

# Association Between the Diabetes Drug Cost and Cardiovascular Events for Type 2 Diabetes in Korea: A National Health Insurance Service Database Analysis

**Seung Min Chung**

Yeungnam University Hospital <https://orcid.org/0000-0003-3336-7557>

**Ji-In Lee**

Research Institute of The Way Healthcare, Seoul, Korea

**Eugene Han**

Keimyung University College of Medicine: Keimyung University School of Medicine

**Hyun-Ae Seo**

Daegu Fatima Hospital

**Eonju Jeon**

Catholic University of Daegu Hyosung School of Medicine: Catholic University of Daegu School of Medicine

**Hye Soon Kim**

Keimyung University College of Medicine: Keimyung University School of Medicine

**JiSung Yoon** (✉ [jsyoons9@yumail.ac.kr](mailto:jsyoons9@yumail.ac.kr))

Yeungnam University College of Medicine <https://orcid.org/0000-0003-3091-3700>

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## Original investigation

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# Abstract

**Background:** We aimed to investigate the long-term effects of diabetes drug costs on cardiovascular (CV) events and death.

**Methods:** This retrospective observational study used the 2009–2018 National Health Insurance data in Korea. Among patients with type 2 diabetes, those who were taking antidiabetic drugs and did not have CV events before 2009 were included. Data on the annual cost of each diabetes drug were collected. The 10-year incidence of CV events (cardiac death, non-fatal myocardial infarction, stroke, hospitalization for heart failure, and coronary revascularization) and CV death were analyzed according to the diabetes drug cost quartiles (Q1 [the lowest] – Q4 [the highest]).

**Results:** A total of 441,914 participants were enrolled (median age, 60 years; male, 57%). CV events and death occurred in 28.1% and 8.36% of patients, respectively. The overall diabetes drug cost was USD 271/year per person (range: 1–18,921). The 10-year incidence of CV events and death was lowest in Q3 and high in Q4 and Q1. After adjusting for CV risk factors, the risk of CV events increased in the sequential order of cost quartiles (hazard ratio (HR)=1 [ref], 1.102 [95% confidence interval (CI): 1.084–1.120], 1.137 [95% CI: 1.118–1.156], and 1.323 [95% CI: 1.3011.346]). The risk of CV death showed U-shaped pattern which was lowest in the Q3 (HR=0.943, 95% CI 0.903-0.984) and highest in the Q4 (HR= 1.234, 95% CI 1.182-1.287).

**Conclusion:** The expenditure for diabetes drug affects 10-year CV events and death. Affording an appropriate diabetes cost at a similar CV risk is an independent protective factor for CV death.

**Trial registration:** retrospectively registered

## Introduction

In recent decades, the prevalence of diabetes mellitus among adults aged 20–79 years has increased worldwide, from 6.6% in 2010 to 9.3% in 2019. Moreover, the annual global health expenditure on the treatment of diabetes was USD 760 billion in 2019 [1, 2]. Diabetes increases the risk of cardiovascular (CV) complications, accounts for 11.3% of the deaths worldwide [3], and imposes a substantial economic burden on society and individuals [4].

The risk factors for CV disease have been identified, and the importance of managing these factors has been consistently emphasized for over 30 years [5]. Diabetes is one of the risk factors, and the ultimate goal of diabetes treatment is to reduce the risk of CV complications, which is 2.4 to 4.0 times higher in patients with diabetes than in those without diabetes [6]. Along with lifestyle modifications, selecting an appropriate drug based on the patients' clinical characteristics can reduce the occurrence of CV events [7]. The rising economic burden of diabetes may cause financial strain on individuals, especially among those with the lower socioeconomic status, and health systems [8]. Despite these limitations, few studies have evaluated the effect of the cost of diabetes drugs on the risk of CV events and death.

In this study, we aimed to analyze the risk of CV events and death according to the diabetes drug cost over a 10-year period using the 2009–2018 National Health Insurance data in Korea.

## Methods

### Study participants

We conducted a retrospective observational study using the National Health Information Database (NHID) of the National Health Insurance Service (NHIS) in Korea. The NHIS operates a mandatory public insurance program for all citizens and supports public health policy and research activities by developing and maintaining the NHID [9]. Before the commencement of the study, approval was obtained from the Institutional Review Board of Yeungnam University Hospital (no. 2019-12-040) and the NHIS review board (no. NHIS-2020-1-159).

