduction).

The following sensitivity analyses were conducted to estimate the PS-adjusted hazard ratios for ever- versus never-users of metformin: 1) dropping all other antidiabetic drugs as covariates, because their uses were also time-dependent and might be affected by prior exposure to metformin; 2) dropping obesity as a covariate, because a huge underestimation of obesity was noted in our previous studies when using the ICD-9-CM codes for the diagnosis of obesity [21,22] and this might potentially distort the estimates; 3) excluding patients with a cumulative duration of metformin use <180 days, because these patients might have used metformin briefly and came off it; 4) excluding users of insulin, because exogenous insulin may affect the development and progression of some cancers [23] and its use is always preserved for patients whose blood glucose cannot be adequately controlled by oral antidiabetic drugs in Taiwan, indicating a more severe diabetes condition; and 5) excluding age <50 years, because endometrial cancer is mainly diagnosed after menopause and only 15% of the patients with endometrial cancer are diagnosed before the age of 50 years [4]. Age was adjusted for as a continuous variable in the models.

Analyses were conducted using SAS statistical software, version 9.3 (SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant.

3. Results

The age-standardized incidence of endometrial cancer calculated from the diabetic cohort was 97.0 per 100,000.

Table 1 summarizes the baseline characteristics between metformin ever-users (n = 193,005) and never-users (n = 285,916). With the exception of rates of ticlopidine and clopidogrel use, all baseline characteristics differed significantly between the two groups.

Table 2 lists endometrial cancer incidence in metformin ever-users and never-users, and among the different tertiles of the dose–response parameters. The incidences of endometrial cancer in metformin ever-users and never-users were 60.00 and 121.69 per 100,000 person-years, respectively, in the primary analyses. With longer cumulative duration and higher cumulative dose, the incidence decreased correspondingly. The accumulated person-years for the 63,618 patients in the first tertile of cumulative duration of metformin use <14.7 months was 277,598.81 in the primary analysis. The large person-years did not include many prior years of non-use before commencement of metformin because these person-years from metformin ever-users before the commencement of metformin were accumulated to the person-years in the never-users. On the other hand, the large

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Table 1
Baseline characteristics of never-users and ever-users of metformin.

Variables	Metformin				*P*
	Never-users		Ever-users		
	n	%	*n*	%	
n = 478,921	285,916		193,005		
Age (years)[a]	54.93	16.68	56.55	12.29	<0.0001
Hypertension	34,640	12.12	34,543	17.90	<0.0001
Chronic obstructive pulmonary disease	7661	2.68	3789	1.96	<0.0001
Stroke	8068	2.82	4524	2.34	<0.0001
Nephropathy	12,908	4.51	3379	1.75	<0.0001
Ischemic heart disease	8600	3.01	6111	3.17	0.0018
Peripheral arterial disease	3428	1.20	2159	1.12	0.0111
Eye disease	741	0.26	695	0.36	<0.0001
Obesity	1062	0.37	1096	0.57	<0.0001
Dyslipidemia	42,092	14.72	23,834	12.35	<0.0001
Urinary tract disease	14,469	5.06	11,066	5.73	<0.0001
Other cancers	18,194	6.36	7637	3.96	<0.0001
Statin	2633	0.92	3798	1.97	<0.0001
Fibrate	2341	0.82	5461	2.83	<0.0001
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	10,523	3.68	14,989	7.77	<0.0001
Calcium channel blocker	11,819	4.13	12,447	6.45	<0.0001
Sulfonylurea	32,078	11.22	174,013	90.16	<0.0001
Insulin	5390	1.89	44,491	23.05	<0.0001
Acarbose	3366	1.18	57,109	29.59	<0.0001
Pioglitazone	965	0.34	35,934	18.62	<0.0001
Rosiglitazone	1371	0.48	38,692	20.05	<0.0001
Aspirin	6151	2.15	6496	3.37	<0.0001
Ticlopidine	312	0.11	193	0.10	0.3399
Clopidogrel	25	0.01	19	0.01	0.6967
Dipyridamole	6003	2.10	5151	2.67	<0.0001
Non-steroidal anti-inflammatory drugs (excluding aspirin)	50,796	17.77	33,003	17.10	<0.0001

[a] Age is expressed as mean and standard deviation.

