Polypharmacy and Risk of Major Cardiovascular Events Among Chinese Patients With Diabetes: A Retrospective Cohort Study Using Instrumental Variable Analysis

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INTRODUCTION

- Polypharmacy—the concurrent use of multiple medications—is common among patients with diabetes, reflecting the need to control hyperglycemia and manage multiple comorbidities.
- Previous studies have associated polypharmacy with a wide range of adverse outcomes, including higher risks of mortality, hypoglycemia, fractures, falls, myocardial infarction, heart failure, stroke, and hospital readmission.
- However, this relationship is complex and potentially bidirectional, as poorer baseline health both necessitates more medications and predisposes patients to adverse outcomes.
- This study examined the nonlinear associations between polypharmacy and composite major adverse cardiovascular events (MACE) in Chinese patients with diabetes, using causal inference methods to address endogeneity.

METHODS

STUDY DESIGN

- We conducted a retrospective observational cohort study using the Yinzhou Regional Health Care Database.

POPULATION

- Adults (≥18 years) with diabetes（≥2 outpatient diagnoses [≥30 days apart] or 1 inpatient diagnosis）and with at least one prescription between 2015 and 2021 were enrolled.
- Patients were followed until death, loss to follow-up, or study end.

VARIABLES

- Dependent variable: composite major adverse cardiovascular events (MACE)
- Independent variable: the number of medications
- Covariates: age, sex, education level, insurance status, marital status, employment status, medical history (including hypertension, hyperlipidemia, liver disease, cancer, depression, stroke, myocardial infarction, ischemic heart disease, heart failure, arrhythmia, kidney disease, retinopathy, neuropathy, peripheral vascular disease, and hypoglycemia)

STATISTICAL ANALYSIS

- We applied an instrumental variable (IV) approach within a Cox proportional hazards framework, using practice-level prescribing preference as the instrument.
- Threshold regression was used to detect nonlinear exposure-response patterns.
- IV validity was confirmed via Hausman tests and Kleibergen-Paap statistics.

RESULTS

- Among 73,766 eligible patients, 5,116 (6.94%) experienced MACE.
- Those with MACE were older (69.3 vs. 61.3 years), had higher unemployment rates (29.4% vs. 23.8%), and exhibited a greater proportion of unmarried individuals (12.9% vs. 9.4%) compared to patients without MACE.

Table1 Incidence of MACE Events in Patients with Different Numbers of Medications

