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Diabetes and cardiovascular disease in the new era: Epidemiology, treatment, and economics, 2nd Edition

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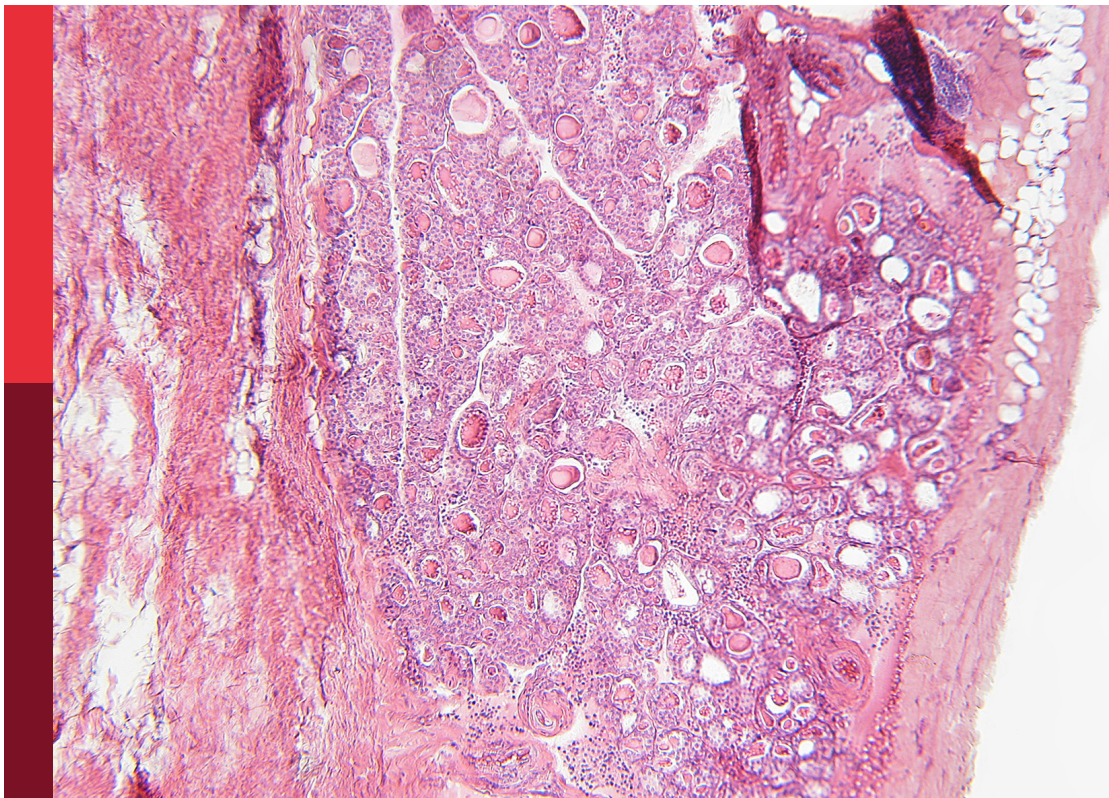

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Diabetes and cardiovascular disease in the new era: Epidemiology, treatment, and economics, 2nd Edition

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Racial and Urban-Rural Difference in the Frequency of Ischemic Stroke as Initial Manifestation of Atrial Fibrillation

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Objective: Atrial fibrillation (AF) may remain undiagnosed until the development of complications. We aimed to examine the epidemiology and racial/ethnic and rural/urban differences in the frequency of newly diagnosed AF manifesting as ischemic stroke in a nationally representative sample of Medicare beneficiaries.

Methods: We used a 5% random sample of Medicare claims to identify patients newly diagnosed with AF in 2016. The primary dependent variable was stroke or transient ischemic attack (TIA) in the 7 days *prior* to the first AF diagnosis, i.e., stroke or TIA as the initial manifestation of AF. We constructed a multivariable logistic regression to quantify the association between race/ethnicity, urban/rural residence, and the primary dependent variable.

Results: Among 39,409 patients newly diagnosed with AF (mean age 77 ± 10 years; 58% women; 7.2% Black, 87.8% White, 5.1% others), 2,819 (7.2%) had ischemic stroke or TIA in the 7 days *prior* to AF diagnosis. Black patients (adjusted OR [95% CI]: 1.21 [1.05, 1.40], vs. White) and urban residents (1.21 [1.08, 1.35], vs. rural) were at increased risk of stroke as the initial manifestation of AF. Racial differences were larger among patients aged ≥75 years, with adjusted ORs of 1.43 (1.19, 1.73) for Black vs. White patients, but non-significant for those aged <75 (*P* for interaction = 0.03).

Conclusion: We observed significant and important differences in the risk of stroke as initial manifestation of AF between White and Black patients and between rural and urban residents. Our results suggest potential disparities in the identification AF across race/ethnicity groups and urban/rural areas.

Keywords: atrial fibrillation, ischemic stroke, racial differences, urban/rural, Medicare claims

INTRODUCTION

Atrial fibrillation (AF) is a strong risk factor for ischemic stroke and is implicated in 15–20% of stroke cases (1). Preventive treatment with oral anticoagulation may reduce stroke risk by two-thirds in patients with AF (2). However, AF can be asymptomatic and remain undiagnosed until the development of complications such as stroke.

Some studies have examined the prevalence of stroke as the initial manifestation of AF but results vary substantially (3–7). The Framingham Heart Study reported that 3.4% of incident AF patients had a stroke or transient ischemic attack (TIA) in the month *prior* to AF detection (3, 5). In a cohort of 3,507 patients newly diagnosed with AF at the University of Pennsylvania system, Patel et al. estimated that 5.3% of patients had a stroke in the week *prior* to AF diagnosis (7). However, these community- and health system- based cohorts may have limited generalizability to the general population of patients newly diagnosed with AF across the US.

In the present study, we aimed to examine the epidemiology of ischemic stroke or TIA occurring in the seven days *prior* to the first AF diagnosis, i.e., stroke or TIA as the initial manifestation of AF, using a nationally representative sample of Medicare beneficiaries. Given the previously recognized health disparities in the awareness of AF (8), we also measured racial/ethnic and rural/urban differences in the frequency of incident AF manifesting as ischemic stroke or TIA.

METHODS

This retrospective cohort study used claims data from a 5% random sample of Medicare Part D beneficiaries obtained from the Centers for Medicare and Medicaid Services (CMS). Using the CMS Chronic Condition Data Warehouse indicator of AF, we identified beneficiaries who were first diagnosed with AF between January 1, 2016, and December 31, 2016. We constrained sampling to those who were continuously enrolled in Medicare Part D in the year *prior* to AF diagnosis (i.e., index date). This ensured that we had access to complete medical information at baseline to make certain that the sample represented incident AF patients. The final sample included 39,409 beneficiaries newly diagnosed with AF in 2016.

The dependent variable was ischemic stroke or TIA as the initial manifestation of AF. We defined this outcome as one claim with a primary or secondary International Classification of Diseases, Ninth Revision (ICD-9) for stroke or TIA based on diagnostic code of 430, 431, 433.x1, 434.x1, 435, or 436 or an ICD-10 diagnostic code of G45 or I63 on the day of or within seven days *prior* to AF diagnosis. The 7 day cutoff was selected based on prior literature that a 7-day period captured majority of prior-AF stroke (7). In identifying stroke events, we used provider claims (carrier claims) instead of institutional claims to be able to capture with higher accuracy the date of the first stroke diagnosis: Inpatient (institutional) claims are often billed on the day of discharge and include codes for primary and secondary diagnoses identified during a hospitalization, which would prevent us from accurately depicting the timing between first AF diagnosis and stroke, if they both happened within a hospitalization. In contrast, claims for physician services provided during an inpatient hospitalization (provider claims) are billed with the date of provision of service, which enabled us to estimate the relative timing between first AF diagnosis and stroke diagnosis with a higher accuracy.

The exposures of interest included race/ethnicity and urban vs. rural residence, which were measured on the index date. We collected self-reported race/ethnicity information from Medicare's administrative files and categorized individuals into three groups: non-Hispanic White, non-Hispanic Black, and other races/ethnicities (hereafter denoted as White, Black, and others). We classified participants as living in an urban or rural area using zip codes and nine-level United States Department of Agriculture (USDA) Rural-Urban Continuum Codes. Consistent with the USDA classification, we defined urban patients as those living in levels 1–3 and rural patients as those living in levels 4–9 (9).

In addition to race/ethnicity and urban vs. rural residence, we also examined information concerning other demographics and clinical characteristics, including age, sex, residence in one of four Census regions (Northeast, Midwest, South, and West), CHA_2DS_2-VASc score, valvular disease, eligibility for Medicaid, receipt of low-income subsidy, end-stage renal disease, and area deprivation index (ADI). A patient's CHA_2DS_2-VASc score was calculated based on age, sex, history of stroke/TIA, vascular disease, heart failure, hypertension, and diabetes.

In the cohort of newly diagnosed AF, we computed age- and sex-adjusted proportion (%) of stroke or TIA as initial manifestation of AF by race/ethnicity and urban/rural area. We then constructed a multivariable logistic regression to quantify the association between race/ethnicity and urban/rural residence and the risk of stroke or TIA as initial manifestation of AF, while adjusting for demographic and clinical characteristics, as listed above. We tested the interaction effects of race/ethnicity and urban/rural residence with age ($<$75 years vs. $\geq$75 years), sex, and ADI ($<90^{th}$ percentile vs. $\geq 90^{th}$ percentile) in the multivariable-adjusted model. A two-sided $p < 0.05$ was considered significant, and analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

Among 39,409 patients who were newly diagnosed with AF, 2,819 (7.2%) had ischemic stroke or TIA in seven days *prior* to AF diagnosis. Mean age of the study cohort was 77 (standard deviation [SD], 10) years; over half (58%) were female, and 80% were urban residents. Compared to White beneficiaries (87.8%) with AF, Black beneficiaries (7.2%) and beneficiaries of other races/ethnicities (5.1%) were younger, more likely to reside in urban areas, and more likely to be eligible for Medicaid coverage and low-income subsidy. Black beneficiaries had higher CHA_2DS_2-VASc scores and were more likely to live in the South and in areas with higher ADIs than White beneficiaries or beneficiaries of other races/ethnicities (**Supplementary Table 1**).

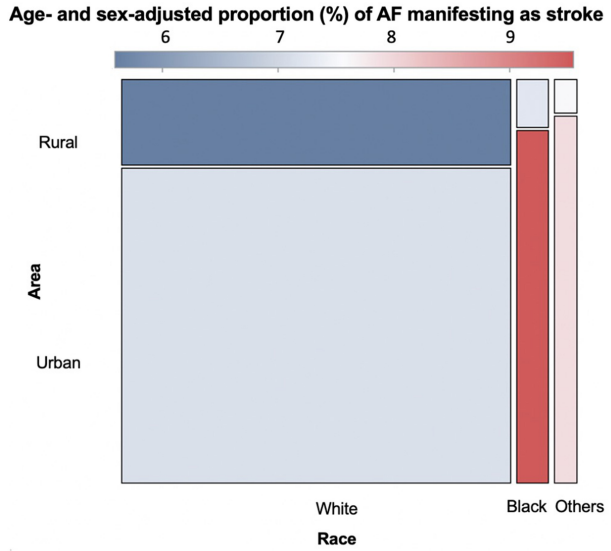

FIGURE 1 | Age- and sex-adjusted proportion (%) of newly diagnosed atrial fibrillation patients with ischemic stroke as the first manifestation of atrial fibrillation by race and urban/rural residence. The x axis shows three race/ethnicity categories (White, Black and Others) and the y axis shows urban and rural areas. Each of the 6 boxes presents one race-area group (White-Urban, White-Rural, Black-Urban, Black-Rural, Others-Urban, and Others-Rural). The size of the box represents the sample size of each group. Dark blue indicates the lowest proportion of AF diagnosis manifesting as stroke, while dark red represents the highest proportion of AF diagnosis manifesting as stroke.

In our cohort of newly diagnosed AF, in urban areas, the age- and sex-adjusted proportion of stroke or TIA occurring 7 days *prior* to AF diagnosis was 7.1% (95% CI: 6.8, 7.5) for White beneficiaries, 9.6% (8.4, 10.8) for Black beneficiaries, and 7.9% (6.8, 9.3) for beneficiaries of other races/ethnicities. In rural areas, the age- and sex-adjusted proportion of stroke or TIA occurring 7 days *prior* to AF diagnosis was 5.6% (5.1, 6.1) for White beneficiaries, 7.2% (4.9, 10.6) for Black beneficiaries, and 7.6% (4.4, 12.9) for beneficiaries of other races/ethnicities (**Figure 1**).

After adjusting for covariates, Black beneficiaries (adjusted OR [95% CI]: 1.21 [1.05, 1.40]) were at significantly increased risk of having stroke or TIA as initial AF manifestation compared to White beneficiaries (**Table 1**). The risk of stroke or TIA as initial AF manifestation did not significantly differ between White patients and patients of other races/ethnicities (adjusted OR: 1.16 [0.97, 1.40]). Urban residents were 21% more likely (adjusted OR: 1.21 [1.08, 1.35]) to have stroke or TIA as initial AF manifestation compared to rural residents.

We observed a significant interaction between race/ethnicity and age ($p = 0.03$). The increased risk of stroke or TIA as initial AF manifestation observed for Black patients compared to White was statistically significant among those aged 75 years or older (adjusted OR: 1.43 [1.19, 1.73], vs. White) but not in those <75 years (adjusted OR: 0.97 [0.76, 1.22]; $p_{interaction} = 0.03$); **Figure 2**.

TABLE 1 | Adjusted odds ratios of new AF diagnosis manifesting as stroke across racial/ethnicity groups and between urban and rural areas.

		Stroke cases% (*n*)	Adjusted odds ratio (95%CI)
Race/ethnicity	White	7.0% ($n = 2,406$)	Reference
	Black	9.1% ($n = 256$)	1.22 (1.06, 1.41)
	Others	7.8% ($n = 157$)	1.16 (0.97, 1.40)
Areas	Urban	7.5% ($n = 2,366$)	Reference
	Rural	5.7% ($n = 453$)	1.21 (1.08, 1.35)

Adjusted for age, sex, CHA_2DS_2-VAS_c score, valvular disease, geographic region (Northeast, South, Midwest, and West), Medicaid enrollment, low income subsidy, end stage renal disease, and area deprivation index.

DISCUSSION

Our study measured the risk of stroke as an initial manifestation of AF in a nationally representative sample of Medicare beneficiaries. We observed that over 7% of Medicare beneficiaries newly diagnosed with AF presented with ischemic stroke or TIA seven or fewer days prior to AF diagnosis. After adjusting for relevant factors, Black race and urban residency were associated with increased risk of stroke or TIA as initial AF manifestation.

The Framingham Heart Study reported a lower frequency of stroke or TIA as an initial manifestation of AF (3.4%) than that estimated in the present study (3); even with the inclusion of stroke cases occurring up to 30 days *prior* to AF diagnosis in Framingham. The Framingham Heart Study report included participants with incident AF diagnosed between 1951 and 2013, whereas the current study reflects the more contemporary era with much more widespread use of telemetry in stroke patients. The secular trends of post-stroke telemetry use over the decades may explain the different estimates between two studies. Differences in the demographic characteristics of study populations may have also contributed to the diverging estimates, since Framingham participants were largely of European ancestry, whereas our Medicare sample is more diverse in terms of race/ethnicity, region of residence, and socioeconomic status. Our results are comparable with data from the Penn Atrial Fibrillation Free study, which estimated that 5.4% of patients newly diagnosed with AF 2004–2009 had a stroke in the 7 days prior to AF diagnosis (7). Quantifying strokes attributable to undiagnosed AF is important because potentially they could be preventable with oral anticoagulation, at least among individuals who would be eligible for anticoagulation, which represents 96% of our sample given CHA_2DS_2-VASc scores $\geq$2 in men or $\geq$3 in women.

Large-scale screening for AF has been widely discussed as a potential public health strategy for early detection and treatment of AF that can help to prevent stroke and other AF-associated complications (10). However, there remain several major concerns, including the identification of target population for screening, its cost-effectiveness, the selection of screening devices, and the development of intervention strategies for detected AF cases (11). In this context, the availability of generalizable estimates of stroke as the initial

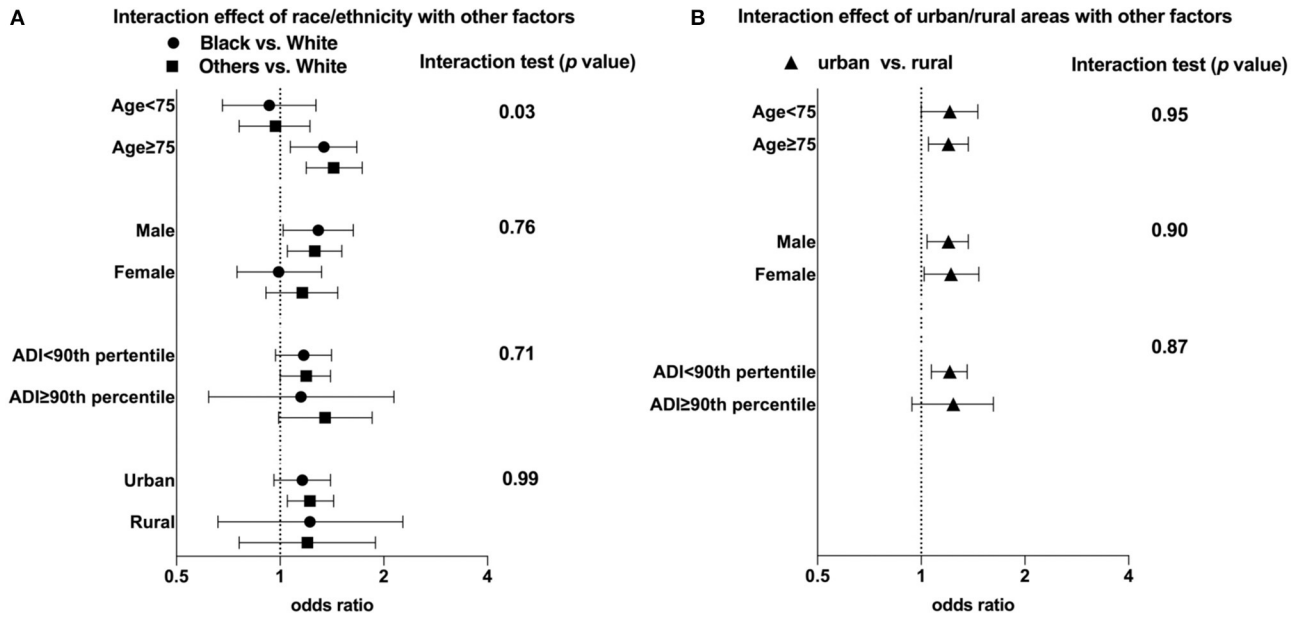

FIGURE 2 | Interactions of race/ethnicity and urban/rural residence with age, sex, and area of deprivation index. ADI, Area of Deprivation Index. In addition to the listed factors, the model was also adjusted for CHA_2DS_2-VAS_c score, valvular disease, geographic region (Northeast, South, Midwest, and West), Medicaid enrollment, low income subsidy and end stage renal disease.

manifestation of AF is paramount to producing robust estimates of the cost-effectiveness of potential AF screening strategies and identifying populations who may benefit the most from screening.

Racial differences in stroke incidence and death have been reported frequently in the general population, with these differences decreasing with older age (12). Similar to the Penn Atrial Fibrillation Free study (7), we observed that Black beneficiaries had a 22% higher risk of having stroke or TIA as initial AF manifestation compared to White beneficiaries. We further observed that such racial differences were larger among patients first diagnosed with AF at an age of ≥75 years. There is increasing awareness that race is a social construct (13). Whereas the pathophysiology of racial differences is uncertain; instead of reflecting biological variation, racial differences in the manifestation of AF may reflect structural inequities including racism, decreased awareness of AF, lower access to care, residential environment, and inequitable control of underlying AF and stroke risk factors.

Although prior work has suggested that rural residents often face barriers to healthcare access in general (14), we observed a lower risk of incident AF manifesting as stroke or TIA in rural residents than in urban residents across all three racial/ethnic subgroups. Similar to our findings, prior data from Medicare claims revealed a greater risk of stroke in urban areas in the year of AF diagnosis (15). Further studies are needed to address the underlying causes of the these observed differences between White and Black patients and between urban and rural residents.

Several limitations of the present study should be noted. First, because some patients may have had fatal strokes or had unrecognized AF, it is possible that our results underestimate the proportion of patients who had an ischemic stroke as fist AF manifestation. On the other hand, it is possible that in some patients, AF occurred as a consequence of the stroke event. Second, we created a binary classification of urban vs. rural residence. We acknowledge that urban and rural are not homogeneous categories; future work might further distinguish urban, suburban, exurban, and rural areas. Last, we acknowledge that the race/ethnicity category "Others" is heterogenous; we did not examine Hispanics and Asian subgroups separately because of a lack of power.

