Association between metformin use and risk of total joint replacement in patients with type 2 diabetes: a population-based matched cohort study

Zhaohua Zhu[1#], PhD; Jing-Yang Huang[2,3#], PhD; Guangfeng Ruan[1#], MD; Peihua Cao[1#], PhD; Shibo Chen[1], MMed;

Yan Zhang[1], PhD; Weiyu Han[1], MD, PhD; Tianyu Chen[1], MD; Xiaoyan Cai[4], MD; Jia Liu[5], MD; Yujin Tang[5], MD;

Na Yu[4], MD; Qian Wang[1], MD, PhD; David J Hunter[1,6], MD, PhD; James Cheng-Chung Wei[3,7,8,9*], MD, PhD;

Changhai Ding[1,4,5,10*], MD, PhD

Affiliations:

[1]Clinical Research Centre, Orthopedic Centre, Zhujiang Hospital, Southern Medical University, Guangzhou, China

[2]Department of Medical Research, Chung Shan Medical University Hospital, Taichung, Taiwan

[3]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan

[4]Department of Rheumatology, Guangzhou First People's Hospital, School of Medicine, South China University of Technology,

Guangzhou, China

[5]Department of Orthopaedics, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China

[6]Department of Rheumatology, Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of

Sydney, Sydney, Australia

[7]Department of Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan [8]Graduate Institute of Integrated Medicine,

China Medical University, Taichung, Taiwan

[9]Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan

[10]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

[#]These authors contributed equally.

*Correspondence: C. Ding. E-mail: Changhai.Ding@utas.edu.au and JCC. Wei. E-mail: jccwei@gmail.com

Supplementary Table 1. Associations of metformin use with osteoarthritis-related total joint replacement

	Prescription time-distribution matching cohort		Propensity score matching cohort	
	Non-Metformin n=20347	Metformin n=20347	Non-Metformin n=10163	Metformin n=10163
OA-related TKR or THR				
Number of event	493	398	241	200
Incidence rate*(95% CI)	4.42 (4.05-4.83)	3.15 (2.86-3.48)	4.51 (3.97-5.11)	3.35 (2.92-3.85)
Crude HR (95% CI)	Reference	**0.72 (0.63-0.82)**	Reference	**0.74 (0.62-0.90)**
aHR[†] (95 % CI)	Reference	**0.72 (0.62-0.85)**	Reference	**0.73 (0.61-0.89)**
Competing outcome[$] aHR (95% CI)	Reference	**0.81 (0.69-0.95)**	Reference	**0.80 (0.66-0.97)**
IPTW[#] aHR (95% CI)	Reference	**0.67 (0.54-0.83)**		
OA-related TKR				
Number of event	449	367	226	182
Incidence rate*(95% CI)	4.03 (3.67-4.42)	2.91 (2.62-3.22)	4.23 (3.71-4.81)	3.05 (2.64-3.53)
Crude HR (95% CI)	Reference	**0.72 (0.63-0.83)**	Reference	**0.72 (0.59-0.88)**
aHR[†] (95 % CI)	Reference	**0.73 (0.62-0.85)**	Reference	**0.71 (0.59-0.87)**
Competing outcome[$] aHR (95% CI)	Reference	**0.81 (0.69-0.96)**	Reference	**0.78 (0.64-0.95)**
IPTW[#] aHR (95% CI)	Reference	**0.66 (0.53-0.83)**		
OA-related THR				
Number of event	44	31	15	18
Incidence rate*(95% CI)	0.39 (0.29-0.53)	0.25 (0.17-0.35)	0.28 (0.17-0.47)	0.30 (0.19-0.48)
Crude HR (95% CI)	Reference	0.63 (0.40-1.00)	Reference	1.09 (0.55-2.17)
aHR[†] (95 % CI)	Reference	0.73 (0.43-1.26)	Reference	1.05 (0.53-2.09)
Competing outcome[$] aHR (95% CI)	Reference	0.81 (0.48-1.37)	Reference	1.14 (0.57-2.28)
IPTW[#] aHR (95% CI)	Reference	0.82 (0.47-1.43)		

* Incidence rate, per 10000 person-months.