A total of 1,494,633 eligible ethnic Korean individuals with type 2 diabetes who did not experience CV events between January 01, 2009 and December 31, 2009 were enrolled in this study. Individuals with type 2 diabetes were selected according to the Korean Standard Disease Code (KCD-7-based International Classification of Diseases, 10th revision (ICD-10); ICD code: E11). The following individuals were excluded from the study: 1) those who had a history of CV events before 2009 or no diabetes medication prescription during the observational period (n=4,057); 2) those who died before 2009 or had no demographic data (sex, age, etc.) in 2009 (n=6,939); 3) those who died before the diabetes medication prescription date or their medication cost was 0 (n=21,149); and 4) those who had no physical examination data (smoking, drinking, and body mass index) in 2009 (n=1,020,574) (Figure 1). A total of 441,914 eligible participants were followed-up until 2018 according to their diabetes drug cost for CV events and death.

## Outcome

The outcomes were CV events and death, which were selected according to the KCD-7-based ICD-10. CV events included cardiac death (ICD codes: I21, I46, I50, I110, I130, and I132 + death), non-fatal myocardial infarction (MI; ICD codes: I21 and I22), stroke (ICD codes: I60, I61, I62, I63, and I64), hospitalization due to heart failure (HF; ICD codes: I50, I110, I130, and I132 + admission), and coronary revascularization (procedure codes: O16 and OA64). CV death was defined as death due to CV events [10].

## Variables

Data on sex, age, region, income deciles (1st to 20th deciles), presence of hypertension (ICD code: I10), dyslipidemia (ICD code: E78), body mass index, smoking (yes/no), and drinking status (yes/no) at the time of enrollment were collected. Obesity was defined as a body mass index of  $\geq 25$  kg/m<sup>2</sup> for Koreans.

The antidiabetic drugs were classified as insulin, sulfonylurea (SU), metformin (MET), dipeptidyl peptidase-4 inhibitor (DPP4i), thiazolidinedione (TZD), other combinations of SU (SU+TZD and SU+MET), MET+DPP4i, MET+TZD, other combinations of MET (MET+SGLT2i and MET+meglitinide), and glucagon-like peptide-1 receptor agonist (GLP1-RA). Data on the annual costs of each diabetes drug from 2009 to 2018 were collected. For further analysis, the overall (2009–2018) diabetes drug cost per person was divided into quartiles (Q1–4). The cost of diabetes drugs was converted to 1,130 KRW, which is equivalent to USD 1 (based on the exchange rate as of July 5, 2021).

## Statistical analysis

The differences in the 10-year incidence of CV events and death by cost groups were evaluated using the chi-square test. The hazard ratios (HRs) of incident CV events and deaths were analyzed using a Cox proportional hazard model. Covariates including the risk factors for atherosclerotic CV disease were adjusted [5]. All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA), and a p value of 0.05 was considered significant.

## Results

### Participants' characteristics

Data from 441,914 participants were analyzed in this study. The median age of the participants was 60 years (range, 18–102), and the male to female ratio was 1.3:1. From 2009 to 2018, CV events occurred in 124,183 participants (28.1%). The demographic characteristics according to the occurrence of CV events are presented in Table 1. The distribution of sex, age, residential area, and income level differed between the CV events group and no-occurrence group (all p<0.001). The proportion of males (56.2% vs. 57.7%) was lower, and the number of individuals aged  $\geq 60$  years (71% vs. 44.1%) was higher in the CV events group than in the no-occurrence group. The proportion of residents in the metropolitan area in the CV events group was lower than that in the no-occurrence group (40.8% vs. 45.3%). The proportion of participants in the lowest (1-4) and highest (17–20) income deciles was higher in the CV events group (45.8% vs. 44.2%). Compared with the no-occurrence group, the CV events group had a higher prevalence of hypertension (69.1% vs. 56.1%), lower prevalence of dyslipidemia

(52.37 vs. 55.02%) and obesity (46.1% vs. 49.1%), and a lower proportion of smokers (17.9% vs. 19.1%) and drinkers (18.2% vs. 21.8%; all  $p < 0.001$ ).