In conclusion, in our cohort of Medicare beneficiaries with AF, we observed a clinically relevant proportion having ischemic stroke or TIA occurring within seven days prior to AF diagnosis. Black patients and urban residents were more likely to present with stroke or TIA as initial AF manifestation. Further research is needed to evaluate the effectiveness of AF screening efforts in reducing inequities in health outcomes associated with AF.

DATA AVAILABILITY STATEMENT

Our Medicare Claims data was obtained from CMS. Requests to access these datasets should be directed to resdac@umn.edu.

AUTHOR CONTRIBUTIONS

JG designed the study, executed the disparities analyses, and drafted the first draft of the manuscript. NG contributed to the study design and executed the data management and statistical analyses. JM, UE, WG, MB, LT, and EB contributed to the generation of the study question, study design, and critical review of the manuscript. IH supervised the project and was

responsible for obtaining funding, coordinating research efforts, and supervising analyses and manuscript writing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: IH reports scientific advisory board fees from Pfizer and Bristol Myers Squibb, outside of the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Distinct Prognostic Role of Serum Uric Acid Levels for Predicting All-Cause Mortality Among Chinese Adults Aged 45~75 Years With and Without Diabetes

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Introduction: The current study sought to explore the effect of baseline serum uric acid (SUA) on the risk of all-cause mortality among Chinese adults aged 45~75 years and to determine its interaction relationship with diabetes.

Methods: The study was designed as a community-based cohort of 4467 adults aged between 45~75 years included in a 6-years follow-up period from 2009 to 2015 years by the China Health and Nutrition Survey (CHNS). Baseline SUA levels were grouped into quartiles and its association on all-cause mortality was explored using multivariate Cox proportional hazards models. Stratified analyses were performed to explore the associations of SUA quartiles with all-cause mortality among diabetic and non-diabetic individuals.

Results: A total of 141 deaths (5.3 per 1000 person-years) were recorded During a follow-up of 26431 person-years. Out of the 141 deaths, 28 deaths (10.1 per 1000 person-years) were reported in the diabetic groups and 113 deaths (4.8 per 1000 person-years) were recorded in the non-diabetic group. An increased risk of all-cause mortality was observed for participants in the first and fourth quartiles compared with the second SUA quartile, (Q1 SUA: aHR=2.1, 95% CI 1.1~4.1; Q4 SUA: aHR=2.1, 95% CI 1.1~4.0). Stratification of participants by diabetes status showed a U-shaped association for non-diabetic individuals. Whereas, declined eGFR, rather than SUA, was an independent risk factor for all-cause mortality in diabetic individuals (aHR=0.7, 95% CI 0.6~1.0).

Conclusion: Our study proved that the prognostic role of SUA for predicting all-cause death might be regulated by diabetes. Both low and high SUA levels were associated with increased mortality, supporting a U-shaped association only in non-diabetic individuals.

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Whereas, renal dysfunction rather than SUA was an independent risk factor for all-cause mortality. Further studies should be conducted to determine the SUA levels at which intervention should be conducted and explore target follow-up strategies to prevent progression leading to poor prognosis.

Keywords: serum uric acid, diabetes, all-cause mortality, epidemiology, China Health and Nutrition Survey

INTRODUCTION

Prevalence of hyperuricemia (HUA) is more than 20% of the general population and presents a rapid increase globally (1). In China, the disease burden of HUA has risen significantly over the recent decades, from approximately 8.5% in 2001 to approximately 18.4% in 2017 (2). Clinical trials report that elevated serum uric acid (SUA) is a strong predictor of poor outcomes in cardiovascular death, acute ischemic stroke, and all-cause death (3–6). Previous studies report that low and high UA levels are correlated with increased mortality with approximately 1.5~5.0 times higher risk. Notably, 1 mg/dL UA levels increase is related to 3 times higher risk, and a U-shaped association occurs between SUA levels and adverse health outcomes (7, 8).

Noteworthy, the risk ratio varies with types of diseases in HUA patients including hypertension, diabetes, chronic kidney disease (CKD) and metabolic syndromes (9–14). A previous study reported that HUA patients have a higher all-cause mortality rate compared to the general population, which is mainly attributed to cardiovascular diseases (CVD), metabolic syndromes and diabetes (15).

Studies should explore whether SUA and diabetes independently or jointly affect prognosis as HUA has a high prevalence and accounts for 13.0%~35.0% of patients with diabetes and owing to the disparity of UA levels in different associated diseases (16–18). Studies on the association between SUA level and mortality in diabetic individuals report conflicting findings. Lamacchia et al. report that SUA was not linearly associated with all-cause mortality in diabetic patients and a higher risk of mortality was observed for the first and third SUA tertiles (HR: 1.34 and 1.61) (19). Another 9-year cohort study reported significantly interactive effect of uric acid with diabetes (RR=1.26) on the risk of all-cause mortality, whereas the findings showed that the effects of uric acid were not significant (20). However, most of the previous studies did not conduct appropriate comparisons (21, 22), and recruited subjects from hospitals (23), thus limiting the ability to fully explore whether SUA independently contributes or acts synergistically with renal function associated with diabetes. Notably, studies have not explored the potential role of SUA on quality of life in the Chinese population with diabetes.

Therefore, we designed a 6-year cohort study based on the China Health and Nutrition Survey (CHNS) to explore the effect of baseline serum uric acid (SUA) on the all-cause mortality among Chinese adults aged 45~75 years and determine its interaction relationship with diabetes was determined.

Abbreviations: AKI, acute kidney injury; BMI, body mass index; BP, blood pressure; CCDC, Chinese Center for Disease Control and Prevention; CHNS, China Health and Nutrition Survey; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HUA, hyperuricemia; HR, hazard ratios; LDL, low-density lipoprotein cholesterol; IQR, interquartile range; MI, myocardial infarction; SD, standard deviation; SUA, serum uric acid; MSM, marginal structure model; WHR, waist to hip circumference ratio; OR, odds ratio; RR, risk ratio; SD, standard drink; ULT, urate-lowering therapy.

MATERIALS AND METHODS

Study Cohorts

The CHNS is an ongoing nationwide prospective cohort study that comprised the Chinese population. The study sought to explore the effects of the health, nutrition, and family planning policies and programs implemented by national and local governments. CHNS was conducted in 1989, and it was subsequently performed in 1991, 1993, 1997, 2000, 2004, 2006, 2009, 2011 and 2015. Details on the design and data collection of CHNS have been reported previously (24). Data on demographic, economic circumstances, diet, behaviors, and health were collected from each household member for all CHNS waves. Written informed consent was obtained from all participants. CHNS was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill and local IRB (institutional review board or ethics committee). Blood samples were collected in 2009. A total of 9546 participants were included in the 2009 wave of CHNS and data on biomarkers were obtained from these subjects. Moreover, death-related information was obtained for the 2009, 2011 and 2015 cohorts.

Considering participants aged above 75 years may exert the effect of age on aging-related variables and no cases of deaths under the age of 45 years were observed due to CHNS being a community-based dataset. Participants aged 45 to 75 years were excluded from the study. A total of 378 (7.8%) participants were excluded as they had less than two visits during the follow-up duration. Demographic and behavioral characteristics of participants included in the final analysis (n=4467) were compared with that of excluded participants (n=378) (**Supplementary Table 1**).

Data Collection

A standardized structured questionnaire was administered by trained health staff to collect socio-demographic variables (in 2009) including age, gender, educational attainment, urban-rural residence, history of diseases (e.g. hypertension, diabetes), smoking habits, drinking status, tea intake, coffee intake, total protein intake and physical activity level. Physical examinations

of waist circumference, hip circumference, height, weight and blood pressures (BP) were performed by trained clinical staff (24). Biomarkers were obtained in 2009. All individuals maintained a regular pattern of life for at least three days before blood sample collection and were required to be collected 12 ml blood (in three 4 ml tubes) on empty stomach. The details were seen on the website: http://www.cpc.unc.edu/projects/china/data/datasets/biomarker-data. Biomarker data collected in CHNS 2009 involves the release of 26 fasting blood measures on individuals aged 7 and older (25). Totle cholesterol (TC) was measured using the Picric acid method (Hitachi 7600, Kyowa, Japan). Low-density lipoprotein cholesterol (LDL) was measured using the Enzymatic method (Hitachi 7600, Kyowa, Japan). Triglyceride (TG) was measured using the GPO-PAP (Hitachi 7600, Kyowa, Japan). Creatinine was measured by certified technicians at each field center using the CHOD-PAP (Hitachi 7600, Randox, UK).

The individuals were categorized as groups, namely, for residence, into urban and rural; for educational attainment, into 0, 6 years or less, 6–8 years, 9–11 years, and 12 years or higher; for smoking status into non-smokers, ex-smokers and current smokers; for alcohol status, into drinker and non-drinker. Individual dietary intake for 3 consecutive days was determined for every household member. This step has been achieved by asking individuals each day to report all food consumed away from home on a 24-hour recall basis, and the same daily interview has been used to collect at-home individual consumption. BMI was calculated as weight (in kilograms) divided by the square of height (in meters) and categorized into four levels including: lean (< 18.5 kg/m^2), normal (18.5~23.9 kg/m^2) and overweight (24.0~27.9 kg/m^2) and obese (≥28 kg/m^2). Waist-to-hip ratio (WHR) was calculated as waist circumference (cm)/height (cm). The cutoffs for the WHR were identified as 0.9 for men and 0.85 for women, using the World Health Organization (WHO) guidelines (26). Systolic blood pressure (BP) and diastolic blood pressure were expressed as the mean of three measurements. Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg or self-reported (27). Diabetes mellitus was defined as HbA1c ≥6.5% or self-reported or having diabetes treatment records. Dyslipidemia was defined as total cholesterol level at 5.2 mmol/L or higher, LDL cholesterol level at 3.4 mmol/L or higher, or triglycerides level at 1.7 mmol/L or higher (28). Estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) (29). The Framingham risk score (FRS) is based on an algorithm derived from a 10-year predicted risk of CVD estimate comprised of age, sex, total cholesterol, HDL cholesterol, smoking history, blood pressure, and diabetes (30). 10-year CVD FRS was classified as low (<10%), intermediate (10-20%), or high risk (>20%).

The quality of the data collection was controlled. The design and implementation of the survey detailed the protocol for training the field staff for data collection and office staff for data entry and how to properly check and clean the data. These procedures have become an established part of work in China after regional staff complete extended trips to the U.S. for training (24).

Exposure

In the 2009 wave of CHNS, 12 ml blood was collected from participants on an empty stomach. Data were deposited on the website: https://www.cpc.unc.edu/projects/china. SUA was selected as the exposure variable. SUA was determined by certified technicians at each field center by the enzymatic colorimetric method (Hitachi 7600, Randox, UK), following the standard procedures. SUA levels were categorized into quartiles (<4.7, 4.7~5.5, 5.6~6.9, >6.9 mg/dL for men and <3.7, 3.7~4.4, 4.5~5.4, >5.4 mg/dL for women).

Analysis of All-Cause Mortality

The variable wave in CHNS represents the "year" of study. The date of death was reported in each wave (wave=2009, 2011 and 2015). Follow-up duration was determined as the time from baseline (survey date in 2009) till the date of death recorded during CHNS or the censoring time. A total of 389 participants were excluded from the study for having less than two visits during the follow-up. In sensitivity analysis, if the event of all-cause death was recorded on the same day as the baseline, the follow-up duration was recorded as 0.5 years or deleted.

Statistical Analysis

Data were presented as mean ± standard deviation (SD) and median with interquartile range (IQR) for continuous variables or N (%) for categorical variables. Data on demographics, physical examinations, and anthropometric indexes were compared between SUA quartiles using the chi-square test and Fisher's exact test for categorical variables. Variance analysis or Wilcoxon rank-sum test were performed for continuous variables. All-cause mortality for SUA quartiles was compared using the Kaplan-Meier (K-M) curve, and the significance was calculated using the log-rank test. Hazard ratios for mortality outcomes were estimated using Cox proportional hazards regression analysis. The second quartile of SUA was used as a reference to explore the statistical power. Multivariable Cox proportional hazards regression was adjusted for: age, gender, BMI, WHR, hypertension, smoking status, drinking status and total protein intake to determine whether each level of SUA quartiles was independently associated with all-cause mortality. Marginal structure model (MSM) was used for inverse-probability weighting analysis to determine the robustness of the findings. Participants who died in the same year were excluded or counted as 0.5 person-year during sensitivity analysis. Prespecified subgroup analyses were conducted based on age, gender, WHR, hypertension, dyslipidemia, CKD, and FRS in secondary analyses. Demographic characteristics of participants in the analytic sample were compared in case the biomarker for SUA was missing and the sample was excluded to explore potential selection bias on study results. The results are presented as hazard ratios (HR) or risk ratios (RR) with 95% confidence intervals (95% CI). $P < 0.05$ (two-sided) was considered statistically significant. Analysis was performed

only on the available data. Data were analyzed using SAS version 9.3 (SAS Institute Inc).

RESULT

Characteristics of the Study Participants

The initial cohort contained 8474 participants included in this study. Of them, participants (n=3996) were excluded on the first round for aging <45 or >75 years (n=3387), being pregnant (n=62), having average protein dietary intake for three consecutive days>110 g/day (n=371) (31) and having a history of myocardial infarction (MI) or apoplexy (n=176). Besides, 389 participants were further excluded for having less than two visits during the follow-up. In total, 4467 individuals were eligible for the formal analysis (**Supplementary Figure 1**). Demographic and behavioral characteristics of participants included in the final analysis (n=4467) and excluded samples (n=389) were compared. The findings showed that most characteristics were showed no significant difference between the two groups (**Supplementary Table 1**).

The mean age of participants was 57.7 ± 8.3 years, 45.3% of the participants were male and the mean follow-up duration was 5.9 ± 0.6 years. Notably, 475 diabetic and 3992 non-diabetic participants are presented in the study. Baseline characteristics of study patients across SUA quartiles are reported in **Table 1**. Analysis of diabetic individuals showed that individuals within the highest SUA level were more likely to be men, with the higher proportions of overweight, hypertension, dyslipidemia, CVD risk, smoking, alcohol drinking compared with the other three SUA quartiles. Moreover, non-diabetic individuals with the highest SUA level were more likely to be men and the elderly, with the higher proportions of senior-school education, urban residence, obese WHR, overweight, hypertension, dyslipidemia, smoking, drinking, and total protein intake were all higher compared with the other three SUA quartiles.

Interactive Effect of SUA and Diabetes on All-Cause Mortality

A total of 141 all-cause deaths (5.3 per 1000 person-years) were recorded during a follow-up of 26431 person-years. Out of the 141 deaths, 28 deaths (10.1 per 1000 person-years) in diabetic group, whereas 113 deaths (4.8 per 1000 person-years) were reported in non-diabetic group. The findings showed that age (per 5-year increase: HR=1.4, 95%CI 1.3~1.6), male (HR=2.5, 95%CI 1.5~4.1), rural residence (HR=1.9, 95%CI 1.2~2.9), BMI (per 5 kg/m^2 increase: HR=0.6; 95%CI 0.5~0.8), first and fourth quartile of SUA level (Q1: aHR=2.1, 95%CI 1.1~4.1, Q4: aHR=2.1, 95%CI 1.1~4.0) were associated with risk of all-cause mortality. In addition, a significant interactive effect between SUA and diabetes on all-cause mortality was observed (Q2 SUA × diabetes: *P*=0.044; Q3 SUA × diabetes: *P*=0.034, **Table 2**).

Stratified Analyses of SUA and All-Cause Mortality in Diabetes and Non-Diabetes

K-M curve analysis was separately performed for participants with and without diabetes. The finding showed that participants with Q4 SUA exhibited higher all-cause mortality compared with participants with those lower SUA quartiles *(Log-rank P<0.001*, **Figure 1B**) in the non-diabetic group. However, the analysis did not show significant differences between SUA quartiles in the diabetic group *(Log-rank P=0.242*, **Figure 1A**). Findings from stratified analyses showed that Q1 and Q4 SUA levels in non-diabetic group were significantly positively associated with a risk of all-cause mortality compared with Q2 SUA levels (Q1 aHR=2.3, 95% CI 1.2~4.6, Q4 aHR=2.0, 95% CI 1.1~3.7) (**Table 3**). However, this effect of SUA quartiles was not observed among diabetic individuals.

Multivariable Cox Regression Analysis of Diabetes and Non-Diabetes Participants

All parameters were included in the multivariate Cox model to explore the most contributing factor. Analysis of the diabetes group showed that only low eGFR, rather than SUA level, was significantly associated with all-cause mortality (HR=0.7, 95%CI 0.6~1.0). Analysis of non-diabetic individuals showed that age (per 5-year increase: HR=1.5, 95%CI 1.3~1.7), male (HR=2.7, 95%CI 1.5~4.9), rural residence (HR=2.0, 95%CI 1.2~3.4), BMI (per 5 kg/m^2 increase: HR=0.6, 95%CI 0.4~0.9), first and fourth quartile of SUA level (Q1 aHR= 2.1, 95%CI 1.1~4.2, Q4 aHR=2.2, 95%CI 1.2~4.2) were associated with risk of all-cause mortality (**Figure 2**).

Sensitivity and Explanatory Analyses

Sensitivity analysis was conducted using MSM with inverse-probability weighting to test the robustness of the findings. A statistically significant association was observed between the fourth SUA quartile and all-cause death in non-diabetic individuals (aHR=2.7, 95%CI 1.5~4.8) (**Supplementary Table 5**). A total of 6 individuals who died in the baseline year were excluded from the second sensitivity analysis (**Supplementary Table 6**). In the third sensitivity analysis, if the event of all-cause death was recorded in the same year as baseline, follow-up duration was expressed as 0.5 years (**Supplementary Table 7**). Sensitivity analysis showed that the results remained robust. In addition, specified subgroup analyses showed significant associations between SUA quartiles and all-cause mortality were found in 45~59 years subgroup, non-hypertension subgroup, non-dyslipidemia subgroup, low FRS subgroup, and CKD subgroup (**Supplementary Table 8**).

DISCUSSION

The current study was a large population-based study with a 6 years follow-up period. The findings showed a U-shaped association between SUA and all-cause mortality among non-diabetic individuals. However, significant associations were not observed between SUA and all-cause mortality among diabetic individuals. Notably, the association between SUA and all-cause mortality was distinct between diabetes and non-diabetes participants. To the best of our knowledge, this is the first study that reports the association between SUA and all-cause

TABLE 1 | Baseline characteristics of the participants and SUA quartiles among individuals with and without diabetes in CHNS Cohort.