[†]The co-variates included demographic variables (sex, age, urbanization, and insurance type), score of adapted Diabetes Complication Severity Index, comorbidities, medications for pain management, and other oral antihyperglycemic agents at baseline.

$^{$}$When defined death, admission for lower limb fracture, amputation or non-OA related total joint replacement as competing-events. OA-related events included TKR or THR with primary diagnosis of ICD codes: 715.x. Non-OA-related events included TKR or THR with primary diagnosis of ICD codes: 733.x, 996.x, 716.x, 714.x, 274.x, 730.x, 755.x, 821.x, 711.x, 720.x, 736.x, 754.x, 820.x. OA, osteoarthritis; aHR, adjusted hazard ratio; TKR, total knee replacement; THR, total hip replacement; IPTW, inverse probability of treatment weighting.

$^{#}$Balance diagnostics showed that covariates were well balanced between groups after IPTW.

Bold denotes statistical significance.

Supplementary Table 2. The primary diagnosis when admission for total knee replacement, n=985

ICD-9		n
715.3	Osteoarthrosis, localized, not specified whether primary or secondary	815
733.4	Aseptic necrosis of bone	50
715.1	Osteoarthrosis, localized, primary	34
715.9	Osteoarthrosis, unspecified whether generalized or localized	31
715.2	Osteoarthrosis, localized, secondary	11
996.4	Mechanical complication of internal orthopedic device, implant, and graft	9
714.0	Rheumatoid arthritis	7
716.1	Traumatic arthropathy	7
274.0	Gouty arthropathy	4
730.1	Chronic osteomyelitis	3

755.6	Other anomalies of lower limb, including pelvic girdle	3
733.8	Malunion and nonunion of fracture	2
821.0	Shaft or unspecified part, closed	2
711.0	Pyogenic arthritis	1
716.9	Arthropathy, unspecified	1
720.0	Ankylosing spondylitis	1
736.3	Acquired deformities of hip	1
754.3	Congenital dislocation of hip	1
820.2	Pertrochanteric fracture, closed	1
996.5	Mechanical complication of other specified prosthetic device, implant, and graft	1

ICD-9 was ordered by frequency. ICD-9, International Classification of Diseases, Ninth Revision.

Supplementary Table 3. The primary diagnosis when admission for total hip replacement, n=148

ICD-9		n
715.3	Osteoarthrosis, localized, not specified whether primary or secondary	64
733.4	Aseptic necrosis of bone	48
996.4	Mechanical complication of internal orthopedic device, implant, and graft	9

715.2	Osteoarthrosis, localized, secondary	7
715.1	Osteoarthrosis, localized, primary	3
716.1	Traumatic arthropathy	3
755.6	Other anomalies of lower limb, including pelvic girdle	3
821.0	Shaft or unspecified part, closed	2
711.0	Pyogenic arthritis	1
715.9	Osteoarthrosis, unspecified whether generalized or localized	1
716.9	Arthropathy, unspecified	1
720.0	Ankylosing spondylitis and other inflammatory spondylopathies	1
730.1	Chronic osteomyelitis	1
733.8	Malunion and nonunion of fracture	1
736.3	Acquired deformities of hip	1
754.3	Congenital dislocation of hip	1
996.5	Mechanical complication of other specified prosthetic device, implant, and graft	1

ICD-9 was ordered by frequency. ICD-9, International Classification of Diseases, Ninth Revision.