**Table 1.** Demographic characteristics

	Occurrence of CV events		P-value**
	No (n=317,731; 71.9%)	Yes (n=124,183; 28.1%)	
Sex, n(%)			<.001
Men	183,347 (57.7)	69,739 (56.2)	
Women	134,384 (42.3)	54,444 (43.8)	
Age, n(%)			<.001
18~29	1,198 (0.4)	71 (0.1)	
30~39	11,438 (3.6)	864 (0.7)	
40~49	57,916 (18.2)	8,294 (6.7)	
50~59	107,069 (33.7)	26,834 (21.6)	
60~69	96,676 (30.4)	46,926 (37.8)	
70~79	39,628 (12.5)	36,289 (29.2)	
80~	3,806 (1.2)	4,905 (4.0)	
Region*, n(%)			<.001
Metropolitan †	143,821 (45.3)	50,711 (40.8)	
Rural ‡	173,891 (54.7)	73,469 (59.2)	
Income deciles*, n(%)			<.001
1~4	50,865 (16.0)	20,524 (16.5)	
5~8	44,754 (14.1)	16,405 (13.2)	
9~12	54,952 (17.3)	20,611 (16.6)	
13~16	71,356 (22.5)	27,534 (22.2)	
17~20	89,727 (28.2)	36,400 (29.3)	
Hypertension, n(%)	178,324 (56.1)	85,820 (69.1)	<.001
Dyslipidemia, n(%)	174,821 (55.02)	65,035 (52.37)	<.001
Obesity, n(%)	155,994 (49.1)	57,285 (46.1)	<.001
Smoking, n(%)	60,685 (19.1)	22,255 (17.9)	<.001
Drinking, n(%)	69,384 (21.8)	22,555 (18.2)	<.001

\* 22 (region) and 8,786 (income) data are missing.

† Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, Ulsan

‡ Gyeonggi, Gangwon, Chungbuk, Chungnam, Jeonbuk, Gyeongbuk, Gyeongnam, Jeju

\*\* Chi-square test.

## Costs of diabetes drugs

The annual diabetes costs for each drug from 2009 to 2018 are presented in **Supplementary Table 1**. The median overall diabetes cost per person was USD 271/year (range, 1–18,921). MET+DPP4i (USD 649/year) had the highest drug cost, followed by DPP4i (USD 489/year), GLP-1RA (USD 413/year), SU (USD 390/year), TZD (USD 284/year), MET+TZD (USD 193/year), MET (USD 190/year), other combinations of SU (USD 390/year), other combinations of MET (USD 135/year), and insulin (USD 11/year).

The upper ranges of the overall diabetes drug cost for each cost quartile were USD 72/year, USD 271/year, USD 646/year, and USD 18,921/year per person (Table 2). In Q1 (the lowest), Q2, and Q3, the expenditure on MET+DPP4i, DPP4i, and GLP-1RA was predominant. In Q4 (the highest), expenditure on other combinations of SU and insulin was predominant.

Table 2  
Overall and each cost for diabetes drugs from 2009 to 2018 by quartiles (USD/year per person)

	Overall	Insulin	SU	MET	DPP4i	TZD	other combinations of SU	MET + DPP4i	MET + TZD	other combinations of MET	GLP-1RA
Q1	72	1	152	80	154	79	48	234	64	56	149
Q2	271	11	391	190	478	284	183	649	193	135	413
Q3	646	234	724	336	965	696	447	1,182	534	262	1,034
Q4	18,921	17,091	6,801	5,881	5,064	4,046	18,921	5,696	4,637	791	5,108
The costs are presented as the upper quartile range.											
SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist											
Other combinations of SU (SU+TZD and SU+MET); other combinations of MET (MET+SGLT2i and MET+Meglitinide)											

## Diabetes cost and incidence of CV events and death

The annual incidence of CV events according to the diabetes drug cost quartiles was analyzed. The annual incidence of CV events was lowest in Q3 through 2009–2014 and lowest in Q1 since 2015. In 2009, the highest incidence of CV events was reported in Q1; since 2010, the highest incidence of CV events was reported in Q4 (Figure 2A). In 2009–2018, the cumulative incidence of CV events was the lowest in Q3. Until 2014, the cumulative incidence of CV events was the highest in Q1. However, in 2015, Q4 showed the highest cumulative incidence of CV events (Figure 2B).

The 10-year incidence of CV events and deaths according to the cost groups were analyzed. Approximately 28.1% of the patients experienced CV events (n=124,183). The incidence of CV events was lowest in Q3 (26.5%), followed by Q2, Q1, and Q4 (29.6%; p<0.001 among quartiles). The 10-year incidence of CV deaths was 8.4% (n=36,949). The incidence of CV death was lowest in Q3 (6.7%), followed by Q2, Q4, and Q1 (10.1%; p<0.001 among quartiles; **Supplementary Figure 1**). In particular, the incidence of non-fatal MI and hospitalization for HF was lowest in Q1 and increased in sequential order of cost quartiles (both p<0.001). On the contrary, the incidence of cardiac death, stroke, and coronary revascularization was lowest in Q3 (all p<0.001). The incidence of death resulting from non-fatal MI, stroke, hospitalization due to HF, and coronary revascularization was lowest in Q3 (all p<0.001; **Supplementary Table 2**).