	Diabetes (n = 475)					Non-diabetes (n = 3992)				
	Q1 (Male: <4.7; Female: <3.7)	**Q2 (Male: 4.7~5.5; Female: 3.7~4.4)**	**Q3 (Male: 5.6~6.9; Female: 4.5~5.4)**	**Q4 (Male:> 6.9;Female: >5.4)**	***P*-value***	**Q1 (Male: <4.7; Female: <3.7)**	**Q2 (Male: 4.7~5.5; Female: 3.7~4.4)**	**Q3 (Male: 5.6~6.9; Female: 4.5~5.4)**	**Q4 (Male:> 6.9; Female: >5.4)**	***P*-value***
Participants (n)	94	108	117	156		1016	1018	994	964	
SUA (mg/dL)	3.5 (0.5)	4.5 (0.3)	5.5 (0.3)	7.6 (2.0)	<0.001	3.4 (0.5)	4.5 (0.3)	5.5 (0.3)	7.4 (1.7)	<0.001
Age (years)	60 (8.8)	59 (8.4)	60.5 (8.5)	60.2 (8.9)	0.607	56.1 (8.2)	57.6 (8.2)	57.9 (8.1)	58.2 (8.2)	<0.001
Male (%)	27 (28.7)	44 (40.7)	54 (46.2)	93 (59.6)	<0.001	175 (17.2)	398 (39.1)	528 (53.1)	705 (73.1)	<0.001
Education (years)					0.178					<0.001
0	20 (21.3)	17 (15.7)	14 (12.0)	16 (10.3)		206 (20.3)	179 (17.6)	157 (15.8)	85 (8.8)	
≤6	37 (39.4)	38 (35.2)	40 (34.2)	52 (33.3)		346 (34.1)	363 (35.7)	339 (34.2)	324 (33.6)	
7–9	25 (26.6)	30 (27.8)	39 (33.3)	45 (28.9)		279 (27.5)	295 (29.0)	290 (29.3)	310 (32.2)	
10–12	7 (7.5)	13 (12.0)	8 (6.8)	21 (13.5)		121 (11.9)	102 (10.0)	114 (11.5)	131 (13.6)	
>12	5 (5.3)	10 (9.3)	16 (13.7)	22 (14.1)		63 (6.2)	77 (7.6)	91 (9.2)	113 (11.7)	
Rural (%)	63 (67.0)	66 (61.1)	72 (61.5)	89 (57.1)	0.481	723 (71.2)	724 (71.1)	694 (69.8)	620 (64.3)	0.002
Anthropometry parameters										
Obese WHR	63 (71.6)	74 (70.5)	92 (82.1)	121 (78.1)	0.146	497 (50.4)	496 (50.0)	518 (53.3)	557 (58.9)	<0.001
BMI (kg/m^2)					0.048					<0.001
Lean (<18.5)	2 (2.1)	1 (0.9)	4 (3.4)	1 (0.6)		73 (7.2)	51 (5.0)	52 (5.2)	35 (3.6)	
Normal (18.5–23.9)	38 (40.4)	41 (38.0)	37 (31.6)	38 (24.4)		606 (59.7)	598 (58.7)	518 (52.1)	424 (44.0)	
Overweight (24.0–27.9)	41 (43.6)	41 (38.0)	47 (40.2)	70 (44.9)		277 (27.3)	307 (30.2)	316 (31.8)	386 (40)	
Obesity (≥28.0)	13 (13.8)	25 (23.2)	29 (24.8)	47 (30.1)		60 (5.9)	62 (6.1)	108 (10.9)	119 (12.3)	
Hypertension	28 (31.5)	48 (47.5)	56 (52.8)	90 (60.8)	<0.001	208 (23.5)	255 (28.4)	311 (35.0)	376 (44.0)	<0.001
Dyslipidemia	69 (73.4)	78 (72.2)	94 (80.3)	140 (89.7)	<0.001	497 (48.9)	626 (61.5)	685 (68.9)	777 (80.6)	<0.001
eGFR (ml/min/l.73m^2)	77.6 (11.9)	75.6 (14.6)	70.2 (15.5)	68.1 (18.9)	<0.001	79.9 (11.9)	75.9 (12.2)	73.4 (13.0)	70.2 (14.6)	<0.001
eGFR<60 (ml/min/l.73m^2)	5 (5.3)	14 (13.1)	27 (23.1)	53 (34.0)	<0.001	43 (4.2)	99 (9.7)	144 (14.5)	213 (22.1)	<0.001
Framingham score (%)	15.6 (8.2)	17.1 (8.7)	19.1 (8.4)	21.6 (7.9)	<0.001	7 (5.6)	10.3 (7.5)	12.2 (7.8)	15.3 (8.3)	<0.001
Health-related behavior										
Smoking status					0.004					<0.001
Never	77 (81.9)	75 (69.4)	74 (63.8)	93 (59.6)		852 (83.9)	732 (72.0)	622 (62.6)	506 (52.5)	
Ever	1 (1.1)	8 (7.4)	4 (3.5)	14 (9.0)		10 (1.0)	33 (3.2)	34 (3.4)	50 (5.2)	
Current	16 (17.0)	25 (23.2)	38 (32.8)	49 (31.4)		154 (15.2)	252 (24.8)	337 (33.9)	408 (42.3)	
Alcohol drinker	18 (19.2)	36 (33.3)	37 (31.6)	63 (40.4)	0.007	176 (17.3)	295 (29.0)	327 (32.9)	492 (51.0)	<0.001
Total protein intake (g)	59.1 (18.6)	62.6 (18.7)	62.3 (17.1)	65.4 (20.2)	0.079	59.8 (18.8)	61.4 (18.5)	63.7 (18.3)	66.5 (19.1)	<0.001
Carbohydrate (g)	281.8 (103.5)	263.6 (98.8)	266.0 (84.1)	276.1 (100.2)	0.474	289.8 (99.7)	292.2 (95.5)	295.8 (93.4)	293.4 (94.2)	0.559
Fat (g)	70.4 (38.4)	83.6 (94.5)	72.5 (32.3)	79.3 (54.2)	0.341	67.5 (32.4)	72.3 (36.6)	73.4 (35.3)	80.0 (37.6)	<0.001
Energy (kcal)	2024.1 (678.8)	2077.9 (1032.4)	1973.1 (526.8)	2135.3 (738.2)	0.345	2012.7 (597.8)	2080.1 (590.9)	2126 (586.2)	2210.8 (616.2)	<0.001

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; SUA, serum uric acid; WHR, waist to hip circumference ratio.

Data are presented as No. (%), mean± SD or median (IQR);

**P values were calculated by using student t-test or Wilcoxon test for continuous variables and χ^2 test or Fisher exact test for categorical variables.*

7 participants were not available for education level; 121 participants were not available for WHR; 537 participants were not available for hypertension; 3 participants were not available for smoking status; 1 participant was not available for drinking behavior.

mortality and the difference between diabetic and non-diabetic individuals in China.

The findings showed that all-cause mortality was 10.1/1000 person-years in diabetic group and 4.8/1000 person-years in non-diabetic group. This finding indicates that diabetic subjects have a 2.1-fold higher risk of death compared with non-diabetic participants. Estimates of all-cause mortality in the current study were similar to an estimation reported in a 7-year cohort study comprising 512,869 Chinese people aged 30-79 years (13.7 per 1000 person-years in diabetes and 6.5 per 1000 person-years in the non-diabetes [adjusted RR, 2.00 (95%CI, 1.93 to 2.08)] (32).

A cohort study conducted in China comprising 127 771 adults 65 years and older report higher CVD-related mortality for SUA level <4 mg/dL and ≥7 mg/dL, revealing a U-shaped association between SUA Levels with CVD and all-cause mortality (33). A previous meta-analysis reported that HUA

TABLE 2 | Hazard ratios of risk factors for all-cause mortality among all individuals.

	Univariable		Multivariable	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Age, per 5 y increase	1.6 (1.4~1.8)	<.001	1.4 (1.3~1.6)	<.001
Male	2.3 (1.6~3.2)	<.001	2.5 (1.5~4.1)	<.001
Rural	1.6 (1.1~2.4)	0.017	1.9 (1.2~2.9)	0.004
Obese WHR	1.1 (0.8~1.6)	0.453	1.3 (0.9~1.9)	0.196
BMI, per 5-unit increase (kg/m^2)	0.6 (0.5~0.8)	<.001	0.6 (0.5~0.8)	0.002
Hypertension	1.7 (1.2~2.4)	0.003	1.3 (0.9~1.8)	0.230
Diabetes	2.2 (1.4~3.3)	<.001	0.4 (0.1~2.7)	0.324
Dyslipidemia	0.8 (0.6~1.2)	0.286	0.8 (0.5~1.2)	0.242
Serum uric acid (mg/dL)				
Q1 (Male: <4.7; Female: <3.7)	1.1 (0.6~2)	0.811	2.1 (1.1~4.1)	0.031
Q2 (Male: 4.7~5.5; Female: 3.7~4.4)	Ref (1.00)		Ref (1.00)	
Q3 (Male: 5.6~6.9; Female: 4.5~5.4)	1.6 (0.9~2.8)	0.077	1.4 (0.7~2.7)	0.290
Q4 (Male:> 6.9; Female: >5.4)	2.5 (1.5~4.1)	<.001	2.1 (1.1~4.0)	0.018
Smoking status				
Never	Ref (1.00)		Ref (1.00)	
Ever	3.3 (1.8~6.1)	<.001	1.2 (0.6~2.6)	0.625
Current	1.8 (1.3~2.6)	<.001	1.2 (0.8~2.0)	0.409
Alcohol drinker	1.2 (0.8~1.7)	0.329	0.9 (0.6~1.3)	0.484
eGFR (ml/min/l.73m2), per 10 unit increase	0.7 (0.6~0.8)	<.001	0.9 (0.8~1.0)	0.102
Interaction: Q2 of SUA * diabetes	1.7 (0.7~4.2)	0.239	10.1 (1.1~96.4)	0.044
Interaction: Q3 of SUA * diabetes	3.6 (1.9~6.8)	<.001	10.1 (1.2~86.0)	0.034
Interaction: Q4 of SUA * diabetes	2.6 (1.4~4.9)	0.002	4.6 (0.6~38.8)	0.158

Variables in multivariate logistic regression included all variables in the univariate logistic model. Other abbreviations are indicated in ***Table 1****.*

was associated with increased risk of CHD morbidity (aRR 1.13; 95% CI 1.05~1.21) and mortality (aRR 1.27; 95% CI 1.16~1.39), with a dose-response in women (34). Of note, this association was mainly confounded by accompanied comorbidities. In addition, findings on association between SUA and mortality in the diabetic population are inconsistent. Lamacchia et al. reported a J-shaped relationship between SUA levels and all-cause mortality rate in patients with type 2 diabetes mellitus (19). On the contrary, Panero et al. reported that uric acid level was not an independent predictor for cardiovascular mortality in

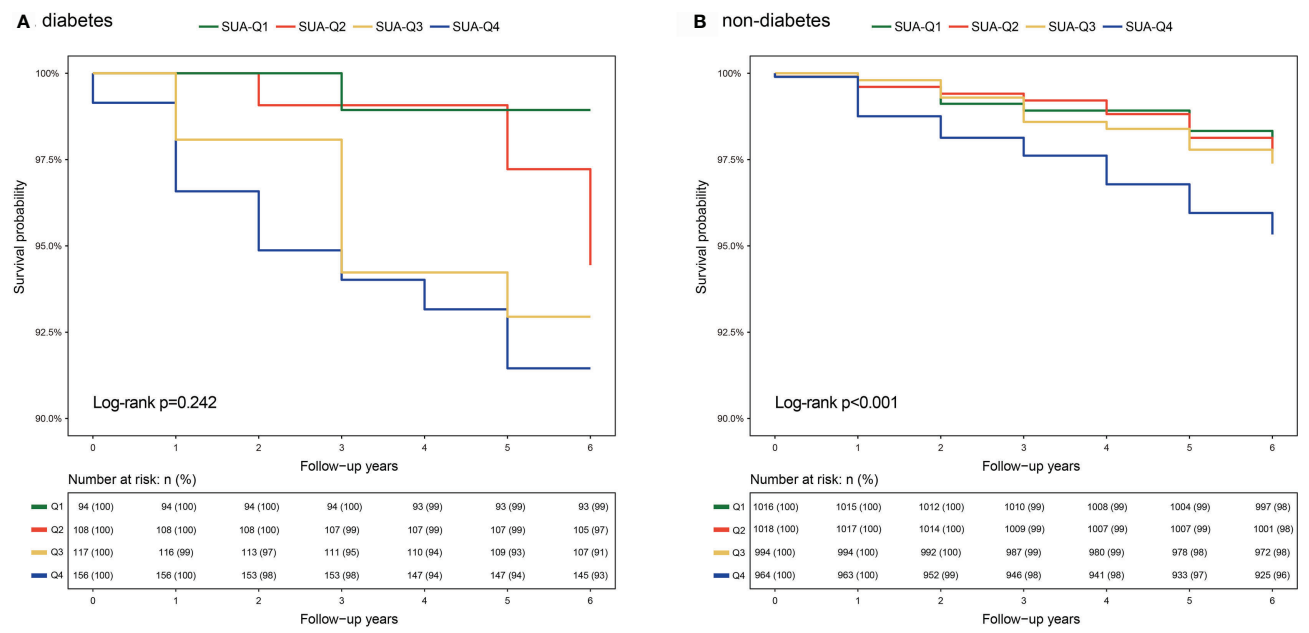

FIGURE 1 | K-M curves of SUA quartiles for all-cause mortality among individuals with and without diabetes **(A)** Diabetic individuals, **(B)** Non-diabetic individuals. Abbreviations are indicated in **Table 1**).

TABLE 3 | Hazard ratios of SUA levels for all-cause mortality among individuals with and without diabetes.

	rate per 1000 person-years	Univariable		age, gender-adjusted		Multivariable	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Diabetes							
Q1 (Male: <4.7; Female: <3.7)	1.8 (1/561)	0.2 (0.1~2.0)	0.186	0.2 (0.1~1.9)	0.164	0.3 (0.1~2.3)	0.226
Q2 (Male: 4.7~5.5; Female: 3.7~4.4)	9.3 (6/642)	Ref (1.00)		Ref (1.00)		Ref (1.00)	
Q3 (Male: 5.6~6.9; Female: 4.5~5.4)	15.0 (10/666)	2.1 (0.7~6.1)	0.183	1.8 (0.6~5.3)	0.283	1.5 (0.5~4.4)	0.507
Q4 (Male:> 6.9; Female: >5.4)	12.2 (11/901)	1.5 (0.5~4.4)	0.429	1.3 (0.5~3.8)	0.616	0.9 (0.3~2.9)	0.900
Non-diabetes							
Q1 (Male: <4.7; Female: <3.7)	3.8 (23/6046)	1.3 (0.7~2.5)	0.391	2.0 (1.0~3.9)	0.039	2.3 (1.2~4.6)	0.015
Q2 (Male: 4.7~5.5; Female: 3.7~4.4)	3.1 (19/6055)	Ref (1.00)		Ref (1.00)		Ref (1.00)	
Q3 (Male: 5.6~6.9; Female: 4.5~5.4)	4.4 (26/5903)	1.5 (0.8~2.8)	0.202	1.3 (0.7~2.5)	0.377	1.4 (0.7~2.7)	0.288
Q4 (Male:> 6.9; Female: >5.4)	8.0 (45/5660)	2.7 (1.5~4.8)	<0.001	1.9 (1.0~3.4)	0.036	2.0 (1.1~3.7)	0.032

*CI, confidence interval; HR, hazard ratio; Other abbreviations are indicated in **Table 1**. Multivariable HR was adjusted for age, gender, BMI, WHR, hypertension, dyslipidemia, smoking status and total protein intake (as 2nd quartile of SUA in non-diabetes individuals for reference).*
Q1, male: <4.7 mg/dL or female: <3.7 mg/dL; Q2, male: 4.7~5.5 mg/dL or female: 3.7~4.4 mg/dL; Q3, male: 5.6~6.9 mg/dL or female: 4.5~5.4 mg/dL; Q4, male:> 6.9 mg/dL or female: >5.4 mg/dL.

type 2 diabetes (35). This discrepancy can be attributed to differences in the study population, sample size, socioeconomic and cultural backgrounds. Most previous studies were limited by insufficient sample size, no appropriate comparisons, or narrow age range, thus limiting the ability to fully explore the independent effect of SUA levels on adverse renal outcomes. In the current study, similar linear associations were found among non-diabetic individuals but not in the diabetes group. This implies that the "U-shape" relationship between SUA levels and mortality may not be applicable to all individuals. This finding indicates that a higher mortality rate in diabetes was not attributable to SUA levels itself, thus it is consistent with previous findings that the mortality risk between diabetic and non-diabetic adults with high UA levels is not consistent (36).

Possible underlying mechanisms included in the pathogenesis of low-and-high SUA level-induced death. Low SUA is an indicator of poor nutritional status and vitamin C vitamin D deficiency, and malnourished status is an important factor in determining long-term survival (37–39). Extracellular UA is an antioxidant that can interact with hydrogen peroxide and hydroxyl radicals to effectively scavenge free radicals in the body, thus protecting vascular endothelial cells against oxidative attack. Also, the enzymatic reactions catalyzed by xanthine oxidase (hypoxanthine to xanthine and xanthine to

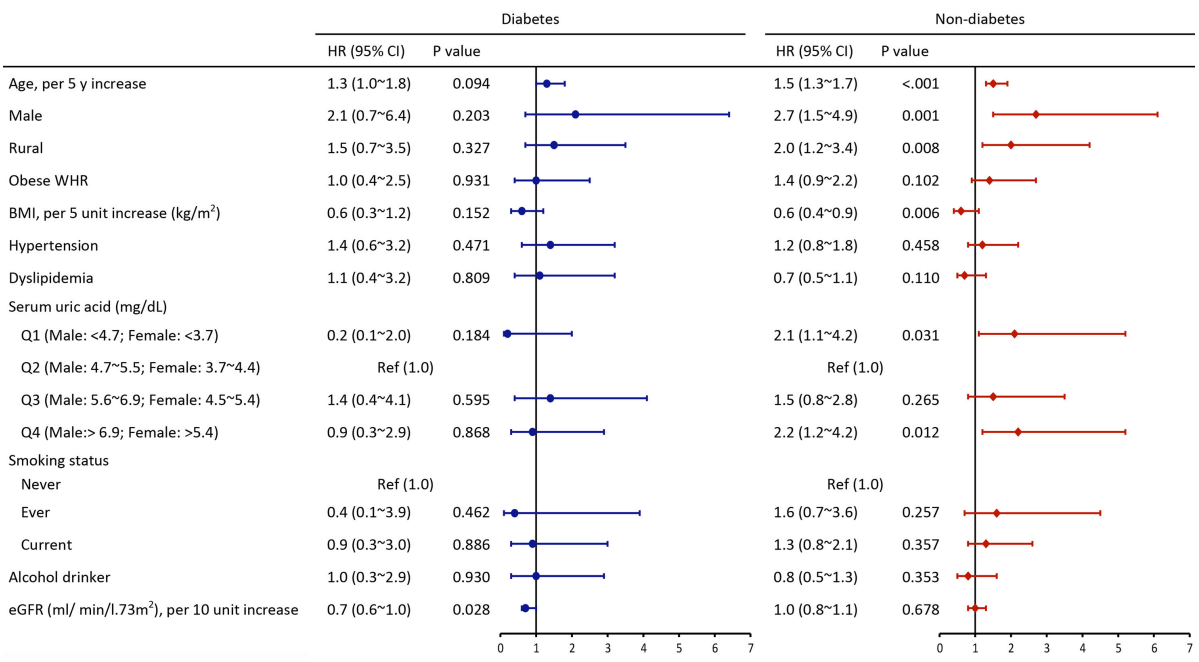

FIGURE 2 | Multivariate adjusted hazard ratios of risk factors for all-cause mortality among individuals with and without diabetes (HR, hazard ratios; CI, confidence interval; Other abbreviations are indicated in **Table 1**).

uric acid) produce a lot of reactive species (ROS). Consequently, both low and high levels of SUA may cause the imbalance of redox state (40). However, high levels of soluble UA and urate crystals can induce the release of inflammatory chemokines, vascular cell muscle proliferation, fat synthesis in hepatocytes, oxidative stress, and decreased adiponectin synthesis in adipocytes, which are correlated with increased mortality (41, 42). Moreover, as the final product of adenosine metabolism, high adenosine plasma concentration is associated with uric acid concentrations in CAD patients, which may lead to a high risk of atrial fibrillation (43, 44).

Statistically significant association between SUA and all-cause mortality was observed only in non-diabetic individuals, implying that SUA levels play a significant role in non-diabetic subjects compared with diabetic adults. In contrast, all-cause death is mainly attributed to renal dysfunction among individuals with diabetes. Therefore, timely interventions in the early phases of prediabetes or even early stages of diabetes may be more effective compared with treatment at later stages, when immune system activation and target organ damage have occurred.

The role of SUA on all-cause mortality should be explored further but the results significantly depend on age, lipid metabolism, the follow-up duration and interplay between SUA and kidney function. Baseline analysis showed associations between SUA and other variables including obese WHR, hypertension, BMI, dyslipidemia and eGFR. These findings are consistent with findings from previous studies that HUA can reflect an underlying renal dysfunction, which is associated with a higher risk of death among diabetic individuals (45, 46). Moreover, changes in uric acid tubular reabsorption in presence of glycosuria can explain the inconsistent role of SUA (47, 48). Further mechanism studies should be conducted to explore the relationship between SUA on all-cause mortality.

A positive association between SUA and all-cause death among non-diabetic individuals was observed in the current study, indicating that SUA is an independent risk factor is strengthened. Significant differences in association of SUA with all-cause mortality observed in the non-diabetic subjects may indicate that SUA plays a larger role among individuals with low CVD risk. Subgroup analyses were conducted after stratification by age, BMI, WHR, hypertension, dyslipidemia, CKD and FRS. The findings showed significant associations between SUA and all-cause death for 45~59 years subgroup, non-hypertension subgroup, non-dyslipidemia subgroup, low FRS groups subgroup. These results further confirm our assumptions that SUA plays a larger role among individuals with low CVD risk. Therefore, target comprehensive treatment should be used to manage risk factors in respective groups. Studies should explore the timely treatment of patients with the abnormal value of SUA with routine urate-lowering therapy (ULT) owing to the disparity of relationship between SUA and death under different disease backgrounds. Studies that are exploring this relationship and effects of therapies at different times are underway.

Some limitations deserve mention. Firstly, analyses were based on baseline SUA levels and its stability during the follow-up period of 5.9 years cannot be definitively determined. Secondly, the cause of death was not reported in the current study. Previous studies with long follow-up periods report that HUA can be an early manifestation of the carcinogenic process and CVD death, thus the association between uric acid, cancer and CVD risk should be explored in further studies (49, 50). Thirdly, the smaller sample size of diabetic individuals can lead to bias in results obtained from analyses across SUA categories. Moreover, differences in all-cause death between the two groups were satisfactory, as only a few events were reported and the wide confidence intervals of estimates were used. Lastly, concomitant medications including ULT, anti-hypertensive agents and diuretics may affect the risk of cardiovascular events and all-cause mortality, however, treatment information was not collected for all participants included in the CHNS study (14, 51, 52).