Table 2
Incidence of endometrial cancer by metformin exposure.

Metformin use	Case number observed	Incident cases of endometrial cancer	Person-years	Incidence rate (per 100,000 person-years)
Primary analyses				
Never-users	446,307	2157	1,772,593.70	121.69
Ever-users	193,005	728	1,213,341.39	60.00
Cumulative duration (months)				
Never-users	446,307	2157	1,772,593.70	121.69
<14.70	63,618	336	277,598.81	121.04
14.70–46.33	63,748	252	383,406.56	65.73
>46.33	65,639	140	552,336.03	25.35
Cumulative dose (mg)				
Never-users	446,307	2157	1,772,593.70	121.69
<407,000	63,685	336	277,181.07	121.22
407,000–1,530,000	63,659	233	387,978.82	60.05
>1,530,000	65,661	159	548,181.50	29.00
Sensitivity analyses				
1. Excluding cumulative duration of metformin use <180 days				
Never-users	446,307	2157	1,772,593.70	121.69
Ever-users	186,106	664	1,172,539.75	56.63
Cumulative duration (months)				
Never-users	446,307	2157	1,772,593.70	121.69
<14.70	56,719	272	236,797.16	114.87
14.70–46.33	63,748	252	383,406.56	65.73
>46.33	65,639	140	552,336.03	25.35
Cumulative dose (mg)				
Never-users	446,307	2157	1,772,593.70	121.69
<407,000	56,790	272	236,389.82	115.06
407,000–1,530,000	63,655	233	387,968.42	60.06
>1,530,000	65,661	159	548,181.50	29.00
2. Excluding follow-up duration <2 years				
Never-users	268,368	1497	1,674,022.57	89.43
Ever-users	170,641	550	1,185,925.84	46.38
Cumulative duration (months)				
Never-users	268,368	1497	1,674,022.57	89.43
<14.70	44,420	186	255,417.99	72.82
14.70–46.33	60,583	224	378,173.74	59.23
>46.33	65,638	140	552,334.11	25.35
Cumulative dose (mg)				
Never-users	268,368	1497	1,674,022.57	89.43
<407,000	44,738	190	255,038.46	74.50
407,000–1,530,000	60,252	201	382,723.22	52.52
>1,530,000	65,651	159	548,164.16	29.01

person-years were due to the contribution from many patients who had used metformin for a short period of time and discontinued to take the drug, and from those who had been followed for a short duration of <2 years (Sensitivity analyses, Table 2). The exclusion of these short term users of metformin (i.e., cumulative duration of metformin use <180 days) or those followed for <2 years actually did not change the negative dose–response relationship between metformin use and endometrial cancer incidence (Sensitivity analyses, Table 2).

Table 3 shows the adjusted hazard ratios for endometrial cancer with regard to metformin exposure in models I to IV. For the overall hazard ratios comparing ever-users versus never-users, there was a significantly lower risk of endometrial cancer associated with metformin use in all models. In all dose–response analyses there was a significant trend of reduced risk of endometrial cancer with increasing cumulative duration or cumulative dose of metformin use. In the fully adjusted models (model I), although a significantly reducing risk was observed with increasing cumulative duration and cumulative dose of metformin use (*P*-trends < 0.0001), only the third tertiles showed significantly reduced risk. The first tertiles of the dose–response parameters showed a significantly higher risk associated with metformin use, and the second tertiles showed a neutral association in the fully adjusted models (model I). In the other models that adjusted for PS, the first tertiles either showed a neutral effect (models II and III) or a protective effect (model IV); and all the second and third tertiles showed a significantly reduced risk of endometrial cancer (models II, III and IV).

The various sensitivity analyses consistently showed a reduced risk of endometrial cancer for metformin ever-users versus never-users (Table 4). The hazard ratio estimated after dropping all other antidiabetic drugs as covariates seemed to deviate from those derived from other models, supporting that the inclusion of the use of other antidiabetic drugs in the model did remarkably affect the hazard ratios. However, this would not affect the conclusion of a protective effect of metformin on endometrial cancer risk.