## Diabetes cost and risk for CV event and death

The risk of incident CV events and deaths was analyzed using a Cox regression analysis. Sex; age; diabetes cost; types of diabetes drugs used (insulin, SU, MET, DPP4i, TZD, other combinations of SU, MET+DPP4i, and MET+TZD); presence of hypertension, dyslipidemia, and obesity; and smoking and drinking status were considered as covariates.

After adjusting for covariates, the risk of CV events was lowest in Q1 and increased in sequential order of cost quartiles: HR=1 (ref), 1.102 (95% confidence interval [CI]: 1.084–1.120,  $p<0.001$ ), 1.137 (95% CI: 1.118–1.156,  $p<0.001$ ), and 1.323 (95% CI: 1.301–1.346,  $p<0.001$ ), respectively (Figure 3A). By contrast, the risk of CV death was significantly lower in Q3 (HR=0.943, 95% CI: 0.903–0.984,  $p=0.008$ ) and higher in Q4 (HR=1.234, 95% CI: 1.182–1.287,  $p<0.001$ ) than in Q1 (Figure 3B).

Among the covariates, age ( $\geq 40$  for CV events and  $\geq 50$  for CV death); use of insulin, SU, MET, TZD (only for CV death), and other combinations of SU; presence of hypertension, and smoking increased the risk of CV events and death. The use of DPP4i, MET+DPP4i (only for CV events), and MET+TZD; presence of dyslipidemia and obesity; and drinking status were related to a decreased risk of CV events and death (Table 3).

Table 3  
Risk factors for incident CV events and death

	CV events		CV death	
	Adjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Sex (ref=men)				
Women	0.870 (0.859-0.881)	<.001	0.621 (0.601-0.641)	<.001
Age(Ref=18~29)				
30~39	1.208 (0.948-1.538)	0.126	0.805 (0.346-1.874)	0.615
40~49	2.282 (1.807-2.883)	<.001	1.895 (0.848-4.234)	0.119
50~59	3.793 (3.005-4.788)	<.001	3.326 (1.493-7.412)	0.003
60~69	6.729 (5.331-8.493)	<.001	8.207 (3.685-18.278)	<.001
70~79	11.154 (8.836-14.081)	<.001	22.268 (9.999-49.591)	<.001
80~	14.779 (11.689-18.686)	<.001	49.582 (22.238-110.546)	<.001
Diabetes drug cost (Ref=Q1, lowest)				
Q2	1.102 (1.084-1.120)	<.001	0.977 (0.938-1.016)	0.246
Q3	1.137 (1.118-1.156)	<.001	0.943 (0.903-0.984)	0.008
Q4 (highest)	1.323 (1.301-1.346)	<.001	1.234 (1.182-1.287)	<.001
Diabetic drug (Ref=No)				
Insulin	1.396 (1.374-1.419)	<.001	1.775 (1.709-1.844)	<.001
SU	1.139 (1.123-1.155)	<.001	1.289 (1.242-1.337)	<.001
MET	1.038 (1.025-1.051)	<.001	1.041 (1.008-1.074)	0.015
DPP4i	0.907 (0.887-0.927)	<.001	0.926 (0.871-0.983)	0.013
TZD	0.984 (0.965-1.003)	0.103	1.051 (1.001-1.104)	0.047
Other combinations of SU	1.051 (1.034-1.068)	<.001	1.123 (1.078-1.169)	<.001
MET+DPP4i	0.940 (0.897-0.985)	0.009	0.887 (0.779-1.010)	0.070
MET+TZD	0.831 (0.781-0.884)	<.001	0.715 (0.593-0.863)	<.001
(Ref=No)				
Hypertension	1.283 (1.267-1.299)	<.001	1.446 (1.397-1.496)	<.001
Dyslipidemia	0.965 (0.955-0.977)	0.007	0.860 (0.835-0.886)	<.001
Obesity	0.977 (0.966-0.988)	<.001	0.830 (0.806-0.855)	<.001
Smoking	1.215 (1.195-1.235)	<.001	1.413 (1.357-1.472)	<.001
Drinking	0.929 (0.914-0.944)	<.001	0.848 (0.813-0.885)	<.001
Cox-regression analysis was performed. Sex, age, diabetes cost, types of diabetes drugs, presence of hypertension, dyslipidemia, and obesity, and smoking and drinking status was adjusted as covariates.				
SU, sulfonylurea; MET, metformin; TZD, thiazolidinedione; DPP4i, dipeptidyl peptidase-4 inhibitor; Other combinations of SU (SU+TZD, SU+MET)				