CONCLUSION

Our study proved that the prognostic role of SUA for predicting all-cause death might be regulated by diabetes. Both low and high SUA levels were associated with increased mortality, supporting a U-shaped association only in non-diabetic individuals. Whereas, renal dysfunction rather than SUA was an independent risk factor for all-cause mortality. Further studies should be conducted to determine the SUA levels at which intervention should be conducted and explore target follow-up strategies to prevent progression leading to poor prognosis.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cpc.unc.edu/projects/china/data/datasets/data-downloads-registration.

ETHICS STATEMENT

CHNS was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill and local IRB (institutional review board or ethics committee). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BZ and XD contributed to the conception or design of the work. BZ, JZ, and YL contributed to the acquisition, analysis, or interpretation of data for the work. BZ and YL drafted the manuscript. YL and YF critically revised the manuscript. BZ, JZ, NS, YS, YF, YL, and XD contribute to analysis, or interpretation of the work. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.782230/full#supplementary-material

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Trends in the Degree of Control and Treatment of Cardiovascular Risk Factors in People With Type 2 Diabetes in a Primary Care Setting in Catalonia During 2007–2018

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Objective: To assess the trends in cardiovascular risk factor control and drug therapy from 2007 to 2018 in subjects with type 2 diabetes mellitus (T2DM).

Materials and Methods: Cross-sectional analysis using yearly clinical data and treatment obtained from the SIDIAP database. Patients aged ≥18 years with a diagnosis of T2DM seen in primary care in Catalonia, Spain.

Results: The number of T2DM patients increased from 299,855 in 2007 to 394,266 in 2018. We also found an increasing prevalence of cardiovascular disease, heart failure, and chronic kidney disease (from 18.4 to 24.4%, from 4.5 to 7.3%, and from 20.2 to 31.3%, respectively). The achievement of glycemic targets (HbA1c<7%) scarcely changed (54.9% to 55.9%). Major improvements were seen in blood pressure (≤140/90 mmHg: from 55% to 71.8%), and in lipid control (low-density lipoprotein cholesterol <100 mg/dl: 33.4% to 48.4%), especially in people with established cardiovascular disease (48.8 to 69.7%). Simultaneous achievement of all three targets improved from 12.5% to 20.1% in the overall population and from 24.5% to 32.2% in those with cardiovascular disease but plateaued after 2013. There was an increase in the percentage of patients treated with any antidiabetic drug (70.1% to 81.0%), especially metformin (47.7% to 67.7%), and DPP4i (0 to 22.6%). The use of SGLT-2 and GLP-1ra increased over the years, but remained very low in 2018 (5.5% and 2.1% of subjects, respectively). There were also relevant increases in the use of statins (38.0% to 49.2%), renin-angiotensin system (RAS) drugs (52.5% to 57.2%), and beta-blockers (14.3% to 22.7%).

Conclusions: During the 2007-2018 period, relevant improvements in blood pressure and lipid control occurred, especially in people with cardiovascular disease. Despite the increase in the use of antidiabetic and cardiovascular drugs, the proportion of patients in which the three objectives were simultaneously achieved is still insufficient and plateaued after 2013. The use of antidiabetic drugs with demonstrated cardio renal benefits (SGLT-2 and GLP-1ra) increased over the years, but their use remained quite low.

Keywords: Type 2 dabetes, antidiabetic drugs, glycemic concrol, epidemiology, observational study

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a global health problem due to its high worldwide prevalence, high cost of management, associated chronic complications, disability, and premature deaths (1). Tight glycemic, blood pressure, and lipid control lower the risk of diabetes-related complications and death, especially when attained concomitantly. Consequently, multifactorial risk-factor control forms the foundation of clinical care for patients with T2DM (2–7). There has been consensus regarding several major goals of diabetes treatment for over two decades: achieving treatment targets for hemoglobin A1c (HbA1c) levels, blood pressure (BP), and low-density lipoprotein cholesterol (LDL-C) levels, as well as promoting smoking cessation (2–7). Previous studies reported that achievement of the three diabetes treatment goals had improved from the late 1990s to 2018 in the United States (US) (8–10), mainly from 1999 to 2010 (8), but recent analyses suggest that progress may have stalled or reversed in later periods (9, 10). Furthermore, a study in the United Kingdom (UK) showed that control of cardiovascular risk factors (CVRFs) remained suboptimal among both sexes (11), while another study reported that CVRFs had worsened especially among the overweight and obese adults (12).

Several studies have been published showing changes in the prescription of antidiabetic drugs (13–18). In the UK, an observational study reported an increase in metformin prescriptions and a decrease in sulphonylureas prescriptions between 2000 and 2017 (13). A study from Austria between 2012 and 2018 reported that metformin (alone or in combination) was the most frequently prescribed drug, and its use increased over the years; the prescriptions of SGLT-2i and GLP-1ra also increased, while prescriptions of sulphonylureas decreased (14). Several studies showed similar trends in the prescription of antidiabetic drugs in the United States (US): metformin remains the dominantly prescribed drug, together with insulins and sulfonylureas, while increased use has been observed mainly for Dipeptidyl peptidase-4 inhibitors (DPP-4i) and Glucagon-like peptide-1 receptor agonist (GLP-1ra) (15–17). In Catalonia, using the SIDIAP (Sistema per el Desenvolupament de la Investigació en Atenció Primària) population database, our group reported that despite the increasing use of new antidiabetic drugs, no clinically relevant changes were observed in glycemic control from 2007 to 2013 (18).

The healthcare system in Catalonia (Spain) is public and universal, where the primary care centers provide first contact and continuing care for persons with any health concerns, and they are usually the principal place where T2DM is diagnosed and managed. The antidiabetic treatment is free of charge for retired and severely ill people, while active subjects pay just a small part of the cost of the drugs. Since 2006, a system of electronic medical records (EMR), called e-CAP, was fully implemented in primary care, which allowed the creation of the SIDIAP population database (19, 20). To date, it is not known whether there has been progress in the degree of control of the three primary objectives (HbA1c, BP, and LDL-C) in our primary care environment.

Due to important changes in the therapeutic guidelines, we hypothesized that there would be changes in the control of cardiovascular risk factors (CVRFs) and pattern of use of antidiabetic drugs in our T2DM population. Our study aimed to describe the degree of control and treatment pattern related to CVRFs during 2007-2018 in primary care centers in Catalonia (Spain).

MATERIALS AND METHODS

Design and Settings

We obtained annual cross-sectional data from 2007 to 2018 using the primary health care SIDIAP database. This database includes secondary pseudo-anonymized routinely collected health data from subjects attended in the primary health care centers (PHCCs) of the leading health care provider in Catalonia (Spain), the Catalan Institute of Health (Institut Català de la Salut, ICS). The SIDIAP database is a well-recognized and valid database for the study of diabetes, including EMR, clinical and laboratory parameters, and medicine prescription and dispensation data. In 2018, the ICS managed 288 PHCCs that served 5,672,956 registered citizens, 75.2% of the Catalan population.

Eligibility Criteria

We included all subjects 18 years or older with a diagnosis of T2DM in the database defined by the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnostic codes (E11 or E14 and sub-codes). We excluded all subjects with diagnostic codes of other types of diabetes such as type 1, gestational, or other (E10, O24, E13, respectively).

Study Variables

For each year evaluated, the "cut-off" date was defined as December 31st. We collected variables related to the social-demographic characteristics (age, sex, smoking status, and alcohol consumption) and duration of T2DM. Comorbidities, such as hypertension and hypercholesterolemia, were defined on the base of the specific diagnostic code and/or drug treatment for any of these conditions. Peripheral artery disease, cerebrovascular disease, heart failure, ischemic heart disease, peripheral neuropathy, retinopathy as well as composite variables for microvascular and macrovascular complications were defined by the diagnostic codes of these conditions. Chronic kidney disease (CKD) was defined by the specific diagnostic code and/or the combination of CKD-EPI glomerular filtration rate <60 ml/min/1,73m2 and/or an albumin/creatinine ratio >30mg/g. The closest measurement to the "cut-off" date for clinical variables (systolic and diastolic blood pressure and body mass index -BMI) and laboratory parameters (HbA1c, lipid profile, renal profile) were considered. Drug treatment dispensations during the whole year (antidiabetic, antithrombotic, antihypertensive, and lipid-lowering drugs) were collected. Six steps of antidiabetic treatment were considered: non-pharmacological therapy (no drugs), non-insulin antidiabetic drug (NIAD) monotherapy, NIAD double therapy, NIAD triple therapy, insulin alone and insulin in combination. The non-pharmacological therapy was defined if there were no records for dispensing antidiabetic drugs during the previous year. Monotherapy was defined for NIADs and insulin separately. Dual therapy was defined as a combination of two NIADs, while triple therapy was a combination of three NIADs. Insulin in combination included all subjects with insulin in combination with any NIAD.

Statistical Methods

Descriptive analysis for study variables was done for each year of observation. We calculated mean and standard deviation for all quantitative variables, and frequencies and percentages for qualitative variables. We calculated the degree of glycemic, blood pressure, and lipid control and the use of antihypertensive, lipid-lowering, antithrombotic, and glucose-lowering therapies. According to local and international guidelines, glycemic control was defined at an HbA1c level below 7%; we also used an HbA1c threshold below 8%, which is the pay-for-performance goal at our institution (ICS). We used the mean of all available BP measurements (usually 3-4 readings) to estimate each patient's systolic and diastolic BP. BP control was defined as a systolic/diastolic BP level equal or less than 140/90 mm Hg. Cholesterol control was defined as having an LDL-C level less than 100 mg/dL. We further defined a composite indicator using the three outcomes (HbA1c, BP, and LDL-C). LDL-C control and the combined indicator were analyzed globally and separately in people with and without cardiovascular disease (CVD). Additionally, we performed trend tests to analyze whether the reported changes were statistically significant. For the continuous variables, we applied one-factor ANOVA, where the factors were the different year periods we wanted to compare (2007-2018). For categorical variables, we used the "prop_trend_test" function of the R Package rstatix (version 0.7.0). This function performs chi-squared test to assess the trend in proportions. Data management and all analyses were performed using R statistical software, version 3.6.3. (2020/02/29).

Institutional Review Board Statement

The studies involving human participants were reviewed and approved by Institutional Review Board (or Ethics Committee) of IDIAP Jordi Gol i Gurina Foundation (protocol code 21/111-P and date of approval 04/05/2021). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

RESULTS

Characteristics of the Subjects

Characteristics of the study subjects at each time-point of the study are presented in **Table 1**. During the 12 years of observation, the population identified with T2DM in our database increased from 299,855 in 2007 to 394,266 subjects in 2018. The mean age increased from 68.4 to 70.3 years, and the proportion of males was from 51.9% to 55%. Regarding toxic habits, smokers decreased from 18.1% in 2007 to 14.4% in 2018, and high-risk alcohol consumption decreased from 2.9% to 1.2%. An increase in the prevalence of cardiovascular disease, heart failure, and chronic kidney disease was observed (from 18.4 to 24.4%, from 4.5 to 7.3% and from 20.2 to 31.3%, respectively).

Concerning comorbidities, hypertension and dyslipidemia were highly prevalent among T2DM subjects; both increased over the years. The prevalence of chronic diabetic complications also increased progressively. We observed a progressive decrease in BP and LDL-C mean values while BMI and HbA1c did not show any relevant changes.

Use of Antidiabetic Treatment

Figure 1A and **Supplementary Table 1** show the proportion of patients in each treatment step (no drugs, NIAD monotherapy, NIAD dual therapy, NIAD triple therapy, insulin alone, and insulin in combination). We observed a considerable decrease (12.1%) in people without pharmacological antidiabetic treatment, from 29.9% to 19.0% at the end of the observation period. NIAD monotherapy increased from 29.9% to 34.2%. The use of double NIAD therapy and insulin alone slightly decreased, while triple NIAD therapy and insulin in combination with NIAD increased over the years.

Figure 1B and **Supplementary Table 1** show the frequencies of antidiabetic drug use. The use of metformin increased from 47.7% to 67.7%, as was the case for DPP-4i: from 0 to 22.6%. The use of sodium-glucose co-transporter 2 inhibitors (SGLT-2i) and GLP-1ra increased over the years, but their use remained low (5.5% and 2.1% of patients, respectively, in 2018). The use of thiazolidinediones, alpha-glucosidase inhibitors, and especially

TABLE 1 | Characteristics of the subjects during the study period.

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	p-value
N	299855	318065	335771	355019	369600	384826	395470	402312	401175	404252	400209	394266	–
Age, mean (SD), years	68.4 (12.2)	68.6 (12.3)	68.8 (12.4)	68.9 (12.5)	69.1 (12.6)	69.3 (12.6)	69.5 (12.7)	69.7 (12.7)	69.9 (12.6)	70.1 (12.6)	70.2 (12.6)	70.3 (12.5)	<0.001*
Age >75 years, n (%)	98104 (32.7)	107607 (33.8)	115629 (34.4)	124675 (35.1)	132801 (35.9)	140657 (36.6)	144226 (36.5)	145462 (36.2)	147890 (36.9)	149950 (37.1)	148749 (37.2)	148385 (37.6)	<0.001**
Diabetes duration, (years)	5.72 (5.58)	6.17 (5.59)	6.56 (5.63)	6.93 (5.71)	7.32 (5.80)	7.68 (5.92)	8.04 (6.03)	8.46 (6.08)	8.89 (6.17)	9.33 (6.30)	9.76 (6.42)	10.2 (6.57)	<0.001*
Sex (male), n (%)	155534 (51.9)	166499 (52.3)	177329 (52.8)	188809 (53.2)	197641 (53.5)	206793 (53.7)	213202 (53.9)	217706 (54.1)	218271 (54.4)	220818 (54.6)	219289 (54.8)	216708 (55.0)	<0.001**
Smoking habit, n (%)													
No smoker	151906 (64.5)	169301 (64.3)	186097 (64.0)	212027 (64.7)	224377 (64.3)	233993 (63.7)	233957 (61.4)	230948 (59.2)	224317 (57.3)	221448 (55.9)	216008 (54.8)	209774 (53.8)	<0.001**
Ex-smoker	42554 (18.1)	46441 (17.6)	49119 (16.9)	50377 (15.4)	50347 (14.4)	51658 (14.1)	54518 (14.3)	56625 (14.5)	56756 (14.5)	57323 (14.5)	57457 (14.6)	56060 (14.4)	<0.001**
Current smoker	40926 (17.4)	47488 (18.0)	55656 (19.1)	65449 (20.0)	74050 (21.2)	81493 (22.2)	92541 (24.3)	102432 (26.3)	110433 (28.2)	117462 (29.6)	120801 (30.6)	124391 (31.9)	<0.001**
Alcohol consumption, n (%)													
No alcohol consumption	82147 (70.0)	93138 (70.9)	108256 (70.7)	129886 (70.5)	137741 (71.0)	151994 (71.6)	169619 (69.5)	159519 (65.5)	160084 (64.4)	166452 (64.2)	161344 (63.7)	167135 (63.9)	<0.001**
Low risk alcohol consumption	31721 (27.0)	34600 (26.3)	41045 (26.8)	50310 (27.3)	52133 (26.9)	56258 (26.5)	70112 (28.7)	79852 (32.8)	84434 (34.0)	88968 (34.3)	88419 (34.9)	91182 (34.8)	<0.001**
High risk alcohol consumption	3492 (2.98)	3578 (2.72)	3781 (2.47)	4069 (2.21)	4021 (2.07)	4038 (1.90)	4328 (1.77)	4303 (1.77)	3977 (1.60)	3803 (1.47)	3525 (1.39)	3335 (1.27)	<0.001**
Comorbidities, n (%)													
Hypertension	222302 (74.1)	237453 (74.7)	253054 (75.4)	269075 (75.8)	281742 (76.2)	294236 (76.5)	304925 (77.1)	311876 (77.5)	312206 (77.8)	315212 (78.0)	312336 (78.0)	308599 (78.3)	<0.001**
Hypercholesterolemia	169551 (56.5)	185959 (58.5)	205119 (61.1)	224327 (63.2)	239694 (64.9)	253181 (65.8)	266431 (67.4)	274067 (68.1)	275969 (68.8)	278764 (69.0)	277187 (69.3)	274519 (69.6)	<0.001**
Obesity	75824 (45.2)	77715 (45.1)	81900 (45.4)	89403 (45.6)	91969 (45.5)	97538 (45.4)	112956 (46.3)	119249 (46.4)	121540 (46.1)	125400 (46.0)	123006 (45.3)	122075 (44.8)	<0.001**
Retinopathy	14466 (4.8)	16976 (5.3)	19892 (5.9)	22930 (6.5)	25440 (6.9)	28177 (7.3)	31020 (7.8)	34166 (8.5)	36446 (9.1)	38403 (9.5%)	39175 (9.79)	40676 (10.3)	<0.001**
Chronic kidney Disease	60473 (20.2)	68120 (21.4)	77217 (23.0)	84019 (23.7)	87471 (23.7)	96813 (25.2)	103750 (26.2)	111530 (27.7)	116389 (29.0)	117985 (29.2)	121388 (30.3)	124078 (31.5)	<0.001**
Cardiovascular disease	55035 (18.4)	61252 (19.3)	67826 (20.2)	74674 (21.0)	80154 (21.7)	85780 (22.3)	90173 (22.8)	93578 (23.3)	94779 (23.6)	97136 (24.0)	97202 (24.3)	96379 (24.4)	<0.001**
Heart failure	13498 (4.5)	15275 (4.8)	17176 (5.1)	19653 (5.5)	21852 (5.9)	24623 (6.4)	27012 (6.8)	28664 (7.1)	29331 (7.3)	30218 (7.5)	29777 (7.4)	28870 (7.3)	<0.001**
Clinical variables, mean, (SD)													
Systolic blood pressure (mm Hg)	138 (16.9)	137 (16.5)	136 (16.1)	135 (15.6)	135 (15.3)	134 (14.8)	133 (14.4)	133 (14.2)	133 (13.9)	133 (13.6)	133 (13.8)	133 (13.7)	<0.001*
Diastolic blood pressure (mm Hg)	76.4 (9.79)	76.1 (9.78)	75.8 (9.81)	75.5 (9.82)	75.2 (9.84)	74.7 (9.74)	74.4 (9.77)	74.5 (9.77)	74.7 (9.73)	74.9 (9.68)	75.0 (9.77)	75.1 (9.74)	<0.001*
BMI >30 kg/m^2	75824 (45.2)	77715 (45.1)	81900 (45.4)	89403 (45.6)	91969 (45.5)	97538 (45.4)	112956 (46.3)	119249 (46.4)	121540 (46.1)	125400 (46.0)	123006 (45.3)	122075 (44.8)	<0.001*
BMI, (kg/m^2)	30.1 (5.02)	30.1 (5.01)	30.1 (5.05)	30.1 (5.07)	30.1 (5.08)	30.1 (5.11)	30.2 (5.18)	30.2 (5.19)	30.2 (5.20)	30.2 (5.22)	30.1 (5.21)	30.0 (5.21)	<0.001*
HbA1c, (%)	7.16 (1.46)	7.23 (1.48)	7.25 (1.47)	7.17 (1.36)	7.25 (1.36)	7.22 (1.33)	7.09 (1.31)	7.07 (1.29)	7.10 (1.29)	7.10 (1.31)	7.07 (1.29)	7.09 (1.29)	<0.001*
Cholesterol Total,(mg/dL)	194 (39.5)	192 (39.9)	193 (39.9)	190 (39.8)	188 (39.3)	187 (39.4)	184 (39.4)	184 (39.2)	183 (39.7)	182 (39.8)	183 (40.5)	182 (40.4)	<0.001*
Cholesterol HDL,(mg/dL)	50.0 (13.3)	49.9 (13.3)	49.1 (13.2)	48.6 (12.9)	48.9 (13.2)	49.0 (13.2)	49.4 (13.2)	49.0 (13.1)	48.9 (13.0)	48.9 (13.0)	49.3 (13.1)	48.7 (12.7)	<0.001*
Cholesterol LDL,(mg/dL)	115 (33.0)	113 (33.3)	114 (33.3)	112 (33.0)	109 (32.8)	109 (32.8)	105 (32.7)	105 (32.5)	105 (32.7)	103 (32.5)	103 (33.1)	103 (33.3)	<0.001*
Triglycerides, (mg/dL)	153 (110)	155 (108)	157 (107)	153 (103)	155 (104)	154 (103)	156 (102)	157 (103)	158 (103)	159 (105)	162 (106)	159 (104)	<0.001*
Estimated glomerular filtration rate (mL/min/1.73m^2)	73.9 (17.0)	73.5 (17.3)	73.0 (17.6)	73.6 (17.5)	74.3 (17.6)	73.8 (17.8)	73.4 (17.9)	72.8 (18.2)	72.7 (18.4)	73.7 (18.4)	73.5 (18.5)	73.4 (18.5)	<0.001*
Albumin/creatinine rat (mg/g)	38.0 (138)	39.3 (141)	39.7 (149)	41.6 (158)	40.7 (153)	42.6 (158)	44.1 (165)	48.7 (181)	54.3 (202)	58.2 (211)	62.3 (223)	64.4 (227)	<0.001*
Drug treatments, n (%)													
Antidiabetic drugs	206701 (68.9)	222751 (70.0)	238624 (71.1)	257162 (72.4)	271761 (73.5)	284746 (74.0)	292978 (74.1)	300237 (74.6)	305678 (76.2)	312368 (77.3)	316072 (79.0)	319272 (81.0)	<0.001**
Antithrombotic drugs	113108 (37.7)	121593 (38.3)	132746 (68.2)	140210 (39.5)	145230 (39.3)	141294 (36.7)	148350 (37.5)	148959 (37.0)	147561 (36.8)	147479 (36.5)	144272 (36.1)	139478 (35.4)	<0.001**

(Continued)

TABLE 1 | Continued

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	p-value
Lipid-lowering drugs	124280 (41.4)	136850 (43.0)	155808 (46.4)	173200 (48.8)	186254 (50.4)	189858 (49.3)	203642 (51.5)	207653 (51.6)	208937 (52.1)	209943 (51.9)	208987 (52.2)	208840 (53.0)	<0.001**
Antihypertensive	189348 (63.1)	200707 (63.1)	215455 (64.2)	229767 (64.7)	240860 (65.2)	247106 (64.2)	261151 (66.0)	268779 (66.8)	271849 (67.8)	276935 (68.5)	278346 (69.6)	278356 (70.6)	<0.001**

*BMI, body mass index; HbA1c, glycated hemoglobin A1c; SD, standard deviation; *Anova 1 Factor; **Chi-square trend test.*

sulphonylureas decreased notably (the latter from 31.7% to 18.8%), while the use of glinides remained stable (5.5% in 2018).