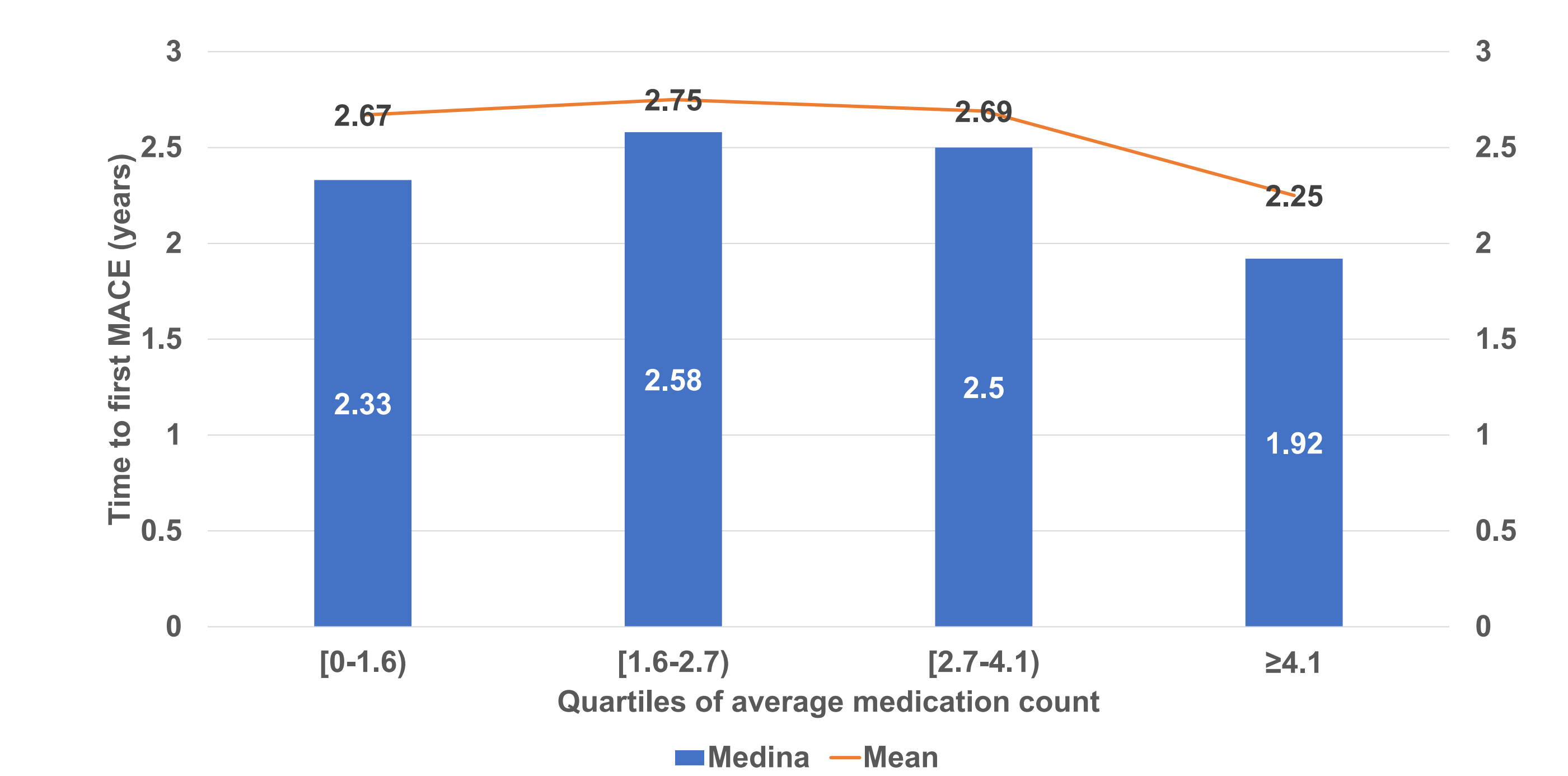| Characteristics	Quartiles of the number of medications			
	[0-1.6)	[1.6-2.7)	[2.7-4.1)	≥4.1
No of participants	18506	18356	18379	18525
Person years	64196.17	68219.66	71618	70654.09
No of cases	601	944	1341	2230
Incidence rate#	93.62	138.38	187.24	315.62
Incidence rate (%)	0.03	0.05	0.07	0.12

#Incident rate per 100 000 person years.

Figure 1 Time to MACE Events in Patients on Different Numbers of Medications

Table 2 Medication Number and MACE Risk: Regression Analysis by Threshold

Variables	(1) IV+Cox	(2) IV+Cox+ $\gamma=3$	(3) IV+Cox+ $\gamma=4$	(4) IV+Cox+ $\gamma=5$	(5) IV+Cox+ $\gamma=6$
$\widehat{Rx_i}$	0.7801***	0.6851***	0.7848***	0.7142***	0.7156***
	(0.0507)	(0.0467)	(0.0478)	(0.0416)	(0.0399)
$\widehat{Rx_i} \times I(\widehat{Rx_i} \geq \gamma)$		1.0409	0.9604***	1.0063	1.0135
		(0.0308)	(0.0124)	(0.0093)	(0.0107)
Control variables	Yes	Yes	Yes	Yes	Yes
Observations	73766	73766	73766	73766	73766
LR（chi^2）	3383.17	3404.91	3412.81	3403.52	3404.65
Prob>chi^2	0	0	0	0	0

γ is threshold

$I(\cdot)$ is an indicator function: I=1,when$\widehat{Rx_i} \geq \gamma$; I=0,otherwise

- A nonlinear relationship was observed: when the average number of medications was below four, medication use was associated with reduced MACE risk (HR = 0.78, p < 0.01). However, when medication use exceeded four drugs, risk increased significantly (HR = 1.75, p < 0.01).
- Instrument validity and strength were confirmed (Hausman p < 0.01; Kleibergen-Paap F = 18.4).

CONCLUSIONS

- Using robust causal methods and longitudinal data, our study suggests an optimal threshold for medication use among patients with diabetes.
- Both undertreatment and excessive polypharmacy were associated with elevated risks of major cardiovascular events.

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