## Discussion

This study analyzed the cost of diabetes drugs and its effect on CV events and deaths in Korea using the National Health Insurance data. From 2009 to 2018, the incidence rates of CV events and deaths were 28.1% and 8.4%, respectively. CV events were higher in older adults, men, rural dwellers, those with the lowest and highest income, and those with hypertension. According to the cost quartiles, the risk of CV events increased in sequential order and CV deaths showed a U-shaped pattern, with Q3 being the lowest. In addition, men, aging, types of diabetes drugs used, presence of hypertension, and smoking status were attributed to CV risks.

The incidence of CV events and deaths has been decreasing over the past two decades [11–13]. However, the healthcare expenditure for CV disease is higher (12–16.5%) than that for other diseases (0.2–0.4%) [14]. The primary prevention of CV disease is important to reduce the diabetes-related financial burden [15, 16]. Globally, the indirect diabetes cost (caused by production losses due to premature mortality and morbidity) accounted for 34.7% of the total expenditures, suggesting that increasing the amount spent on paying the direct diabetes cost (diabetes prevention and treatment) might reduce the total economic burden of diabetes [4].

In Q1, the annual incidence of CV events was the highest in the first year but was lowest in the seventh year and thereafter. After adjustments, the risk of CV events was lowest. It is presumed that over time, the proportion of individuals who only took a few diabetic drugs with good glucose control increased in this group. By contrast, Q4 showed the highest 10-year incidence of CV events. The high expenditure on insulin and SU is likely to suggest that there were many patients with advanced stage of diabetes in this group. After adjustments, the risk of CV events and death was the highest. The highest expenditure reflects poor blood glucose control, and appropriate management is required for clinical intervention, patient self-management education, and social support for diabetes patients [8].

In Q3, the 10-year incidence of CV events and death was the lowest. After adjustment, the risk of CV events was lower than Q4 but higher than Q1, while that of CV death was the lowest. The most expensive diabetes drug was GLP-1RA (80 USD/year per prescription), whereas traditional therapies were cheap (insulin, 14 USD/year per prescription; SU, 7 USD/year per prescription; MET, 4 USD/year per prescription; data not shown). Considering that Q3 had the highest expenditure on GLP-1RA after MET+DPP4i, and Q4 had the highest expenditure on SU combination and insulin, the affordability of diabetes drugs might affect the incidence of CV events and death among individuals with similar CV risk.

This study reflects the real-world trends of diabetes drug prescription and its cost, and not a randomized control trial. Therefore, the results of the Cox regression analysis in this study showed that MET+DPP4i or MET+TZD decreased and insulin, SU, or MET increased the risk of CV events and death, and this finding should not be interpreted based on the CV benefit of the drug. Moreover, only short-term data of GLP-1RA (2016-2018) were included, mainly dulaglutide which was launched in 2016. Recently, the results of the Glycemia Reduction Approaches in Diabetes study, a comparative study on the effect of adding insulin (glargine), SU (glimepiride), GLP1-RA (liraglutide), or DPP4i (sitagliptin) to pre-existing metformin, were presented at the 2021 American Diabetes Association meeting [17]. As for the incidence of major CV events, the incidence of hospitalization for HF and all-cause mortality did not differ among the four classes of medications. However, liraglutide was associated with a lower incidence of CV events than the other three agents.

Along with lifestyle modification, appropriate prescription based on the patients' clinical characteristics, drug efficacy, and side effects can help prevent the occurrence of diabetes complications and improve the patient's quality of life [18, 19]. Various cost patterns exist depending on the combination of antidiabetic drugs, and treatment strategies often change because of the patient's ability to afford the cost of treatment or medications [20]. The effective combination of diabetic drugs is more costly [1, 21], which might not be affordable for individuals living in low-and lower-middle-income countries [22, 23].

The direct medical costs for diabetes treatment is determined early, which seems to be cost-ineffective in the short term; however, many health benefits accrue late [8]. In the long run, diabetic patients without complications can save nine times of

the direct medical costs compared with those with diabetes-related complications [24]. The scenario analysis using the Italian National Health Service revealed that integrated management, such as control of HbA1c, microalbuminuria, cholesterol, and blood pressure levels, can reduce the diabetes costs by 17% [25]. In addition, a 5-year prospective cohort study in Hong Kong revealed that multidisciplinary risk assessment and management of diabetes reduced the cumulative incidences of complications and all-cause mortality and had a net saving of USD 7,294 per participant [26]. Taken together, the long-term benefits can be achieved by appropriate treatment of diabetes and ensuring an adequate medical expenditure.