Trends in HbA1c levels are presented in **Figure 2** and **Supplementary Tables 2**, **3**. Small changes were observed throughout the study period for the different categories of HbA1c: from 54.9% to 55.9% for the HbA1c<7% threshold and from 79% to 81.1% for HbA1c<8% (**Figure 2A**). At the end of the observational period, more than a third of subjects (34.9%) had an HbA1c<6.5% (47.5 mmol/mol) while 18.9% were poorly controlled (HbA1c>8%, 64 mmol/mol). When we analyzed the mean HbA1c for each step of treatment (i.e., no drugs, NIAD monotherapy, NIAD dual therapy, NIAD triple therapy, insulin

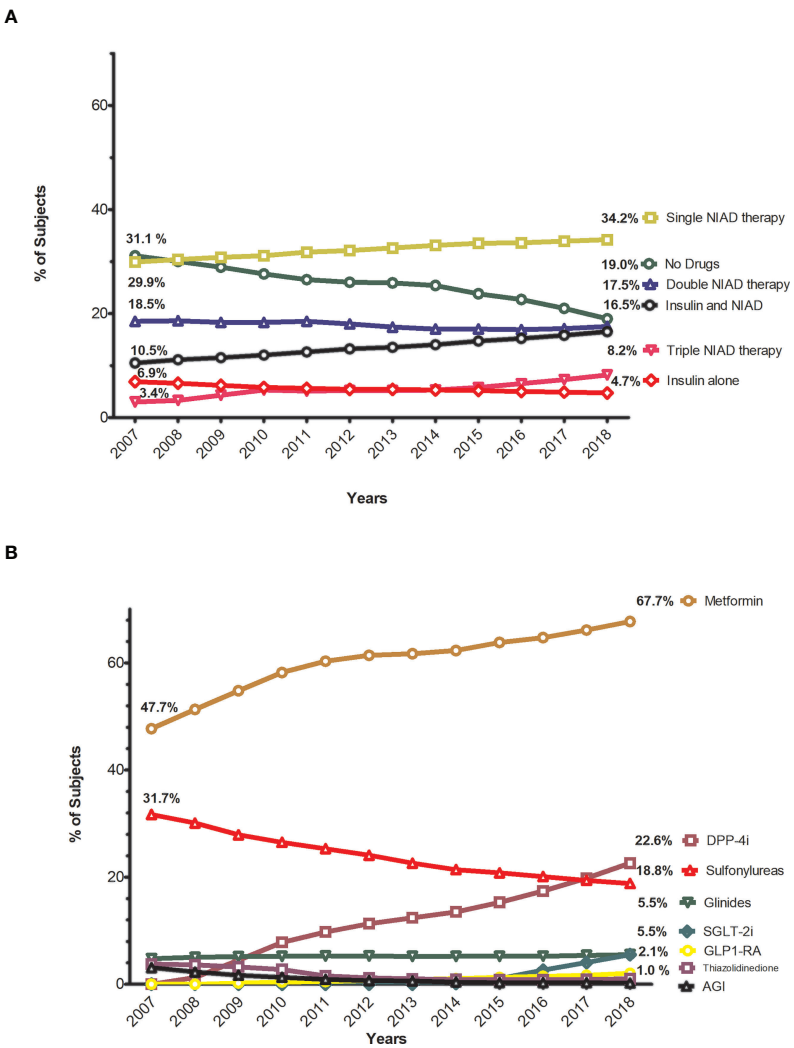

FIGURE 1 | Trends in the proportion of subjects by different steps of antidiabetic treatment and using non-insulin antidiabetic drugs. **(A)** Annual trends in the proportion of subjects by steps of antidiabetic treatment. **(B)** Annual trends in the proportion of subjects treated with non-insulin antidiabetice drugs.

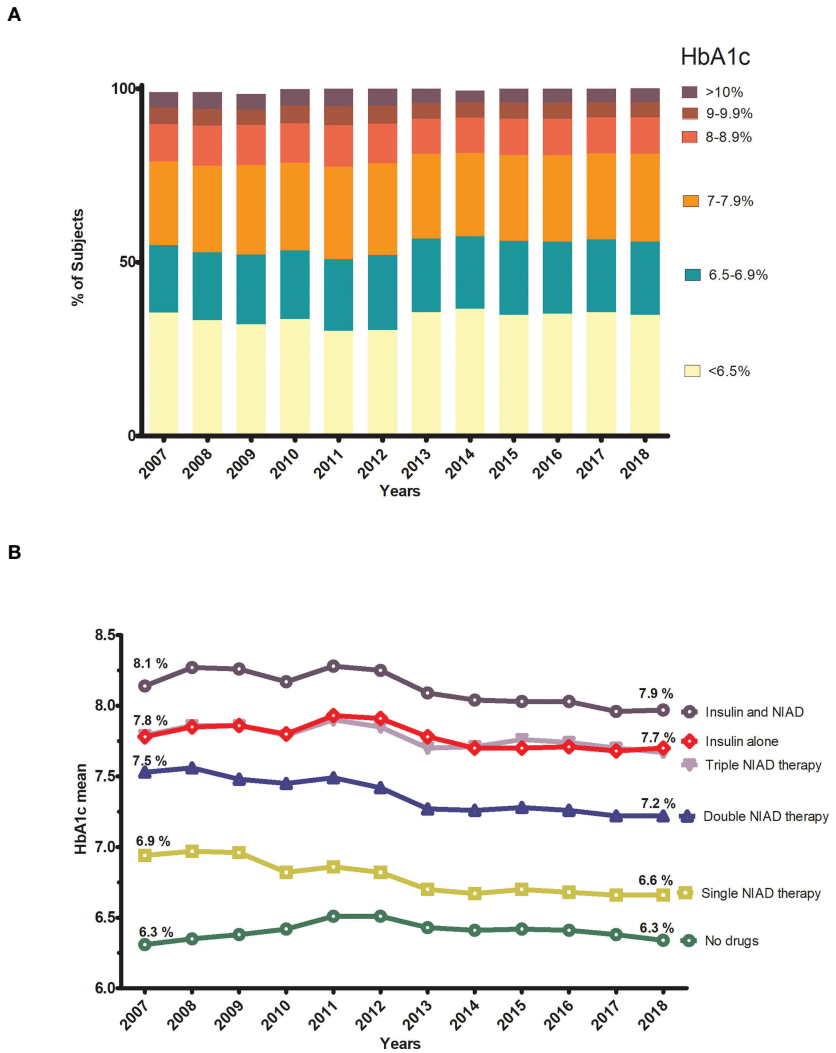

FIGURE 2 | Trends in glycemic control by HbA1c categories and by step of treatment. **(A)** Annual trends in distribution of subjects according to HbA1c categories. **(B)** Annual trends in the mean HbA1c for each step of treatmet.

alone and insulin in combination), in general, glycemic control worsened with the more complex treatments, but a trend to improvement was observed for all drug strategies from 2013 to 2018 (**Figure 2B**). The more pronounced reductions of mean HbA1c were observed in those subjects receiving double NIAD who experienced a reduction of mean HbA1c of -0.33% (from 7.5% to 7.2%) and in those under monotherapy treatment with a reduction of -0.28% (from 6.9% to 6.6%), while non-pharmacological treatment (no drugs) remained stable (6.3%).

Use of Antithrombotic, Antihypertensive, and Lipid-Lowering Agents

Figure 3 and **Supplementary Table 4** show the use of antithrombotic, antihypertensive, and lipid-lowering drugs over the years. During the study period, the use of antihypertensive increased from 63.1% in 2007 to 70.6% in 2018, the use of lipid-lowering drugs increased from 41.4% to 53.0%, while the use of antithrombotic drugs slightly decreased (from 37.7% to 35.4%) (**Table 1**). The use of antiplatelet drugs slightly decreased over the years (from 32.5% to 29.2%), while the use of anticoagulants increased (5.2% to 6.2%) (**Figure 3A**). Among the antihypertensive drugs, renin-angiotensin system (RAS) drugs (Angiotensin-converting-enzyme inhibitors-ACEI or Angiotensin II receptor blocker-ARB) and diuretics were principally used and gradually increased (from 52.5% to 57.2% and from 38.7% to 42.3%, respectively) (**Figure 3B**). There was an increase in the use of ACEI, ARB, and especially beta-blockers (1.3%, 3.4%, and 8.4%, respectively). Regarding the lipid-lowering agents, statins were by far the most widely used lipid-lowering drugs in all years, and their use greatly increased (11.2%), from 38.0% to 49.2%, at the end of the study period (**Figure 3C**).

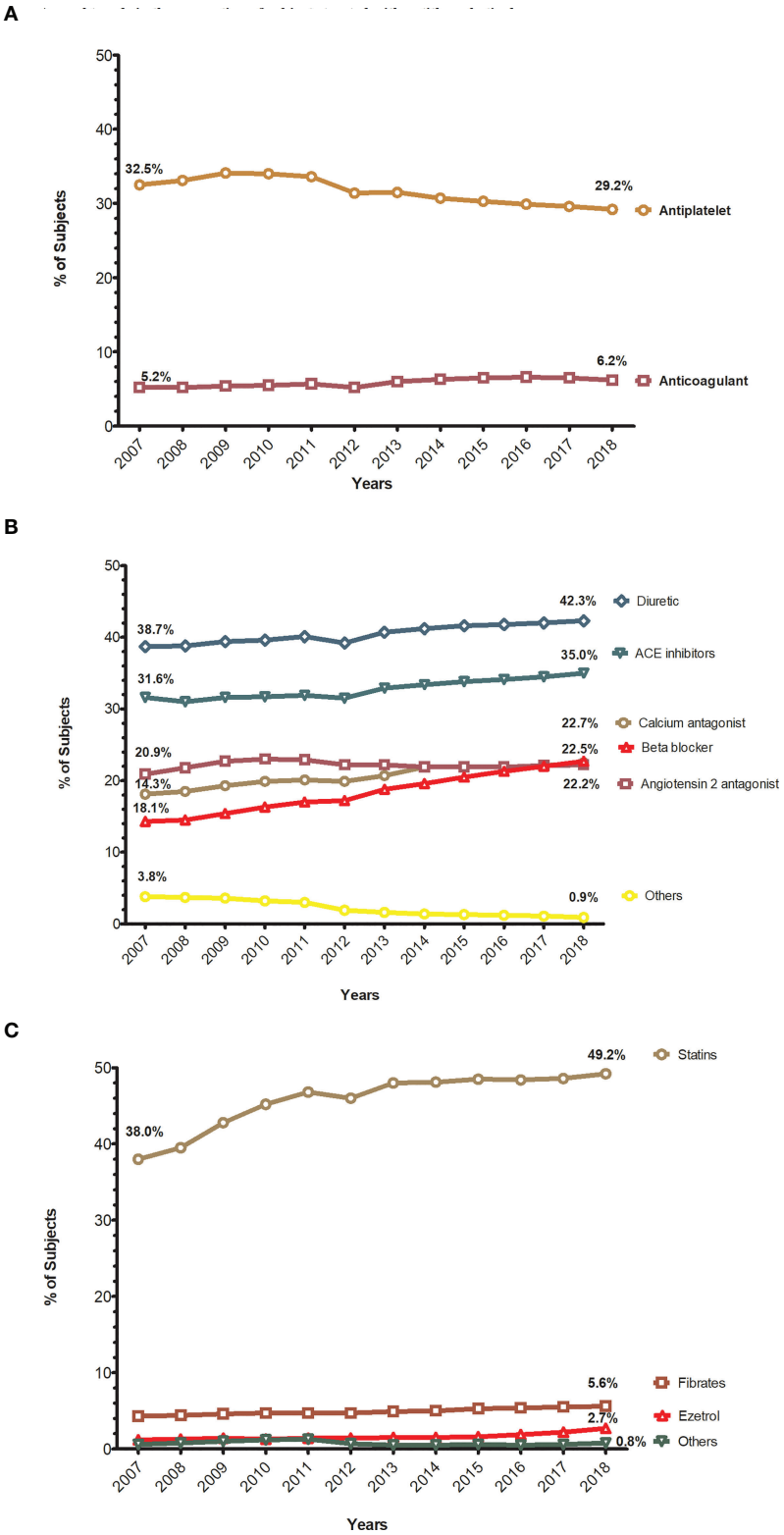

FIGURE 3 | Trends in the proportion of subjects treated with antithrombotic, antihypertensive, and lipid-lowering drugs. **(A)** Annual trends in the proportion of subjects treated with antithrombotic drugs. **(B)** Annual trends in the proportion of subjects treated with antihypertensive drugs. **(C)** Annual trends in the proportion of subjects treated with lipid lowering drugs.

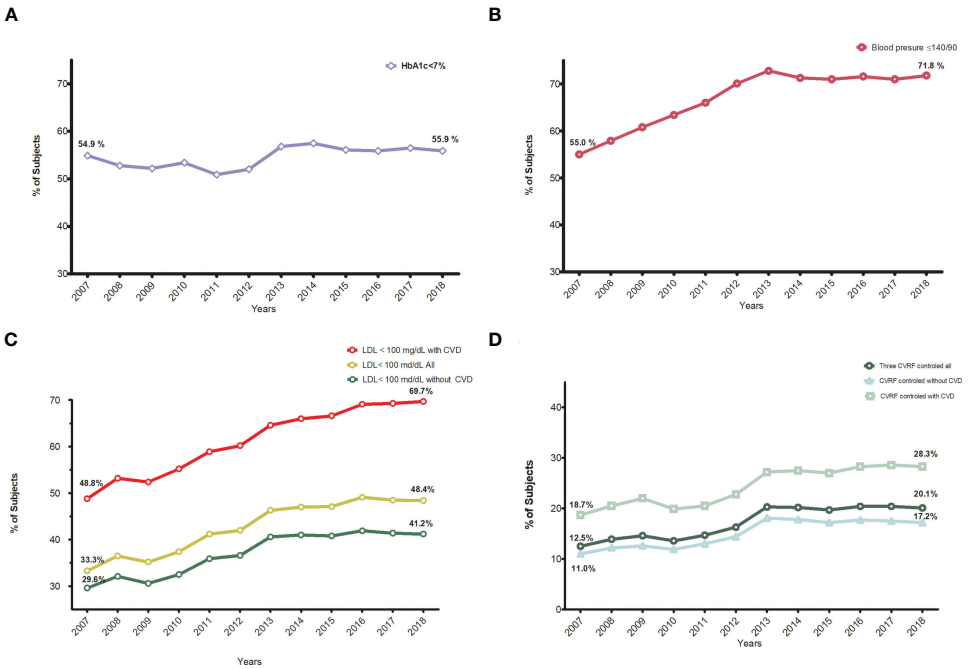

FIGURE 4 | Trends in the proportion of subjects achieving different therapeutic goals. **(A)** Annual trends in the proportion of subjects reaching HbA1c <7%. **(B)** Annual trends in the proportion of subjects reaching blood pressure ≤140/90 mmHg. **(C)** Annual trends in the proportion of subjects reaching LDL-C<100 mg/dl, global,with and without cardiovascular disease. **(D)** Annual trends in the proportion of subjects reaching all three goals, global, with and without cardiocvascular disease.

Therapeutic Goals

Trends in achieving the therapeutic goals are presented in **Figure 4** and **Supplementary Tables 5**, **6**. The percentage of subjects achieving an HbA1c target <7% (53.0 mmol/mol) remained fairly stable over the years, with some smooth oscillations: the percentage of subjects meeting this goal was lowest in 2011 (50.9%) and highest in 2014 (57.5%), and at the end of the observation period it was 55.9% (**Figure 4A**). According to the threshold of our institution (HbA1c<8%), there was a 2% increase, from 79.0% to 81.1%. These results are presented in the **Supplementary Table 5**.

Major improvements were seen in the proportion of people with blood pressure control (≤140/90 mm Hg), from 55% to 71.8% (**Figure 4B**). The same trend was seen with lipid control (low-density lipoprotein cholesterol <100 mg/dl): from 33.4% to 48.4%, especially in people with CVD: 48.8 to 69.7% (**Figure 4C**). Finally, achievement of all three targets (combined indicator) improved from 12.5% to 20.1% in the whole population and from 18.7% to 28.3% in those with CVD (**Figure 4D**).

Improvements in all indicators, except LDL-C in patients with CVD, plateaued after 2013. The percentage of patients with CVD with LDL-C control continued increasing from 64.6% in 2013 to 69.7% in 2018.

Trend Tests Analysis

We observed significant p values for trend test for nearly all of the variables over the years, except for the distribution of subjects according to HbA1c categories and the use of angiotensin receptor blockers.

DISCUSSION

This cross-sectional study shows the trends in the degree of cardiovascular risk factor control and prescribing practices between 2007 and 2018 in primary care in a Mediterranean area. During this period, a 31% increase (94,411 subjects) was observed in the registered T2DM population, and in the prevalence of cardiovascular disease, heart failure, and chronic kidney disease (from 18.4 to 24.4%, from 4.5 to 7.3% and from 20.2 to 31.3%, respectively). This could be probably due to an improvement in registration and the aging population. In fact, there was an increase in the mean age (from 68.4 to 70.3 years) and in the percentage of patients older than 75 (from 32.7% to 37.6%). The unexpected low diabetes duration could be explained by the EMR system (eCAP), which was widely introduced in 2006 in Catalonia. The accuracy of patients' diagnosis dates reported in the first years could be affected by memory, while further diagnoses based on laboratory results were probably more accurately registered after the implementation of the eCAP. There was also an increase in the records of chronic complications, especially chronic kidney disease (CKD), retinopathy, and heart failure. At the end of the study, nearly a quarter of patients (24.4%) had CVD and 31% CKD. These figures align with those of other studies on the prevalence of chronic complications (21, 22).

Concerning the control of CVRFs, greater improvements have been observed for cholesterol and BP than for glycemic control, as described in previous reports in the US and the UK

(8–12). In our database, glycemic control slightly improved from 54.9% to 55.9% for the HbA1c<7% threshold and from 79 to 81.1% for HbA1c<8%, which is the pay-for-performance goal of our institution (ICS). These changes do not seem to be outstanding, but at least they have not decreased as recently described in the US (10), in Germany and Austria (15), and in an international collaboration study of 49 countries (16). Moreover, regarding the treatment steps, a slight trend in the reduction in the mean HbA1c was seen in all pharmacological steps, the greatest seen with one or two NIAD starting in 2013, with a 0.3% reduction in both cases.

Major improvements were seen in the percentage of people achieving target blood pressure, from 55% to 71.8%. The same trend was seen for LDL-C targets: 33.4% to 48.4%, especially in people with CVD: 48.8% to 69.7%. Nevertheless, only one in five patients achieved all three risk factor control goals, increasing from 12.5% to 20.1% in the whole population, but stagnation occurred after 2013. This improvement was greater for those with CVD (from 18.7% to 28.3%), probably due to more intense treatment with lipid-lowering drugs. Published data from the US, based on NHANES surveys from 1999 to 2018, showed a worsening of glycemic control (HbA1c<7%) between the 2007–2010 and 2015–2018 surveys: from 57.4% to 50.5% of people achieving this target (10). In the same study, the percentage of people with blood pressure control (BP <140/90 mmHg) decreased from 74.2% to 70.4%, and minimal improvements were seen in lipid control, while the percentage of people in whom all three targets were simultaneously achieved plateaued after 2010 at around 22.2% in 2015–2018 (10). This percentage in the composite indicator is similar to the 20% observed in our database that also plateaued from 2013 to 2018.