4. Discussion

In consistence with previous reports showing a higher risk of endometrial cancer in diabetes versus non-diabetes people [24], the age-standardized incidence of endometrial cancer of 97.0 per 100,000 calculated from this diabetic cohort was much higher than the reported age-standardized incidence ranging from 5.9 to 12.9 per 100,000 in the general population of different countries [1], and also higher than the reported age-standardized incidence of 20.4 per 100,000 in the UK [25].

This study is the first to show an inverse association between metformin use and endometrial cancer risk in Chinese female patients with T2DM in Taiwan. The protective effect of metformin was consistent in various models with a dose–response relationship (Tables 2 and 3) and in the sensitivity analyses (Table 4).

Both the UK study [10] and the US study [11] did not support a protective effect of metformin. Ethnicity differences might partly

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Table 3
Metformin exposure and hazard ratios for incident endometrial cancer.

Metformin use	Model I (fully adjusted)			Model II (PS-adjusted)			Model III (PS-adjusted)			Model IV (PS-adjusted)		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Ever-users	0.842	(0.761–0.931)	<0.0001	0.675	(0.614–0.742)	<0.0001	0.723	(0.573–0.911)	0.0060	0.556	(0.498–0.621)	<0.0001
Cumulative duration (months)												
<14.70	1.361	(1.186–1.561)	<0.0001	1.089	(0.966–1.228)	0.1630	1.111	(0.865–1.426)	0.4118	0.744	(0.636–0.870)	0.0002
14.70–46.33	1.057	(0.908–1.229)	0.4754	0.707	(0.616–0.812)	<0.0001	0.360	(0.193–0.671)	0.0013	0.667	(0.574–0.775)	<0.0001
>46.33	0.404	(0.337–0.484)	<0.0001	0.313	(0.262–0.374)	<0.0001	0.097	(0.024–0.388)	0.0010	0.327	(0.272–0.393)	<0.0001
P-trend			<0.0001			<0.0001			<0.0001			<0.0001
Cumulative dose (mg)												
<407,000	1.338	(1.165–1.536)	<0.0001	1.062	(0.942–1.197)	0.3236	0.998	(0.775–1.285)	0.9873	0.737	(0.631–0.860)	0.0001
407,000–1,530,000	0.884	(0.757–1.032)	0.1182	0.620	(0.538–0.715)	<0.0001	0.371	(0.205–0.673)	0.0011	0.569	(0.487–0.665)	<0.0001
>1,530,000	0.482	(0.405–0.573)	<0.0001	0.376	(0.317–0.447)	<0.0001	0.154	(0.038–0.615)	0.0081	0.393	(0.329–0.469)	<0.0001
P-trend			<0.0001			<0.0001			<0.0001			<0.0001

Referent group: never-users of metformin; HR: hazard ratio, CI: confidence intervals; PS: propensity score.
Model I: Adjusted for all variables in Table 1.
Model II: Adjusted for PS derived from all variables in Table 1.
Model III: These models compared patients treated with metformin only versus patients without antidiabetic drugs after excluding patients who used antidiabetic drugs other than metformin.
Model IV: These models were created after excluding patients who had been followed for <2 years during the non-use or use period of metformin to allow a "washout" period to reduce detection time bias.

explain the different findings. The UK study used the UK-based General Practice Research Database, which contained the healthcare data on some 7 million individuals attended by general practitioners in the UK. The results might well be applied to the white people because they represented 92% of the individuals living there [10]. The US study used the Truven Health Analytics' MarketScan® and Medicare supplemental databases [11], with data of some 129 million individuals covered by employer-based insurance [11]. Although no information on the ethnicities was available in this US study, the majority of the patients might be either white or African Americans because they represent 72.4% and 12.6%, respectively, of the total US population in 2010 [26]. Asian Americans represent only 4.8% of the US population [26]. Therefore, the lack of a protective effect of metformin in either the UK study or the US study could not be immediately applied to the Asian populations. The patients recruited into the present study are more homogeneous in terms of ethnicity because Chinese Han represents approximately 98% of the total population living in Taiwan [27].