Supplementary Table 4. Associations of metformin use with incidence of the hospitalization due to knee or hip osteoarthritis

|	Prescription time-distribution matching cohort		Propensity score matching cohort	
	Non-Metformin n=20347	Metformin n=20347	Non-Metformin n=10163	Metformin n=10163
Median follow up months	45	54	42	50
Observed person-months	1108877	1259813	531635	595409
Admission for knee or hip OA				
Number of event	672	490	324	249
Incidence rate*(95% CI)	6.06 (5.62-6.54)	3.89 (3.56-4.25)	6.09 (5.47-6.80)	4.18 (3.69-4.73)
Crude HR (95% CI)	Reference	**0.65 (0.58-0.73)**	Reference	**0.690 (0.59-0.82)**
aHR[†] (95% CI)	Reference	**0.67 (0.58-0.76)**	Reference	**0.681 (0.58-0.80)**
Competing outcome[$] aHR (95% CI)	Reference	**0.68 (0.59-0.77)**	Reference	**0.740 (0.63-0.87)**
IPTW[#] aHR (95% CI)	Reference	**0.65 (0.56-0.76)**		
Admission for knee OA				
Number of event	566	432	280	214
Incidence rate*(95% CI)	5.10 (4.70-5.54)	3.43 (3.12-3.77)	5.27 (4.68-5.92)	3.59 (3.14-4.11)
Crude HR (95% CI)	Reference	**0.68 (0.56-0.77)**	Reference	**0.68 (0.57-0.82)**
aHR[†] (95% CI)	Reference	**0.68 (0.59-0.79)**	Reference	**0.68 (0.57-0.81)**
Competing outcome[$] aHR (95% CI)	Reference	**0.71 (0.62-0.82)**	Reference	**0.74(0.62-0.88)**
IPTW[#] aHR (95% CI)	Reference	**0.67 (0.57-0.78)**		
Admission for hip OA				
Number of event	107	60	44	36
Incidence rate*(95% CI)	0.96 (0.80-1.17)	0.48 (0.37-0.61)	0.83 (0.62-1.11)	0.60 (0.44-0.84)
Crude HR (95% CI)	Reference	**0.51 (0.37-0.70)**	Reference	0.75 (0.48-1.16)
aHR[†] (95% CI)	Reference	**0.59 (0.41-0.85)**	Reference	0.73 (0.47-1.13)
Competing outcome[$] aHR (95% CI)	Reference	**0.51 (0.35-0.74)**	Reference	0.80 (0.51-1.24)
IPTW[#] aHR (95% CI)	Reference	**0.60 (0.41-0.87)**		

*Incidence rate, per 10000 person-months.

[†]The co-variates including demographic variables (sex, age, urbanization, and insurance type), score of adapted Diabetes Complication Severity Index, comorbidities, medications for pain management, and other oral antihyperglycemic agents at baseline.

[$]When further defined non-OA related hospitalization as competing-events (rheumatoid arthritis, gout and osteoporosis).

[#]Balance diagnostics showed that covariates were well balanced between groups after IPTW.