A matter of concern is the fact that the composite indicator plateaued after an initial and progressive improvement. A possible explanation would be a ceiling on glycemic and blood pressure improvements, beyond which it is difficult to improve since relevant factors such as patient adherence, tolerance to drugs, and especially the need for less stringent goals in patients of advanced age. More than a third of the subjects were 75 years or older, and the benefits of strict glycemic control this population has not yet been fully demonstrated (23, 24). Overcoming clinical inertia by healthcare professionals, improving adherence to medications and healthy lifestyle behaviors in patients, and providing necessary health care access and resources, education, and self-management support by the healthcare system are challenges that need to be tackled (25).

Regarding pharmacological treatment, there was an increase in the proportion of subjects receiving antidiabetic drugs, especially for metformin and DPP4i. The use of newer classes of glucose-lowering drugs rose, whereas older classes such as sulfonylureas, pioglitazone, and alfa glucosidase inhibitors declined; these findings reflect a shift toward safer or better-tolerated drugs. Although increasing, the use of SGLT-2i and GLP-1ra agents with demonstrated cardiovascular benefits (2–7), remained low, probably because they are newer, more expensive, and have prescription restrictions in our country. For instance, there were negative economic incentives during this period for the prescription of SGLT-2i and GLP-1ra that may have contributed to their limited use. In addition, in Spain, GLP-1ra are only reimbursed, after administrative validation, in combination with other antidiabetic drugs for subjects with a BMI>30. This was not the case for SGLT-2i despite a more recent introduction in our country (from 2013 on). The increase after 2015 was very impressive, quickly surpassing the GLP-1ra prescription rate in 2018 (5.5% vs. 2.1%, respectively). DPP4i had the greatest increase in use, in agreement with other reports conducted worldwide (8–10, 13–18). They are an alternative to sulfonylureas for their lower risk of hypoglycemia, bodyweight increase, and greater convenience as an oral treatment instead of injectable drugs (26).

The percentage of people treated with statins, beta-blockers, and RAS drugs increased notably. Similar figures have been observed in the NHANES (National Health and Nutrition Examination Survey) study as mentioned earlier: 56.3% used statins, and 60.3% used a RAS antihypertensive (10). Use of antithrombotic therapies (mainly aspirin) showed a slight reduction, probably because of the recommendation against the prescription of aspirin in primary prevention since 2010 (27).

This study has some strengths and limitations. The main strength is that we used a large database to determine trends in primary care. However, this was a retrospective study, and missing data should be noted, especially in the first years of the study. For instance, the percentage of missing values for HbA1c was 36.9% in 2007, which decreased to 25% in 2018. This was also the case for the available values for calculating the combined 3 CVRF indicators: only 48.9% of patients had both three measurements in 2007 but this increased to 62.1% in 2018. Lack of data could be explained due to some patients not attending their routine visits, incomplete recording of patient information by some health professionals, and that a small proportion of subjects are under the care of endocrinologists in hospitals or private clinics. In studies like the current one that include a very large sample of participants, even small differences are statistically significant. Actually, the statistical differences found in our study do not add relevant information for the final interpretation of the findings. Nevertheless, a large number of measurements and the consistency of similar annual results contribute to the validity of our conclusions.

In conclusion, in our country, during 2007-2018, relevant improvements were observed in blood pressure and lipid control, especially in people with cardiovascular disease. Despite the increase in the use of antidiabetic and cardiovascular drugs, the proportion of patients in which the three objectives were simultaneously achieved is still insufficient and plateaued after 2013. Finally, the use of antidiabetic drugs with demonstrated cardio renal benefits like SGLT-2 and GLP-1ra increased over the years, but their use remained very low.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data controller for SIDIAP does not

allow the sharing of raw data. Requests to access these datasets should be directed to JF-N, josep.franch@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board (or Ethics Committee) of IDIAP Jordi Gol i Gurina Foundation (protocol code 21/111-P and date of approval 04/05/2021). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MM-C and BV have contributed equally to this work and share the first authorship. MM-C, JF-N, JR, RP-T, MB, DM, and BV conceived the research and participated in its design. JR and RP-T performed statistical analysis. MM-C and BV wrote the initial draft of the manuscript, which MM-C, JF-N, JR, RP-T, MB, DM, and BV edited. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2021.810757/full#supplementary-material

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Does Having a Usual Primary Care Provider Reduce Polypharmacy Behaviors of Patients With Chronic Disease? A Retrospective Study in Hubei Province, China

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Background: Within China's hierarchical medical system, many patients seek medical care in different hospitals independently without integrated management. As a result, multi-hospital visiting is associated with fragmented service utilization and increased incidence of polypharmacy behaviors, especially for patients with chronic disease. It has been confirmed that factors from the perspective of patients may cause polypharmacy behaviors in Chinese community patients; whether having a usual primary care provider for chronic disease patients could reduce the polypharmacy behaviors and the effect size remains unanswered, and that is what our study aimed to answer.

Methods: Our study adopted a cluster sampling method to select 1,196 patients with hypertension or diabetes and measured some information about them. The propensity score weighting method was adopted to eliminate the influence of confounding bias, and then a multivariate logistic regression model was conducted to test the relationship between having a usual primary care provider and polypharmacy behaviors.

Results: Patients without usual primary care providers were significantly correlated with polypharmacy behaviors (OR = 2.40, 95%CI: 1.74–3.32, $p < 0.001$), and the corresponding marginal effect is 0.09 (95%CI: 0.06–0.12). Patients who suffer from two kinds of diseases (OR = 3.05, 95%CI: 1.87–5.10, $p < 0.001$), with more than three kinds of diseases (OR = 21.03, 95%CI: 12.83–35.65, $p < 0.001$), with disease history of 20 years and above (OR = 1.66, 95%CI: 1.14–2.42, $p = 0.008$), who communicate frequently with doctors (OR = 3.14, 95%CI: 1.62–6.19, $p < 0.001$), alcoholic patients (OR = 2.14, 95%CI: 1.08–4.19, $p = 0.027$), who used to have meat-based food (OR = 1.42, 95%CI: 1.00–2.00, $p = 0.049$), and have vegetarian-based diet (OR = 1.42, 95%CI: 1.00–2.00, $p = 0.049$) are more likely to have polypharmacy behaviors, while patients aged between 65 and 75 years (OR = 0.50, 95%CI: 0.33–0.77, $p = 0.020$), used to be brain workers (OR = 0.67, 95%CI: 0.45–0.99, $p = 0.048$), with disease history

between 10 and 20 years (OR = 0.56, 95%CI: 0.37–0.83, $p = 0.005$), have had adverse drug reactions (OR = 0.64, 95%CI: 0.45–0.93, $p = 0.019$), and participated in medical insurance for urban and rural residents (OR = 0.35, 95%CI: 0.21–0.58, $p < 0.001$) were less likely to have polypharmacy behaviors.

Conclusion: The results suggest that having a usual primary care provider may reduce the incidence of having polypharmacy behaviors; we can take intervention measures to promote establishing a long-term relationship between patients and primary care providers.

Keywords: polypharmacy, chronic disease, usual primary care providers, propensity score weight, service utilization

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INTRODUCTION

Chronic non-communicable diseases (NCDs) are a kind of disease with insidious onset, long incubation period, long and slow course, uncured, lack of convinced evidence of biological etiology, and no clear indications for treatment. As the population ages, NCDs have become one of the greatest threats to public health. According to the World Health Statistics Report 2021 released by the WHO, 7 of the top 10 causes of death in 2019 were chronic diseases. In 2000, 60.8% of patients died from NCDs, and the proportion rose to 73.6% in 2019. Demographic changes such as the aging of the population promote the development of multimorbidity of chronic conditions (Xu et al., 2017). Multimorbidity always leads to polypharmacy behaviors among patients with chronic diseases. Polypharmacy behaviors have been considered to be an increasingly serious public health problem worldwide, especially among the elderly (Payne and Avery, 2011; Wastesson et al., 2018). The vast majority of studies defined taking five or more drugs at the same time as polypharmacy behaviors (Kaufman et al., 2002; Fialová, 2005; Payne and Avery, 2011; Mortazavi et al., 2016; Masnoon et al., 2017; Wastesson et al., 2018). A study in United States showed that 29.0% of elderly people used at least five prescription drugs. Another survey on community residents showed that 37.1% of men aged 75 to 85 years and 36.0% of women took five or more prescription drugs at the same time (Hoel et al., 2021). In the 2016 UK Health Survey, 56.0% of people aged ≥85 years took five or more drugs (UK.GOV, 2021), while about 9.0% of people aged 45–54 years took the same. A review report of polypharmacy behaviors found that the incidence of polypharmacy behaviors in various countries ranged from 38.1% to 91.2% (Jokanovic et al., 2015). Polypharmacy behaviors are becoming increasingly popular.

It has been reported that patients who take five medications have at least one serious medication problem (Strand et al., 1990; Hanlon et al., 2006). Polypharmacy behaviors are associated with an increase in adverse drug reactions, lower compliance, inappropriate drug therapies, and higher medical expenditure (Field et al., 2001; Goulding, 2004; Lau et al., 2005; Payne and Avery, 2011; Wastesson et al., 2018). Some other studies have also found that polypharmacy behaviors are associated with rehospitalization, falls, death, and poor health outcomes (Bushardt et al., 2008; Cooney and Pascuzzi, 2009; Dhalwani et al., 2017; Leelakanok et al., 2017). It also increases the economic burden of the health system (Fulton and Riley Allen, 2005).

The occurrence of polypharmacy behaviors is related to many factors. From the patients' perspective, demographic factors such as age, education, health behaviors (smoking, drinking, exercise, and daily eating habits) have significantly related to polypharmacy behaviors. In addition, disease-related factors have also been confirmed to cause polypharmacy behaviors in patients with chronic diseases. Many studies have found that the type of disease, the number of diseases, and the severity of the disease will affect the occurrence of polypharmacy behaviors in patients with chronic diseases (Bronskill et al., 2012; Liu et al., 2021). Medical cause has also been confirmed to be related to patients' polypharmacy behaviors. Inpatients had an average of two more drugs when compared with outpatients (Betteridge et al., 2012; Viktil et al., 2012). The disorder of multi-institution medical treatment and the lack of comprehensive management of patients' multi-institution medical treatment leads to problems such as repeated prescription, excessive prescription, misuse of prescription, and prescribing cascade, thus leading to polypharmacy behaviors (O'Connor et al., 2012). Moreover, from the care provider perspective, patients were consulted in different medical institutions and departments, resulting in doctor–patient communication not being smooth, fragmentation of medication regimen, and increased risk of polypharmacy behaviors. Some patients prefer to seek healthcare in different hospitals, which could not provide integrated medication recommendations and always resulted in repeat or unnecessary medication. However, few studies measured the factors that influenced polypharmacy behaviors in terms of service utilization and usual primary health care in China; whether having a usual primary care provider for chronic disease patients could reduce the polypharmacy behaviors and the effect size remains unanswered. On the whole, there is a research gap in exploring the relationship between usual care provider and polypharmacy behaviors. Our study aimed to explore the relationship between the usual primary health care and polypharmacy behaviors of patients with chronic diseases and quantify the impact effect.

METHODS

Study Settings and Sampling

The data were collected by a cluster sampling method from April to June 2021, in which we first selected four cities (Zhijiang, Qianjiang, Yichang, and Wuhan) from Hubei province, China. Wuhan and Yichang were taken as urban sample areas, while Zhijiang and Qianjiang were taken as rural sample areas. Three streets or towns were randomly selected from each city (a total of 12), and every street or town needed to collect 100 patients diagnosed with hypertension or diabetes, which can be managed by primary health care providers. Exclusion criteria included those who had not been taking medicine for more than 3 months, those who were younger than 18 years, those who cannot express themselves clearly, those who were unwilling to cooperate with this investigation, those who were severely ill and cannot complete the questionnaire, and those diagnosed with acute complications. In total, 1,205 participants joined the survey; 9 of them were excluded due to lack of information.

Variables and Measurement

The primary predictor of interest in this study was whether a patient reported having a usual primary care provider. In this study, the usual primary care providers were determined by asking the patients "Which of the following institutions have you frequently visited in the past 3 months?" Respondents who frequently visited primary health care institutions were considered to have primary health care providers, and the others were considered to have no primary health care providers.

The dependent variable was whether patients had polypharmacy behaviors; they were considered to have polypharmacy behaviors if they took five or more drugs per day, and other patients were regarded as non-polypharmacy.

Confounding variables included demographic characteristics, clinical conditions, medical treatment behavior data, health information data of patients with chronic diseases, and medication knowledge of patients.

Demographic data included the patient's domicile, gender, age, education level, annual income, job type, and residence status. Job type is classified into brain workers and manual workers. Residence status is divided into live alone and not live alone.

Clinical conditions included the number of chronic diseases, disease history, adverse drug reactions (ADRs), and severity of disease. Disease history is calculated based on the question "when were you diagnosed with chronic disease?"

Patients' medical treatment behaviors data included whether in hospital in the past year, type of medical insurance, the frequency of communication with doctors, etc. The type of medical insurance was divided into employee health insurance and urban and rural resident medical insurance. The frequency of communication with doctors is classified as none, rarely, occasionally, often, and always.

Health information data included smoking status, drink status, physical activity, and whether people with chronic diseases had their blood pressure or blood sugar checked regularly.

Patient knowledge was evaluated through administration of a questionnaire adapted from the study by McPherson et al. (Mcpherson et al., 2008; Okuyan et al., 2013); the median was taken as the critical value to divide the total score of medication knowledge into high and low score groups of medication knowledge.

Statistical Analysis

A descriptive analysis of sample characteristics was performed on SPSS 24.0, and the other statistical analyses were performed on R Commander Version 4.04, which is a graphical user interface for R software. Multivariate logistic regression analysis was conducted to model the association between having a usual primary care provider and participants' polypharmacy behaviors. Propensity-score weighting approach was applied to adjust for the observed difference in characteristics between those having a usual primary care provider and those not having and therefore could better tease out the net influence of having a usual primary care provider on patients' polypharmacy behaviors. Odds ratios (ORs), marginal effects, and their 95% confidence intervals were reported to indicate the relationship between the two variables. Statistical significance was defined as a two-tailed p-value <0.05 in all analyses.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. This study was approved by the Medical Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology, and the approval number is 2020 (S223).

RESULTS

Interviewee Information

As shown in **Table 1**, the characteristics of a total of 1,205 patients with chronic diseases who participated were collected in this survey, of which 1,196 completed questionnaires. About 71.0% (849/1,196) were 65 years old and above; the youngest patient was 26 years old, the oldest patient was 92 years old, and the average age was 68.55 years old. About 58.0% (693/1,196) were female. Approximately 48.3% (578/1,196) were living in the urban area. About 62.6% (749/1,196) were manual workers; 10.4% lived alone. In general, there were two kinds of chronic diseases per capita and three kinds of medication per capita taken. Two hundred fifty-two patients (21.1%) had polypharmacy behaviors. Adverse reactions occurred in 242 patients (20.2%), and 399 (33.7%) patients frequently visited primary medical institutions.

Propensity Score Weighted Results

Standardized mean difference is an indicator used to evaluate the balance between the experimental group and the control group before and after weighting, using a threshold of 0.10 to indicate imbalance. As shown in **Table 2**, after propensity score weighting, covariates with large deviations in the

TABLE 1 | Characteristics of the study population.

	Non-polypharmacy N (%)	Polypharmacy N (%)	χ^2	*p*
A usual primary care provider				
Yes	352 (37.3)	47 (18.7)	31.077	<0.001
No	592 (62.7)	205 (81.3)		
Gender				
Male	397 (42.1)	106 (42.1)	0.000	0.998
Female	547 (57.9)	146 (57.9)		
Age (years)				
18–65	280 (29.7)	67 (26.6)	5.249	0.072
66–75	508 (53.8)	124 (49.2)		
>75	156 (16.5)	61 (24.2)		
Domicile				
Urban area	436 (46.2)	142 (56.3)	8.226	0.004
Rural area	508 (53.8)	110 (43.7)		
Education				
Primary school	437 (46.3)	106 (41.9)	5.723	0.126
Middle school	285 (30.2)	76 (30.0)		
High school	174 (18.5)	49 (19.4)		
University	47 (5.0)	22 (8.7)		
Job				
Manual worker	611 (64.7)	138 (54.8)	8.435	0.004
Brain worker	333 (35.3)	114 (45.2)		
Residence status				
Live alone	93 (9.9)	31 (12.3)	1.285	0.257
Not live alone	851 (90.1)	221 (87.7)		
Annual income per year				
0–9,999	276 (29.2)	67 (26.6)	0.683	0.711
10,000–50,000	310 (32.8)	86 (34.1)		
>50,000	358 (37.9)	99 (39.3)		
Number of diseases				
1	445 (47.1)	24 (9.5)	134.176	0.000
2	494 (52.3)	216 (85.7)		
≥3	5 (0.5)	12 (4.8)		
Disease history/year				
0–10	497 (52.6)	104 (41.3)	14.249	0.001
11–20	254 (26.9)	71 (28.2)		
>20	193 (20.4)	77 (30.6)		
Adverse disease reaction				
No	783 (82.9)	171 (67.9)	28.054	<0.001
Yes	161 (17.1)	81 (32.1)		
Severity of disease				
Mild	433 (45.9)	48 (19.0)	97.158	0.000
Moderate	386 (40.9)	111 (44.0)		
Severe	125 (13.2)	93 (36.9)		
Medical insurance				
Employee health insurance	367 (38.9)	120 (47.6)	6.297	0.012
Resident health insurance	577 (61.1)	132 (52.4)		
Hospitalization				
Yes	291 (30.8)	141 (56.0)	54.422	<0.001
No	653 (69.2)	111 (44.0)		
Communication frequency				
No	127 (13.5)	22 (8.7)	22.421	<0.001
Rare	291 (30.8)	64 (25.4)		
Occasionally	180 (19.1)	50 (19.8)		
Often	276 (29.2)	75 (29.8)		
Always	70 (7.4)	41 (16.3)		
Drink				
Never	733 (77.6)	214 (84.9)	7.945	0.047
Occasionally	115 (12.2)	16 (6.3)		
Often	29 (3.1)	7 (2.8)		
Always	67 (7.1)	15 (6.0)		
Smoking				
Never	685 (72.6)	195 (77.4)	7.459	0.024
Have quit smoking	105 (11.1)	33 (13.1)		
Smoking	154 (16.3)	24 (9.5)		

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of the study population.

	Non-polypharmacy N (%)	Polypharmacy N (%)	X^2	*p*
Diet				
Balance	522 (55.3)	115 (45.6)	7.925	0.019
Mainly meat	65 (6.9)	18 (7.1)		
Mainly vegetarian	357 (37.8)	119 (47.2)		
Exercise				
Never	109 (11.5)	43 (17.1)	8.402	0.038
Occasionally	166 (17.6)	52 (20.6)		
Often	193 (20.4)	50 (19.8)		
Always	476 (50.4)	107 (42.5)		
Blood pressure measurement				
Irregular	178 (18.9)	33 (13.1)	4.543	0.033
Regular	766 (81.1)	219 (86.9)		
Knowledge of medication				
Low	482 (51.1)	125 (49.6)	0.169	0.681
High	462 (48.9)	127 (50.4)		

TABLE 2 | The standardized mean difference of each covariable before and after weighting.

Variable	Standardized mean difference	
	Before weight	After weight
Gender	−0.09	0.09
Age	0.27	0.00
Domicile	−1.07	0.06
Education	0.53	0.00
Job	0.58	0.04
Residence status	0.00	0.11
Annual income	0.63	0.06
Number of diseases	0.29	0.00
Disease history	0.29	0.05
Adverse disease reaction	−0.16	−0.09
Severity of disease	0.49	−0.11
Medical insurance	−0.90	−0.07
Hospitalization	−0.18	0.11
Communication frequency	−0.3	−0.05
Drink	−0.08	−0.05
Smoking	−0.03	−0.07
Diet	−0.26	−0.06
Exercise	−0.04	−0.05
Regular blood pressure measurement	−0.10	−0.07
Knowledge of medication	0.18	−0.03

original data are balanced, and the overall distribution of the data is more balanced.

Regression Analysis Results

Tables 3, **4** present the results from multivariate logistic regressions and propensity scores weighting regressions. In this model, we calculated both ORs and marginal effects of each variable. The results of the weighted regression are different from the results of the multivariate logistic regression. The multivariate logistic regression underestimates the impact of having a usual primary care provider on the patient's multiple medication behaviors due to crowd confounding factors. Result from the propensity scores weighted regression showed that having no usual primary care providers was significantly associated with the odds of polypharmacy behaviors (OR = 2.40, 95%CI: 1.74–3.32, $p < 0.001$), and the corresponding marginal effect was 0.09 (95% CI: 0.06–0.12), indicating that patients having a usual primary care provider are less likely to have polypharmacy behaviors.