The main strength of this study is that it documented the impact of diabetes cost on the risk of CV events and death, a less explored area of research. In addition, this study is based on a high-quality data source, the National Health Insurance data, which is the most representative health data in Korea. Using big data, our results show the overall diabetes cost, prescription pattern, and incidence of CV events.

Despite these strengths, there are also some limitations. First, the data does not contain laboratory levels; hence, we could not evaluate the severity of diabetes and comorbidities. Second, the treatment (e.g., statin) and improvement of comorbidities within the 10-year period were not reflected; hence, the results were affected, and it was not emphasized that the presence of dyslipidemia and obesity at baseline was a protective factor for CV events and death. Third, diabetes drugs with established cardiovascular benefits (SGLT2i and GLP1-RA) were not adjusted during the performance of a Cox regression analysis as they were prescribed only after a 3–4-year follow-up. Lastly, Korea's unique health insurance system and diabetes drug prescription trends [27], which is insufficient to reflect the global trends, should be taken into account.

## Conclusions

In conclusion, the cost of diabetes is an independent risk factor for 10-year CV events and death. The ability to afford an appropriate diabetes cost at a similar CV risk is an independent protective factor for CV death.

## Abbreviations

CI

confidence interval

CV

cardiovascular

DPP4i

dipeptidyl peptidase-4 inhibitor

GLP1-RA

glucagon-like peptide-1 receptor agonist

HF

heart failure

HR

hazard ratio

ICD-10

International Classification of Diseases, 10th revision

KCD-7

Korean Standard Disease Code

MET

metformin

MI

myocardial infarction

NHID

National Health Information Database

NHIS  
National Health Insurance Service  
SU  
sulfonylurea  
TZD  
thiazolidinedione

## Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Yeungnam University Hospital (no. 2019-12-040) and the NHIS review board (no. NHIS-2020-1-159).

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study are available from NHIS but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of NHIS.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: SMC and JIL had equal contributions to this study, including the conception or design of the work, acquisition, analyses, and interpretation of data, and drafting of the manuscript. EH, HAS, EJ, HSK, and JSY contributed to the conception of the work and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy. All authors read and approved the final manuscript.