OA, osteoarthritis; aHR, adjusted hazard ratio; IPTW, inverse probability of treatment weighting; TKR, total knee replacement; THR, total hip replacement.
Bold denotes statistical significance.
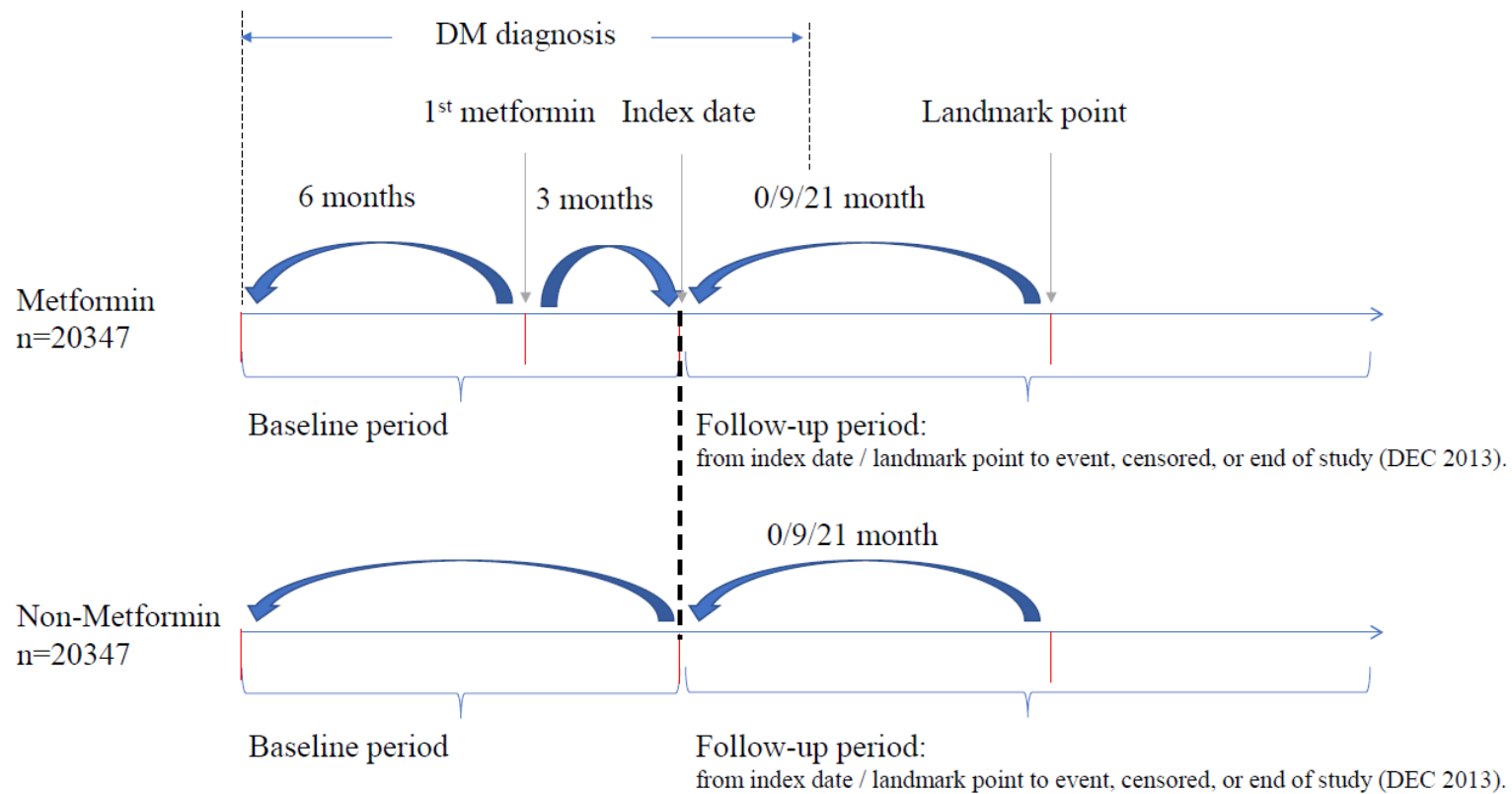
Supplementary Figure 1. Time schedule since the diagnosis of diabetes mellitus in metformin users (above) or non-users (below) during 2000 to 2013.
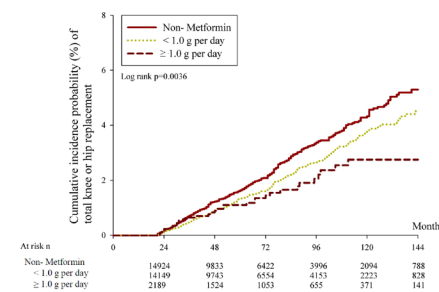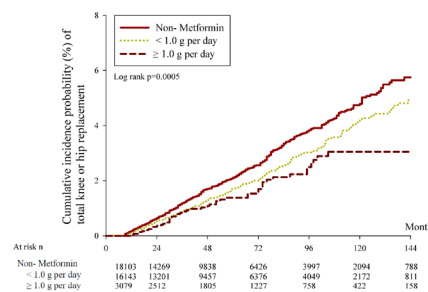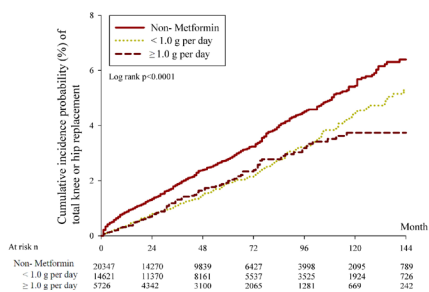The index date was defined as 3 months after the first prescription of metformin. The duration from 9-month before index date to the index date were defined as baseline period. The landmark points were 3, 12 and 24 months after the first prescription of metformin.