With regard to the covariates, we found that patients who aged between 65 and 75 years (OR = 0.50, 95%CI: 0.33–0.77, $p = 0.020$), used to be brain workers (OR = 0.67, 95%CI: 0.45–0.99, $p = 0.048$), have been sick for 10–20 years (OR = 0.56, 95%CI: 0.37–0.83, $p = 0.005$), have had adverse drug reactions (OR = 0.64, 95%CI: 0.45–0.93, $p = 0.019$), and purchased resident health insurance (OR = 0.35, 95%CI: 0.21–0.58, $p < 0.001$) were less likely to have polypharmacy behaviors. But patients who have two kinds of diseases (OR = 3.05, 95%CI: 1.87–5.10, $p < 0.001$) and above (OR = 21.03, 95%CI: 12.83–35.65, $p < 0.001$), have been sick for 20 years and above (OR = 1.66, 95%CI: 1.14–2.42, $p = 0.008$), with serious diseases (OR = 1.63, 95%CI: 1.00–2.67, $p = 0.049$), communicated with doctor frequently (OR = 3.14, 95%CI: 1.62–6.19, $p < 0.001$), with alcoholism (OR = 2.14, 95% CI: 1.08–4.19, $p = 0.027$), have a meat-based diet (OR = 1.42, 95% CI: 1.00–2.00, $p = 0.049$), and have a vegetarian-based diet (OR = 1.42, 95%CI: 1.00–2.00, $p = 0.049$) were more likely to have polypharmacy behaviors.

DISCUSSION

The Effect of Having a Usual Primary Care Provider on Polypharmacy Behaviors

This study provided evidence that patients who did not have a usual primary care provider were more likely to have polypharmacy behaviors than those who had a usual primary care provider (OR = 2.40, 95%CI: 1.74–3.32, $p < 0.001$), with a marginal effect of 0.09 (95%CI: 0.06–0.12), which means that at the average level of other conditions, the probability of polypharmacy behaviors increased by 9.0% when patients who had a usual primary care provider changed to not having a usual primary care provider. In China, medical staff in primary medical

TABLE 3 | ultivariate logistic regression before and after propensity score weighting.

Variable	Before weighting		After weighting	
	OR (95%CI)	*p*	OR (95%CI)	*p*
A usual primary care provider				
Yes				
No	1.5 (0.98–2.31)	0.065	2.40 (1.74–3.32)	<0.001
Gender				
Male				
Female	0.76 (0.48–1.21)	0.248	1.32 (0.87–2.03)	0.192
Age (years)				
18–65				
66–75	0.65 (0.42–1.01)	0.053	0.50 (0.33–0.77)	0.002
>75	0.97 (0.56–1.68)	0.914	1.03 (0.62–1.69)	0.921
Domicile				
Urban area				
Rural area	0.47 (0.25–0.89)	0.02	1.21 (0.68–2.17)	0.523
Education				
Primary school				
Middle school	1.24 (0.79–1.97)	0.350	1.13 (0.72–1.76)	0.593
High school	1.41 (0.78–2.55)	0.256	1.45 (0.84–2.50)	0.184
University	2.48 (1.09–5.6)	0.030	1.70 (0.81–3.57)	0.161
Job				
Manual worker				
Brain worker	1 (0.66–1.53)	0.992	0.67 (0.45–0.99)	0.048
Residence status				
Live alone				
Not live alone	1.06 (0.61–1.86)	0.840	1.41 (0.85–2.37)	0.191
Annual income				
0–9,999				
10,000–50,000	1.14 (0.7–1.85)	0.602	1.06 (0.67–1.69)	0.809
>50,000	1 (0.57–1.77)	0.991	1.28 (0.77–2.15)	0.345
Number of diseases				
1				
2	3.35 (2.02–5.71)	<0.001	3.05 (1.87–5.10)	<0.001
≥3	14.01 (8.34–24.39)	<0.001	21.03 (12.83–35.65)	<0.001
Disease history/year				
0–10				
11–20	0.85 (0.56–1.28)	0.435	0.56 (0.37–0.83)	0.005
>20	1.12 (0.73–1.72)	0.603	1.66 (1.14–2.42)	0.008
Adverse disease reaction				
No				
Yes	0.81 (0.54–1.21)	0.294	0.64 (0.45–0.93)	0.019
Severity of disease				
Mild				
Moderate	1.47 (0.96–2.25)	0.079	1.36 (0.90–2.09)	0.150
Severe	2.3 (1.38–3.82)	0.001	1.63 (1.00–2.67)	0.049
Medical insurance				
Employee health insurance				
Resident health insurance	1.01 (0.55–1.82)	0.975	0.35 (0.21–0.58)	<0.001
Hospitalization				
No				
Yes	0.54 (0.38–0.77)	<0.001	0.83 (0.60–1.15)	0.260
Communication frequency				
No				
Rare	1.39 (0.76–2.64)	0.296	1.06 (0.62–1.85)	0.838
Occasionally	1.41 (0.73–2.77)	0.313	1.14 (0.62–2.10)	0.673
Often	1.44 (0.77–2.8)	0.265	1.19 ((0.68–2.14)	0.561
Always	3.17 (1.51–6.82)	0.003	3.14 (1.62–6.19)	<0.001
Drink				
Never				
Occasionally	0.53 (0.26–1.02)	0.066	0.69 (0.36–1.28)	0.254
Often	1.26 (0.42–3.45)	0.663	1.12 (0.38–3.00)	0.828
Always	1.42 (0.66–2.94)	0.354	2.14 (1.08–4.19)	0.027
Smoking				
Never				
Have quit smoking	0.83 (0.45–1.51)	0.555	1.36 (0.81–2.28)	0.245

(Continued on following page)

TABLE 3 | (*Continued*) ultivariate logistic regression before and after propensity score weighting.

Variable	Before weighting		After weighting	
	OR (95%CI)	*p*	OR (95%CI)	*p*
Smoking	0.58 (0.3–1.06)	0.084	0.60 (0.32–1.10)	0.105
Diet				
Balance				
Mainly meat	1.78 (0.88–3.48)	0.098	2.01 (1.05–3.73)	0.030
Mainly vegetarian	1.67 (1.16–2.41)	0.006	1.42 (1.00–2.00)	0.049
Exercise				
Never				
Occasionally	1.29 (0.72–2.32)	0.387	1.20 (0.70–2.05)	0.504
Often	1.01 (0.56–1.82)	0.984	1.33 (0.78–2.27)	0.296
Always	0.95 (0.56–1.61)	0.836	1.00 (0.63–1.61)	0.993
Blood pressure measurement				
Regular				
Irregular	0.91 (0.55–1.49)	0.724	0.96 (0.59–1.53)	0.859
Knowledge of medication				
low				
high	0.99 (0.68–1.44)	0.974	0.91 (0.63–1.29)	0.581
Intercept	0.248 (0.01–0.2)	<0.001	0.03 (0.01–0.09)	<0.001

institutions have more time to communicate with patients compared to the medical staff in general hospitals. Patients had established a close relationship with primary medical institutions so that they were more willing to seek the guidance of doctors from primary medical institutions in their daily lives (Starfield et al., 2005; Kruk et al., 2010; Feng et al., 2016). In addition, doctors in primary medical institutions are more familiar with patients, which reduces the enthusiasm of patients to seek doctors in advanced medical institutions and reduces the probability of doctors' repeated prescriptions due to untimely sharing of patient's information by patients (Zhang et al., 2013; Duckett et al., 2016).

Although China has established a hierarchical medical system for a long time, many patients go directly to general hospitals instead of primary medical institutions, which may be related to the unbalanced allocation of medical resources (Zhou et al., 2021). At present, there are fewer specialized medical staff in primary medical institutions (Chen et al., 2021), a higher turnover rate of grassroots medical staff (Dale et al., 2015), lower education (Chen et al., 2021), poor medical equipment, and lack of conventional drugs, which makes patients have low trust in primary medical institutions and reluctant to go to primary medical institutions.

With a study showing that patients with primary care providers are likely to reduce patient self-referrals in rural China's rural multi-tiered medical system (Feng et al., 2017) and another study showing that general practitioners (GPs) can effectively reduce patient referral behavior, health maintenance organizations (HMOs) in the United States require patients to consult a primary care physician firstly before considering a referral (Sekhri, 2000; Hoel et al., 2021). Many European countries have GP systems that can effectively guide patients through graded care (Verhaak et al., 2004; Brown et al., 2014).

We need to give play to the role of primary medical institutions. On the one hand, we need to strengthen the construction of primary medical institutions and ensure the complete resources of personnel, equipment, drugs, and other resources in primary medical institutions, so as to restore the trust of patients in primary medical institutions (Liu et al., 1996; Yip and Hsiao, 2014; Shi et al., 2015; Duckett et al., 2016). On the other hand, we need to strengthen the active health management role of primary medical institutions for patients with chronic diseases; establish a community comprehensive medical team including doctors, pharmacists, nurses, and other professionals; and actively manage the diseases of patients in the local area to regain patients' confidence to primary medical institutions (Li et al., 2020; World Bank Group, 2021). In addition, some patients with chronic diseases do not realize the impact of national policies on the improvement of primary medical institutions; we need to strengthen the publicity of the improvement of primary medical institutions to patients, so that patients can understand and trust the medical service capability of new primary medical institutions and to have a usual primary care provider.

The Effect of Demographic and Clinical conditions on Polypharmacy Behaviors

With regard to the demographic and disease-related factors, patients with more diseases, severe disease, and disease history of more than 20 years are more likely to have polypharmacy behaviors. Patients aged 65–75 years, used to be brain workers, with disease history between 10 and 20 years, had adverse drug reactions, and insured by urban and rural residents' medical insurance were less likely to have polypharmacy behaviors.

The younger patients were associated with polypharmacy behaviors, which is consistent with existing studies (Dwyer et al., 2010; Olsson et al., 2010; Bronskill et al., 2012; Ruths et al., 2013; Nørgaard et al., 2017). The incidence of polypharmacy behaviors decreases with age, which may be related to the increased focus on discontinuing unnecessary medications in older adults with limited life expectancy (Holmes, 2009; Onder et al., 2012).

TABLE 4 | The marginal effect of each variable after propensity score weighting.

Variable	*p*	Marginal effect (95%CI)
A usual primary care provider		
Yes		
No	<0.001	0.09 (0.06–0.12)
Gender		
Male		
Female	0.192	0.03 (–0.00 to 0.08)
Age (years)		
18–65		
66–75	0.002	–0.08 (–0.12 to 0.03)
>75	0.921	0.00 (–0.08 to 0.06)
Domicile		
Urban area		
Rural area	0.523	0.02 (–0.04 to 0.08)
Education		
Primary school		
Middle school	0.593	0.01 (–0.03 to 0.06)
High school	0.184	0.04 (–0.02 to 0.10)
University	0.161	0.06 (–0.03 to 0.15)
Job		
Manual worker		
Brain worker	0.048	–0.04 (–0.08 to 0.00)
Residence status		
Live alone		
Not live alone	0.191	0.04 (–0.02 to 0.09)
Annual income		
0–9,999		
10,000–50,000	0.809	0.01 (–0.04 to 0.06)
>50,000	0.345	0.03 (–0.03 to 0.08)
Number of diseases		
1		
2	<0.001	0.09 (0.05–0.12)
≥3	<0.001	0.40 (0.34–0.45)
Disease history/year		
0–10		
11–20	0.005	–0.06 (–0.10 to 0.02)
>20	0.008	0.06 (0.01–0.11)
Adverse disease reaction		
No		
Yes	0.019	–0.05 (–0.09 to 0.01)
Severity of disease		
Mild		
Moderate	0.150	0.03 (–0.01 to 0.08)
Severe	0.049	0.05 (–0.03 to 0.11)
Medical insurance		
Employee health insurance		
Resident health insurance	<0.001	–0.12 (–0.17 to 0.06)
Hospitalization		
No		
Yes	0.260	–0.02 (–0.06 to 0.02)
Communication frequency		
No		
Rare	0.838	0.01 (–0.05 to 0.06)
Occasionally	0.673	0.01 (–0.05 to 0.08)
Often	0.561	0.02 (–0.04 to 0.08)
Always	<0.001	0.14 (0.06–0.22)
Drink		
Never		
Occasionally	0.254	–0.04 (–0.10 to 0.02)
Often	0.828	0.01 (–0.10 to 0.13)
Always	0.027	0.09 (0.00–0.18)
Smoking		
Never		
Have quit smoking	0.245	0.04 (–0.03 to 0.10)
Smoking	0.105	–0.05 (–0.11 to 0.08)
Diet		
Balance		
Mainly meat	0.030	0.08 (0.00–0.16)
Mainly vegetarian	0.049	0.04 (0.00–0.08)
Exercise		
Never		
Occasionally	0.504	0.02 (–0.04 to 0.08)
Often	0.296	0.03 (–0.00 to 0.09)
Always	0.993	0.00 (–0.05 to 0.05)
Regular blood pressure measurement		
Regular		
Irregular	0.859	0.00 (–0.06 to 0.05)
Knowledge of medication		
low		
high	0.581	0.01 (–0.05 to 0.03)
Intercept	<0.001	—

(Continued in next column)

TABLE 4 | (*Continued*) The marginal effect of each variable after propensity score weighting.

It is well known that patients with more diseases are more likely to have polypharmacy behaviors (Dwyer et al., 2010), but this study shows that the incidence of multiple drugs' exponential growth as the disease increased should be noted. For patients with chronic diseases, the marginal effect increased by 0.09 from having one disease to having two diseases, indicating a 9.0% increase in the incidence of polypharmacy behaviors. For patients with chronic diseases, the marginal effect increased by 0.40 from having one disease to have three or more diseases, indicating that when other variables were kept at the average level, changes in the number of cases from 1 to 3 or more resulted in a 40.0% increase in the incidence of polypharmacy behaviors.

Patients with a disease history between 11 and 20 years have a lower incidence of polypharmacy behaviors, while patients with a disease history of 21 years and above have a higher incidence of polypharmacy behaviors, which may be related to the health awareness and disease situation of patients with chronic diseases. Patients with a disease history of 11–20 years are aware of the physical damage caused by taking multiple drugs, so they will consciously reduce unnecessary drugs. But patients who had been ill for 21 years or more had to take multiple drugs for their poor health.

Brain workers were less likely to have polypharmacy behaviors, which may be related to the greater job pressure of physical workers (Tan et al., 2020). The incidence of polypharmacy behaviors was lower in patients with adverse drug reactions, which may be because patients with chronic disease are afraid of adverse drug reactions and become more careful in drug use, resulting in a lower incidence of polypharmacy behaviors.

The Influence of Medical Treatment and Health Behavior on Polypharmacy Behaviors

The incidence of polypharmacy behaviors is higher among patients who participated in urban employee medical insurance. Most of the patients who buy urban employee

medical insurance are in economically developed areas; they have access to more sources of drugs, such as pharmacies, hospitals, and primary medical institutions. Therefore, polypharmacy behaviors are prone to occur. In addition, some patients who purchase urban employee medical insurance even have designated cooperative hospitals; it has been shown that patients who frequently visit hospitals have a higher incidence of polypharmacy behaviors than those who tend to visit primary medical institutions.

Patients who had frequent communication with their physicians had a higher incidence of polypharmacy behaviors; doctor–patient shared decision-making has been promoted in recent years, which can effectively improve patient compliance, patient satisfaction, and curative effect and make more beneficial choices for patients (Légaré et al., 2014; van Hoorn et al., 2016; Spatz et al., 2017). Doctor–patient shared decision can promote effective communication between doctors and patients to make medical decisions, rather than increasing the frequency of doctor–patient communication. The frequency of communication between doctors and patients indicates that patients may be treated in multiple departments or places, resulting in repeated prescriptions or prescription cascades that will increase the incidence of polypharmacy behaviors.

The incidence of polypharmacy behaviors is higher in patients with alcoholism. Previous studies have confirmed that moderate alcohol consumption has certain effects on control of chronic diseases (Ford et al., 2012; Loef and Walach, 2012; Zhu et al., 2019; Minzer et al., 2020), but alcoholism was associated with diseases such as cancer, hypertension, and liver disease, so patients who drink frequently were more likely to suffer from more diseases; polypharmacy behaviors were also more likely to happen. It was found that patients who have a meat-based diet or vegetarian-based diet are more prone to polypharmacy behaviors compared to patients who have a balanced diet. Patients with a meat-based diet are more prone to be diagnosed with hypertension, hyperlipidemia, diabetes, and other chronic diseases, so they are more prone to have polypharmacy behaviors happen, and the vegetarian-based patients may have lower body immunity and are prone to disease. In addition, some patients are recommended by doctors to use dietary therapy and other drug substitution therapy to treat chronic diseases, so patients with balanced meat and vegetable may use dietary therapy instead of drug therapy and take fewer drugs (Morgan et al., 2004; Hoel et al., 2021).

According to the findings in this study on the impact of patients' health behaviors and medical treatment behaviors on polypharmacy behaviors, corresponding intervention measures can be taken to prevent polypharmacy behaviors. For the patients who purchase urban employees' medical insurance, we should strengthen the publicity of rational drug use knowledge to avoid polypharmacy behaviors due to their exposure to multiple drug sources. Moreover, we should encourage effective communication between doctors and patients, instead of frequent communication. We should also encourage patients to use alternative therapies such as dietary therapy instead of drug therapy to reduce the possibility of polypharmacy behaviors, while encouraging patients to maintain a reasonable diet and moderate alcohol consumption is also very important to control polypharmacy behaviors.

STRENGTHS AND LIMITATIONS

Our study has several limitations. Various definitions of polypharmacy existed in the literature; we only considered the number of drugs used, namely ≥5 drugs as polypharmacy, so it is difficult to make a distinction between necessary prescribing and polypharmacy medication. Secondly, patients were recruited to search for samples, and patients who were unwilling to participate in the study were not investigated, which may lead to certain data bias. Third, since not all patients can remember all the medications, an underestimation of polypharmacy behaviors could not be completely ruled out.

Despite these limitations, this is a rare study in China that explores the impact of having a usual primary care provider on polypharmacy behaviors. Second, we used the propensity score weighting method to adjust for the observed difference in characteristics between those who have a usual primary care provider and those who do not. Third, the data we analyzed come from a large number of patients with hypertension or diabetes equally distributed throughout the 12 regions involved, which makes these evidences characteristic of and comparable to all patients with chronic diseases in Hubei province, China.

CONCLUSION

This study provides evidence that patients who had a usual primary care provider had a lower risk of polypharmacy. As we all know, in primary hospitals, the medical staffs have more time to communicate with patients and have a closer relationship with the patients; therefore, patient could have access convenient and economical services and obtain more guidance about drug use. Moreover, with the implementation of the hierarchical diagnosis and treatment and family physician system, the role and function of the primary care hospital in the system are providing integrated service for local residents. In consequence, the healthcare government should make efforts to construct community level medical institutions and improve the quality of health service to attract more patients, especially those with hypertension and diabetes.

DATA AVAILABILITY STATEMENT

The data analyzed in this study are subject to the following licenses/restrictions: Because the data involve the patient's personal information, it cannot be provided. Requests to

access these datasets should be directed to fengda@hust.edu.cn.

AUTHOR CONTRIBUTIONS

All authors contributed to drafting and revising the manuscript. DF designed the study and reviewed the manuscript. JW completed the data analysis and drafted the initial manuscript. ZF, ZD, WL, CC, ZG, and AW critically reviewed the manuscript and proposed amendments.

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Patient Preferences for Diabetes Treatment Among People With Type 2 Diabetes Mellitus in China: A Discrete Choice Experiment

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Introduction: Preferences for diabetes treatment-related attributes may be significant in diabetes management. However, there is a lack of evidence on patient preferences for diabetes in China.

Methods: A large-scale questionnaire survey was conducted in the hospitals of mainland China. Participants' preferences for six attributes were evaluated *via* a discrete choice experiment (DCE) using the conditional logit model. Patients' willingness to pay (WTP) for each attribute was calculated based on the cost attribute.

Results: The sample consisted of 709 patients (male 51.9%; female 48.1%). The results of the model indicated that patients' preference weight (PW) of days on which the blood glucose level is under control per week was the highest (1.41), and the PW of blood glucose monitoring frequency was the lowest (0.642). Patients were generally willing to pay for improvements in their type 2 diabetes mellitus (T2DM) treatment, and they had relatively higher WTP to avoid the blood glucose level within a normal value of 1 day/week (¥176.01) and also to avoid the frequency of hypoglycemic events within the range of 1–2/month (¥144.53).

Conclusion: The number of days on which the blood glucose level is under control per week is the most important attribute in the treatment choice for patients with T2DM in China, followed by the frequency of hypoglycemic events, medication regimen, weight change, and blood glucose monitoring.