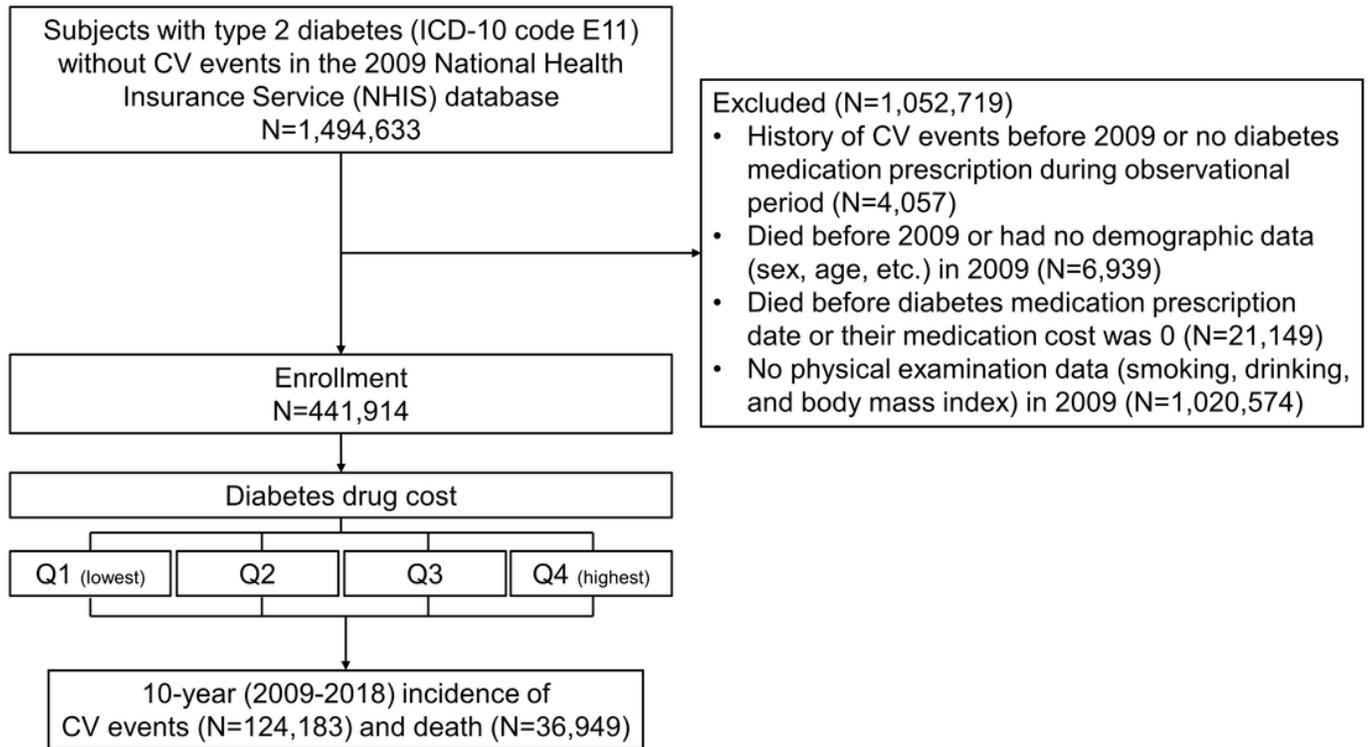
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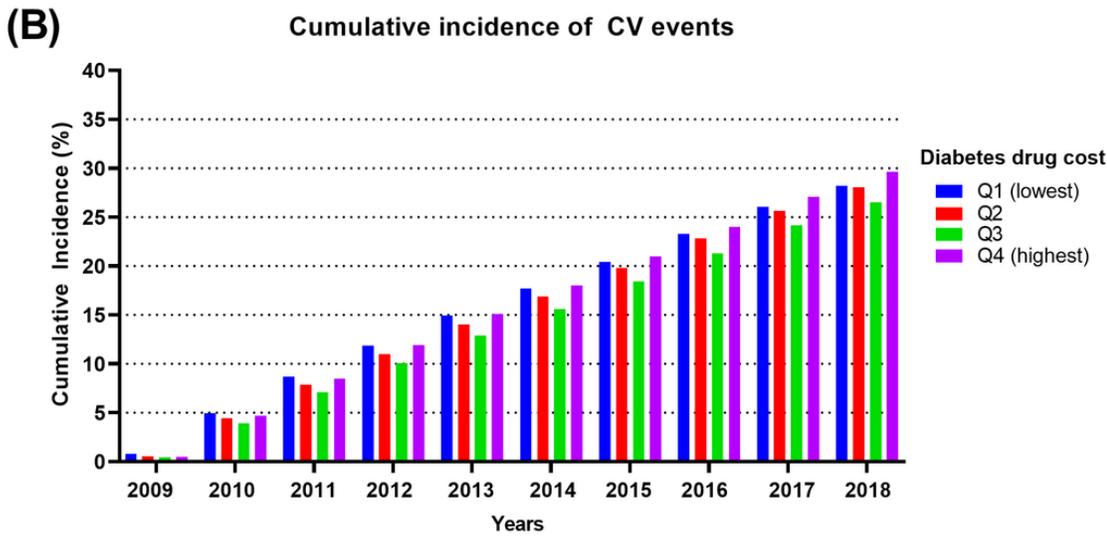
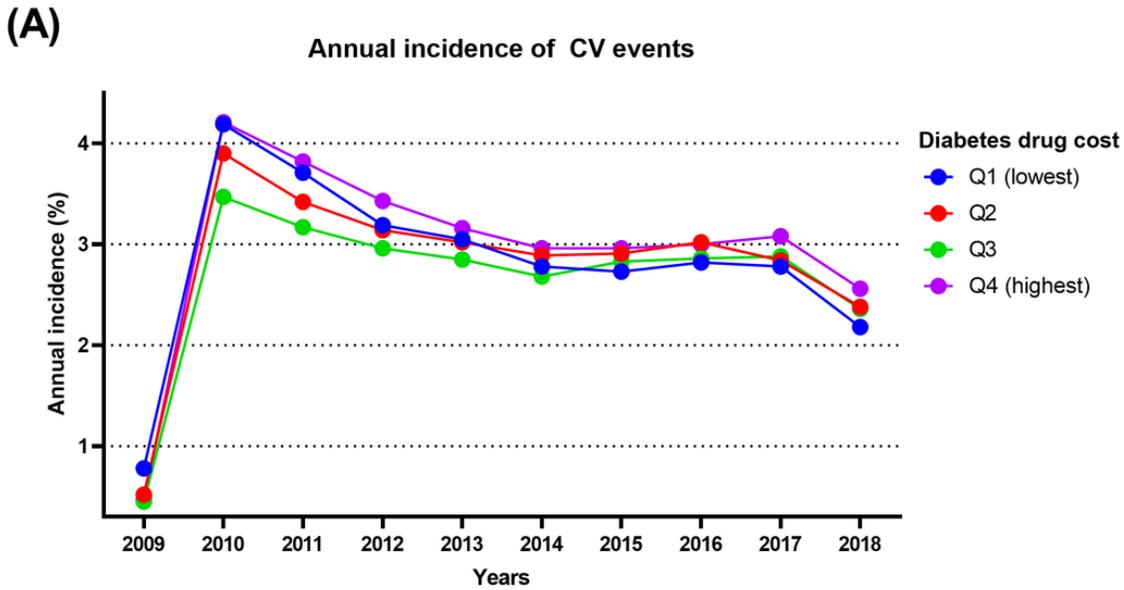
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## Figures