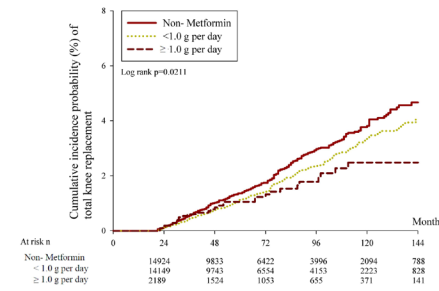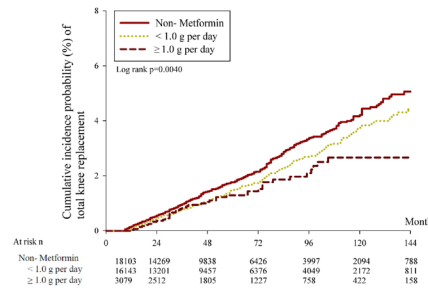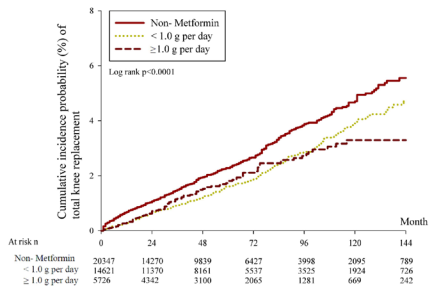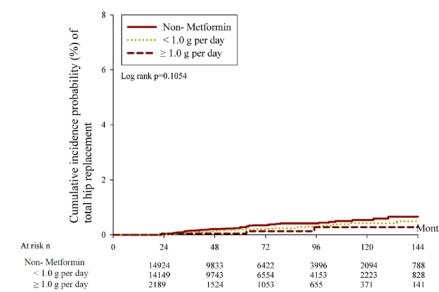
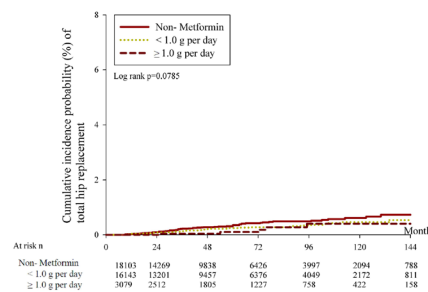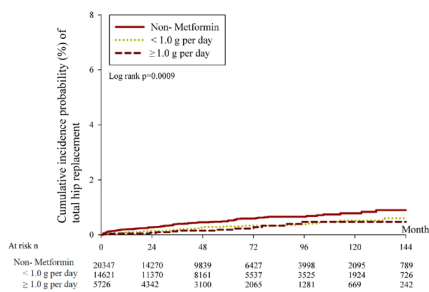**Supplementary Figure 2. Cumulative probability of total joint replacement in metformin (2 dosages) users or non-users.** (a) metformin average daily dosage (gram per day) estimated during the period from first prescription to 3 months; (b) metformin average daily dosage estimated during the period from first prescription to 12 months landmark point; (c) metformin average daily dosage estimated during the period from first prescription to 24 months landmark point. The log-rank tests were conducted to compare the

distributions of cumulative incidence curves that estimated by the Kaplan-Meier method between 3 groups (Non-metformin, metformin < 1 g / day, and >=1 g / day).