There may also be some other explanations for the lack of a protective effect of metformin in either the UK study [10] or the US study [11]. The UK study used a case–control design by including 2554 cases with incident endometrial cancer and 15,324 matched controls in the main analyses [10]. The investigators tried to evaluate a dose–response relationship by comparing 1–24 and ≥25 prescriptions versus no prior use. The adjusted odds ratio (95% confidence interval) was 0.92 (0.65–1.31) and 0.79 (0.54–1.17), respectively. Although none of the odds ratios was significant, a trend of decreasing risk with increasing prescriptions of metformin was observed. The investigators conducted additional subgroup analyses in patients with diabetes, including only 291 cases with endometrial cancer and 1746 controls. The adjusted odds ratio for 1–24 and ≥25 prescriptions versus no prior use was 0.88 (0.61–1.25) and 0.88 (0.58–1.32), respectively. The small numbers of cases and controls in the diabetes subgroup did not provide sufficient power for evaluating the risk in this specific group of patients. Although not statistically significant, diabetic patients who used metformin did show a 12% risk reduction. Furthermore, the UK study could not exclude prevalent user bias related to metformin use.

Similar to the present study, the US study [11] used a retrospective cohort analysis and attempted to minimize the prevalent user bias and immortal time bias. Over a median follow-up of 1.2 years (interquartile range: 0.4–2.3), the investigators showed a significantly protective effect of metformin in the unadjusted model [hazard ratio (95% confidence interval) = 0.81 (0.67–0.97)], but not in the adjusted model [hazard ratio (95% confidence interval) = 1.09 (0.88–1.35)]. In this US study, no dose–response analysis was performed, and the follow-up information suggested that only approximately one quarter of the patients had been followed for >2 years. Because a cumulative duration of >2 years may be required to demonstrate a protective effect of metformin on endometrial cancer (Table 3), the lack of dose–response analysis and the small number of patients with a follow-up duration >2 years might have explained the lack of a protective effect of metformin in the US study [11].

Endometrial cancers can be divided into type I (endometrioid) and type II (non-endometrioid), which are estrogen-dependent and estrogen-independent, respectively [3]. Only approximately 6% of the tumors are type II [3]. Type I tumors are more correlated with obesity [3] and therefore may be more "susceptible" to the protective effect of metformin because of its weight losing effect. However, because diabetic patients with type II cancer who used metformin might have a better survival than those who did not use metformin and patients with type II cancer but without diabetes [28], metformin may exert beneficial effects in both type I and type II cancers. Neither the previous studies from the UK [10] and the US [11] nor the present study could differentiate between type I and type II cancers. Because gynecologists may like to know what types of endometrial cancer the administration of metformin could reduce, the lack of the histopathological types of endometrial cancer can be an important limitation of these studies using big databases.

A slightly but significantly higher risk for the first tertiles of the cumulative duration and cumulative dose of metformin was shown in the fully adjusted models (model I, Table 3). This might be due to biased estimates resulting from the different baseline characteristics between metformin ever-users and never-users (Table 1), as such increased risk attenuated and became non-significant when the models were

Table 4
Sensitivity analyses for metformin and incident endometrial cancer.

Model	PS-adjusted HR[a] (95% CI)	*P*
Dropping all other antidiabetic drugs as covariates	0.420 (0.384–0.459)	<0.0001
Dropping obesity as a covariate	0.676 (0.615–0.744)	<0.0001
Excluding cumulative duration of metformin use <180 days	0.633 (0.574–0.699)	<0.0001
Excluding users of insulin	0.679 (0.615–0.749)	<0.0001
Excluding age <50 years	0.683 (0.604–0.773)	<0.0001

HR: hazard ratio, CI: confidence interval, PS: propensity score.
[a] Hazard ratios were estimated for ever-users versus never-users of metformin.