**Figure 1**

Flowchart for participants inclusion



**Figure 2**

The annual and cumulative incidence of CV events according to diabetes drug cost. The (A) annual and (B) cumulative incidence of CV events are presented. CV events were defined as the occurrence of cardiac death, non-fatal myocardial infarction, non-fatal stroke, hospitalized due to heart failure, and coronary revascularization.

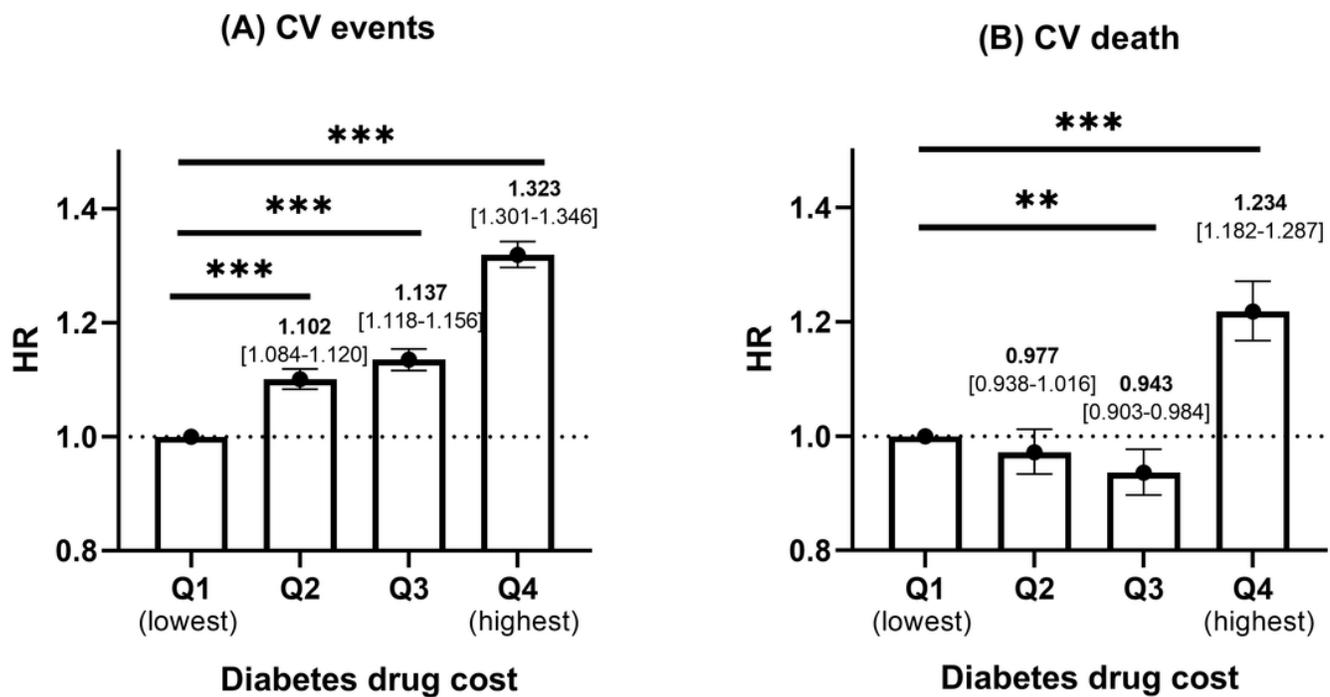


Figure 3

Diabetes drug cost and the risk for CV events and death  $**p<0.01$ ,  $***p<0.001$  between groups Cox-regression analysis was performed. Sex, age, diabetes cost, types of diabetes drugs, presence of hypertension, dyslipidemia, and obesity, and smoking and drinking status was adjusted as covariates.

## Supplementary Files

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