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adjusted for PS (model II, Table 3). Early users of metformin might have a higher risk of endometrial cancer which was carried over from the diet control/lifestyle modification period to the early phase of metformin therapy. The analyses allowing a 2-year "washout" (model IV, Table 3) supported such an explanation. Additionally, because metformin is always prescribed for patients with obesity (Table 1), a residual confounding of obesity in early metformin users is also possible.

There is a 2–3 fold difference in the incidences and hazard ratios between the second and the third tertiles of cumulative duration of metformin use (e.g., from 14.7–46.3 months to >46.3 months, Tables 2 and 3). Such an extraordinary reduction in risk might be due to bias of an uncertain nature. One explanation is the weight reduction effect of metformin in patients who had been using it for a longer duration in comparison to a referent group who mainly used other antidiabetic drugs that may cause weight gain (e.g., sulfonylurea, rosiglitazone, pioglitazone and insulin). Future studies are required to verify this hypothesis and to confirm whether the risk reduction effect of metformin can be independent of its weight losing effect.

Some potential adverse effects related to short-term or long-term use of metformin may affect the prescription of the drug and the continuation of its use. For example, gastrointestinal side effects are very common at the initiation of metformin [29]. Patients with preexisting gastrointestinal symptoms may be less likely to be given metformin, and patients who develop intolerable gastrointestinal symptoms after its use may not be kept on using this drug for a long duration. Metformin has also been known for a rare but severe side effect of lactic acidosis, especially when it is prescribed in patients with certain medical conditions characterized by liver or kidney disease, or by a low oxygen level in the blood (e.g. recent stroke or myocardial infarction and congestive heart failure) [29]. With marked elevation of blood glucose or long duration of diabetes, metformin may not be able to lower glucose level with sufficient power, and it may be discontinued or other more potent drugs will be added. Vitamin B12 deficiency has also been reported in 5.8 to 33% of patients using metformin for a long duration [30]. A recent study in Australia suggested that metformin use may be associated with impaired cognitive performance, probably due to vitamin B12 deficiency [31]. Therefore, a lack of information on these adverse effects may potentially lead to undetected selection bias.

The present study has several strengths. First, it has merits of a large sample size recruited from the whole nation, which avoided the chance of sampling error. Second, for complete ascertainment, endometrial cancer was obtained from claim records in various sources including outpatient visits, emergency department visits, and hospital admission. Third, the detection rate of endometrial cancer would not tend to differ among different socioeconomic classes because patients with cancer can be waived for most medical co-payments in the NHI. Fourth, bias from self-reporting could be prevented by the use of medical records.

Some limitations of the study deserve mentioning. It is certainly incorrect that only a very small proportion (<1%) of the patients was obese (Table 1). According to our previous epidemiological study, the prevalence of obesity in women with T2DM defined by a body mass index $\geq$30 kg/m^2 and $\geq$25 kg/m^2 was 8.4% and 41.7%, respectively [32]. A lack of actual measurement of anthropometric factors for evaluating the effect of different degrees of obesity is a limitation.

Family history and genetic factors may contribute to a higher risk of endometrial cancer [4,33,34], but physical activity [35] and intakes of coffee [36] and flavonoids [37] may protect against endometrial cancer. Because of lack of information, the potential confounding of these factors could not be evaluated. Other limitations included a lack of actual measurement for biochemical data (e.g., glucose, insulin, C-peptide and insulin-like growth factors) and hormonal and inflammatory factors [38], and a lack of information on reproductive history, menopausal status, past history of oligomenorrhea and amenorrhea (and hence the risk for polycystic ovary syndrome, another risk factor of endometrial cancer) [39], and the pathology, grading, and staging of endometrial cancer. Finally, because this is an observational study, bias or residual confounding may not be completely excluded.

In conclusions, metformin use in the Chinese female patients with T2DM in Taiwan is associated with an overall risk reduction of endometrial cancer. Since obesity is a major risk factor for endometrial cancer, the lack of data of body mass index is a major limitation. The protective effect of metformin should better be confirmed in future studies taking full consideration of body weight changes associated with various antidiabetic drugs.

Conflict of interest

None.

Ethics approval statement

The study was approved by the ethic review board of the National Health Research Institutes (registered approval number: 99274).

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