Keywords: diabetes, discrete choice experiment, preferences, willingness to pay, Chinese

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INTRODUCTION

Diabetes has become a major health problem worldwide due to multiple reasons, including the rapid growth of the world economy, changes in people's lifestyles, and the aging of the population. Globally, in 2017, there are 425 million adults (age 20–79 years) with diabetes, with an estimated prevalence of 8.8% (1). The situation of China is also severe. The number of adult patients with diabetes in China is as high as 114 million, which ranks the first in the world and will expectedly increase to 120 million by 2045 (1). In China, the prevalence of diabetes has increased from 2.51 in 1994 to 10.9% in 2013, while the prediabetes prevalence rate has increased from 3.20 to 35.7% (2, 3). Diabetes has become the eighth leading cause of death in 2017

in China (4). Diabetes and its associated chronic complications have become one of the most important health burdens for the Chinese public (5).

In China, type 2 diabetes mellitus (T2DM) is the dominant type of diabetes, which accounts for more than 90.0% of the overall diabetic population (6). In the past few decades, the effectiveness and safety of therapies for diabetes have been tremendously improved in China, and patient adherence to treatment may have become a major factor affecting the quality of long-term blood glucose control. Existing studies have shown that patient preferences toward factors other than the effectiveness of their diabetes treatment can also affect their compliance to a certain extent, which in turn can alter the treatment effectiveness (7). Figuring out what patients expect and value for the regiments of managing chronic diseases, like diabetes, is increasingly significant in the design and delivery of diabetes treatment (8). Therefore, the healthcare providers need to recognize and well-utilize the characteristics of the treatment that patients want to incorporate into their diabetes management (9). The optimal diabetes treatment for each individual patient should be both clinically effective and consistent with the patient's needs and preferences.

Existing studies focus on patient preferences for the treatment of diabetes in developed countries, and several studies have shown that a variation of socioeconomic and cultural backgrounds among populations may lead to differences in patient preferences (10, 11). However, there is a lack of evidence on patient preferences for diabetes in developing countries with low levels of economic development, and specifically, there is no such study in China, a developing country with a large diabetic patient population.

Based on the above-mentioned reasons, this study aims to assess the preferences for diabetes treatment among patients with T2DM in China, to deepen the understanding of the health preferences of Chinese patients with diabetes, and to help medical staff implementing the targeted disease management scheme. To improve the applicability of the results, this study introduced discrete choice experiments (DCEs) to measure the preferences for each of the important attributes of the treatment by asking respondents to choose one set of attributes from a number of presented sets of attributes that simulate real situations (12). When cost is included as an attribute in the DCE, the results can be used to calculate the willingness to pay (WTP) for the attributes being measured (13). The results of this study would allow health professionals to quantitatively compare patients' preference for specific treatments in China based on the evaluation of the attributes of each treatment.

METHODS

Discrete Choice Experiment

A discrete choice experiment draws upon Lancaster's economic theory of value (14) and the random utility theory (15, 16). This technique is used in market research to assess how consumers value the underlying attributes that comprise different kinds of products and make choice decisions. The last few decades have seen an increasing use of this technique in health economics (17, 18). The decision-making process within a DCE is seen as involving a comparison of indirect utility functions (19). In making a series of choices, in each case, the subject chooses the option that leads to a higher level of utility.

Sampling

In this study, the inclusion criteria were: (1) patients have a self-reported physician's diagnosis of T2DM for 2 years or longer; (2) patients used antidiabetic medications in the past 2 weeks; (3) patients aged 18 years or older; and (4) patients be able to and willing to participate in this study, and willing to sign the informed consent.

The minimum sample size was calculated using the formula for estimating the sample size requirement for DCE (20):

$$n = 500\,c/(t\times a). \quad (1)$$

In this formula, "c" is the largest number of levels for any of the attributes, "t" is the number of choice sets, and "a" is the number of alternatives in each choice set. And, for this study, the minimum sample size was $500\times4/(8\times2)=125$.

A stratified sampling strategy was used in this study: (1) all 31 provincial administrative regions (including provinces, autonomous regions, and municipalities directly under the central government) in mainland China were covered in the sampling; (2) cities in each province/autonomous region or districts in each municipality were evenly divided into three groups according to their 2017 per capita gross domestic product, thereby generating 93 groups; (3) within each group, one city or district was selected using the random number method, thus 93 cities or districts were selected; (4) in each selected city or district, 1–2 secondary hospitals and 1–2 tertiary hospitals (primary healthcare facilities were excluded because, under the current hierarchical healthcare system of China, only patients with light symptoms or health problems are encouraged to visit primary facilities, but all the patients are accessible in secondary and tertiary facilities) were surveyed based on the hospital administrators' permission to conduct the survey, and the hospital level was verified by consulting the hospital information tool by National Health Commission of China (http://61.49.18.120:9090/unit/index). This ensured that 186–372 hospitals would be selected. In each surveyed hospital, two participants who met the inclusion criteria mentioned above were surveyed. Overall, 744 questionnaires were distributed.

Survey Design

In accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) good practices for a conjoint analysis in health, the survey instrument in this study was developed using the following steps: (1) the identification of medication attributes and levels; (2) medication attribute and level selection; and (3) experimental design (21). The questionnaire used in this survey consisted of the following parts: (1) the introduction of this survey; (2) questions of the patient's current conditions about the disease, like the type of disease, course of the disease, and disease complications; (3) a preference survey section; and (4) other sociodemographic

information questions, like gender, age, education level, monthly income, and exercise frequency.

For the identification of attributes and levels, a comprehensive literature review was performed with an aim to identify, select, and summarize existing research until March 2018 that assessed patient preferences for T2DM for the attributes of antidiabetic treatments and/or their WTP using DCE. Keywords ("Diabetes Mellitus," "Type 2 Diabetes Mellitus," "Disease management," "Willingness to Pay," "DCE," "Discrete Choice Experiment," "Patient Preference," "Conjoint," and "Conjoint Analysis") in English and Chinese were used. The search was carried out in a pool of databases (Medline, Web of Science, SpringerLink, Elsevier ScienceDirect, Wiley Online Library, CNKI, CSPD, and VIP).

After excluding the duplicate papers, 34 studies were collected. Then, by manually excluding the studies that were not in accordance with the description of the abovementioned literature, 15 studies were collected. (22–36) Among the studies using the DCE, the most frequently studied attributes were as follows: the control of glycated hemoglobin (HbA_{1c}) level/days on which the blood glucose level is under control per week ($n = 14$; 93.33%), (22–35) the frequency of hypoglycemic events ($n = 14$; 93.33%), (22–35) weight change ($n = 13$; 86.67%), (22–24, 26–34, 36) medication regimen ($n = 10$; 66.67%), (22, 23, 25–27, 31–33, 35, 36) cost ($n = 9$; 60.00%), (22–24, 26, 27, 29, 31, 33, 35) blood pressure/heart function ($n = 8$;53.33%), (22, 23, 27, 28, 30, 31, 33, 34) and blood glucose monitoring ($n = 4$; 26.67%). (22, 23, 30, 31) An online consultation with a group of six clinical physicians who devoted more than 10 years to diabetes treatment was made to select the attributes and levels throughout a group discussion. The result of such consultations was reached until all clinical physicians' consensus on the selection or exclusion of each attribute and each level. Totally, six attributes and 24 levels were identified.

Six attributes were eventually selected, and each of them had four levels. Theoretically, there were $4^6 = 4{,}096$ possible scenarios. An orthogonal experimental design was carried out to generate the DCE design that was in compliance with the desirable design properties, like orthogonality, level balance, utility balance, and minimum overlap (37). After the design, 16 choice sets containing 32 scenarios were produced. Each respondent would answer these choice set questions (shown in **Supplementary Materials**), and their answers were used to analyze the preference and WTP for each attribute and level.

During April and May 2018, a pretest of the questionnaire was conducted in Nanjing, Changzhou, and Yangzhou, and 43 valid questionnaires were collected. The results showed that the questionnaire had acceptable understandability and readability.

Table 1 presents the abbreviated names, definitions, and levels selected in this study.

Data Collection

About 279 undergraduate students majoring in pharmacy-related disciplines were recruited as data collectors. Then, they were

TABLE 1 | Attributes and levels for the questionnaire.

Name	Definition	Levels
Convenience attributes		
Medication regimen	Mode and frequency of administration	Injection two times a day in relation to meals Injection once a day in relation to meals Injection once a day irrespective of meals Oral antidiabetics (OAD) up to three times a day without injection
Blood glucose monitoring frequency	Frequency of blood glucose monitoring	Once a day Three times per week Once a week No need for monitoring test
Clinical outcome attributes		
Weight change	Weight change in the first 6 months	Gain 3 kg/6 months Remain the same/6 months Lose 3 kg/6 months Lose 6 kg/6 months
Hypoglycemic event frequency	Frequency of occurring hypoglycemic events	Usually occur (1–2/month) Sometimes occur (1–2/three months) Occasionally occur (1–2/six months) Nearly not occur
Blood glucose controlled days	Number of days per week glucose level will be within normal range	1 day/week 3 days/week 5 days/week 7 days/week
Other attributes		
Cost	Payment per month	¥ 100 ¥ 70 ¥ 40 ¥ 0

trained with the backgrounds, purposes, and goals of this study, as well as the procedures, the etiquette, and the techniques of performing the survey. Every three of the data collectors worked as a group for the data collection in one sampled city or district.

One group of data collectors randomly visited one of the secondary or tertiary hospitals in this city or district, and if the verbal permission of the dean/deputy director of this hospital was obtained, the data collector would conduct the survey, and if the verbal permission was not obtained, they would randomly visit another hospital, until the expected number of hospitals was surveyed. To conduct the survey, the data collectors randomly accessed a patient and orally introduced the background, content, purpose, and inclusion criteria of the survey to patients with diabetes who were leaving the endocrinology department. Patients who met the inclusion criteria and signed the informed consent were asked to complete a self-administered questionnaire. If the accessed patient did not meet the inclusion criteria and refused to participate or sign the informed consent, the data collector would randomly access another potential participant until the expected number of participants was surveyed.

Using an online survey system on mobile phones or tablet computers, the data collectors orally interviewed participants with each item of the questionnaire and recorded their responses, and then the survey system converted the data into electronic documents. The data collectors were not only allowed to provide any view on the questionnaire, but also the requirements or instructions of questionnaire filling. The survey system allowed the users to set restrictions on the format of responses and ensured the quality of data. About 15 postgraduates were recruited and trained to review the uploaded documents and immediately return those with data entry errors or data damages, which were corrected through return visits by data collectors whenever possible. The survey was carried out between July and August 2018.

Statistical Analysis

The conditional logit model was used to analyze the results of choice sets. Each choice set had two alternatives, and the alternatives were assigned 0 if the respondent did not choose this alternative and 1 if he or she chose the alternative in the choice set. Within the model calculation, an effects coding system [instead of a dummy coding, the reference categories were estimated as the negative sum of the included categories (38, 39)] was used for five attributes other than cost attribute, which was defined as a numeric continuous variable based on the presence of a linear relationship between the levels for it. Similar to some other studies using the DCE, (22, 23) this study divided the attributes into two groups for analysis because the attributes related to the type of treatment are theoretically correlated with the attributes related to the outcomes of the treatment and this may lead to an inaccuracy in the estimation. The two groups are: (1) medication regimen, blood glucose monitoring frequency, and cost and (2) weight change, hypoglycemic event frequency, blood glucose controlled days, and cost. The cost was included in both groups for estimating the WTP for all attributes.

Coefficients estimated from the model can be interpreted as the relative strength of preference for each attribute level (21, 23). The difference between the coefficients for the best and worst levels of an attribute could be interpreted as the relative preference weight (PW) for that attribute. (24, 28) The relative importance (RI) of an attribute was obtained from the quotient between its PW and the sum of PWs of the five attributes other than cost (34). Based on the economic theory of demand, Willingness to pay for the attribute levels was calculated using the estimated coefficients divided by the coefficient of cost. (22, 26, 31) For the first level in each attribute, WTP should be interpreted as the "maximum amount of money a patient was willing to pay to experience this level." For other levels, if WTP was positive, WTP should be interpreted as "maximum additional amount of money a patient was willing to pay to experience this level instead of the first level," and if WTP is negative, its absolute value is presented in (**Table 4**) and should be interpreted as "maximum additional amount of money a patient was willing to pay to avoid

TABLE 2 | Respondent characteristics.

Characteristic	*n* (%)
Gender	
Female	341 (48.1)
Male	368 (51.9)
Age	
18–30	6 (0.8)
31–40	32 (4.5)
41–50	162 (22.8)
51–60	184 (26.0)
61–70	198 (27.9)
71–80	110 (15.5)
>80	17 (2.4)
Duration of diabetes	
2–5 years	308 (43.4)
5–10 years	202 (28.5)
>10 years	199 (28.1)
Frequency of blood glucose monitoring	
Once a day	132 (18.6)
Three times per week	153 (21.6)
Once a week	238 (33.6)
Once a week	186 (26.2)
Complication	
None	420 (59.2)
Present	289 (40.8)
Monthly income	
<¥1000	144 (20.3)
¥1000–2000	54 (7.6)
¥2000–3000	112 (15.8)
¥3000–4000	136 (19.2)
≥¥4000	263 (37.1)
Frequency of exercise	
Often	250 (35.3)
Sometimes	227 (32.0)
Occasionally	232 (32.7)

experiencing this level instead of the first level." Just to be clear, in the cases that x was negative, the descriptions of the levels were reversed (avoid . . .) to make them understandable.

Stata/MP statistical software version 13.0 was used to conduct all statistical analyses.

Ethics Approval and Funding

All participants in this study signed the informed consent. The study protocol was reviewed and approved by the Ethics Committee of China Pharmaceutical University to ensure that the study was in accordance with the ethical guidelines of clinical investigation in China (as shown in **Supplementary Materials**). The study was funded by The Project of "Double First-Class" Construction of Discipline Innovation Team, China Pharmaceutical University (CPU2018GY39).

RESULTS

Respondent Characteristics

A total of 709 patients with T2DM were surveyed. In **Table 2**, the demographics of the sample are summarized. The results showed that gender and most of the other characteristics of samples were evenly distributed.

Results of PWs for China

Analysis results from the model are provided in (**Table 3**). The chi-squared value of the model likelihood ratio test was statistically significant ($p < 0.05$). In addition, the estimated coefficients were all statistically significant ($p < 0.05$) except for the "remain the same/6 months" and "lose 3 kg/6 months," indicating that patient preferences for these levels compared to the first level of their attributes were unclear. Cost was statistically significant ($p < 0.05$) in both models, indicating that cost significantly influenced patients' choice of treatment.

The PW and RI of each attribute other than cost were calculated. The PW and corresponding RI values were the highest for three attributes: blood glucose controlled days (PW = 1.41; RI = 29.1%), the frequency of hypoglycemic events (PW = 1.18; RI = 24.4%), and medication regimen (PW = 0.926; RI = 19.1%), indicating that these attributes were relatively more concerned when patients with T2DM were choosing their treatment.

Results of WTP

The calculated monthly WTP results are provided in (**Table 4**). The WTP analysis demonstrated that medication regimens without injection, the avoidance of blood glucose monitoring, the avoidance of hypoglycemic events, and the time at which

TABLE 3 | Model analysis results.

Attribute	Patients ($n = 709$)			
	Coefficient	SE	95% CI	
Medication regimen				
Injection two times a day in relation to meals	−0.446	-	-	-
Injection once a day in relation to meals	0.166***	0.0319	0.103	0.228
Injection once a day irrespective of meals	−0.199***	0.0327	−0.263	−0.134
OAD up to three times a day without injection	0.479***	0.0332	0.414	0.544
Blood glucose monitoring frequency				
Once a day	−0.236	-	-	-
Three times per week	−0.276***	0.0327	−0.340	−0.211
Once a week	0.107**	0.0328	0.0424	0.171
No need for monitoring test	0.405***	0.0328	0.341	0.470
Cost	−0.00610***	0.000512	−0.00711	−0.00510
Weight change				
Gain 3 kg/6 months	−0.309	-	-	-
Remain the same/6 months	−0.0160	0.0347	−0.0841	0.0520
Lose 3 kg/6 months	−0.0486	0.0338	−0.115	0.0175
Lose 6 kg/6 months	0.374***	0.0354	0.304	0.443
Hypoglycemic event frequency				
Usually occur (1–2/month)	−0.753	-	-	-
Sometimes occur (1–2/3 months)	−0.103**	0.0332	−0.168	−0.0379
Occasionally occur (1–2/6 months)	0.429***	0.0352	0.360	0.498
Nearly not occur	0.427***	0.0347	0.359	0.495
Blood glucose controlled days				
1 day/week	−0.917	-	–	–
3 days/week	0.217***	0.0334	0.151	0.282
5 days/week	0.212***	0.0335	0.146	0.278
7 days/week	0.488***	0.0355	0.419	0.558
Cost	−0.00521***	0.000536	−0.00626	−0.00416

SE, standard error; CI, confidence interval.
$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

TABLE 4 | Willingness to pay (WTP) for diabetes treatment.

Unit change	Monthly WTP(¥)
Medication regimen	
Avoid injection two times a day in relation to meals	73.11
Injection once a day in relation to meals	27.21
Avoid injection once a day irrespective of meals	32.62
OAD up to three times a day without injection	78.52
Blood glucose monitoring frequency	
Avoid one blood glucose monitoring test/day	38.69
Avoid three blood glucose monitoring tests/week	45.25
One blood glucose monitoring test/day	17.54
No need for monitoring test	66.39
Weight change	
Avoid gain 3 kg/6 months	59.39
Avoid remain the same	3.07
Avoid lose 3 kg/6 months	9.33
Lose 6 kg/6 months	71.79
Hypoglycemic event frequency	
Avoid usually occur (1–2/month)	144.53
Avoid sometimes occur (1–2/3 months)	19.77
Occasionally occur (1–2/6 months)	82.34
Nearly not occur	81.96
Blood glucose controlled days	
Avoid glucose level within normal range 1 day/week	176.01
Glucose level within normal range 3 days/week	41.65
Glucose level within normal range 5 days/week	40.69
Glucose level within normal range 7 days/week	93.67
Cost	Reference

the blood glucose level is under control were the more valued attributes of the treatment, and participants were willing to pay for these experiences or outcomes.

DISCUSSION

This study aimed to examine patient preferences for the treatment of T2DM and their WTP for the treatment with different characteristics. Participants in our sample were patients with a self-reported physician's diagnosis of T2DM for more than 2 years. Their trade-offs for convenience of medication (medication regimen and blood glucose monitoring frequency), clinical outcomes of medication (weight change, hypoglycemic event frequency, and blood glucose controlled days), and the cost of medication were analyzed. As the results indicated, the most valued treatment attribute was blood glucose controlled days, followed by the frequency of hypoglycemic events, medication regimen, weight change, blood glucose monitoring, which means Chinese patients with T2DM believed that a steady, normal blood glucose level was more important than other treatment factors. Also, in this study, some interesting phenomena were identified.

Weight gain is a common symptom of T2DM, and as a well-known and sometimes severe side-effect of the treatment for diabetes, (40) a hypoglycemic event, such as weight loss, is a major concern for many patients, which may contribute to optimal treatment (41, 42). Mohamed et al. performed an analysis of preferences for oral antidiabetics (OAD) in Sweden and Germany and demonstrated that weight gain was the most important attribute, followed by glucose control (24). BØgelund et al. showed that, for Danish patients, weight change was the most important attribute (22). Similarly, Morillas et al. found that weight gain was the most important factor affecting patients' and physicians' medication choices in Spain and Portugal (23). In the UK, Gelhorn et al. proved that weight change was of primary importance to patients in their OAD preferences in T2DM. (34) One possible explanation for patients' concerns of weight change is that patients usually believe that weight gain will hamper blood glucose control and lead to an increasing risk in other diabetes-related complications in the long term, such as cardiovascular risk, and weight loss will lead to weakening and dysfunction of the body. However, the results of this study showed that the weight gain and a slight weight loss were not specifically concerned by patients with T2DM in China. A few studies showed that preferences were related to the cultural background of the study samples (43). Similar to our study's results, Brooks et al. in a recent preference study about two kinds of OAD in Japan found that according to patients' thought, the weight loss effect was the least important attribute (44). It is possible that, due to the regional and cultural differences in people's concepts and thoughts, (45) a mild or moderate weight change was of less importance to the East Asian population than to the European population.

Specific to the levels of each attribute, most of their estimated coefficients were in a monotone ascending or descending order as expected, but some of the levels did not comply with this order, such as comparisons of adjacent levels for the frequency of hypoglycemic events (occasionally vs. nearly not) and blood glucose controlled days (3 vs. 5 days/week). This phenomenon could be due to that patients would value the specific levels based on realistic factors rather than their hypothetical preference. Many possible realistic factors may influence patient preferences, such as whether the primary healthcare institutions in China were capable of providing management regiments with such levels of attributes and their quality, or whether the higher level of an attribute contained significantly added value compared to the lower level of the same attribute in the real world.

There was another unusual phenomenon in our study. For the attribute of medication regimen, the coefficients of injection once a day in relation to meals and injection once a day irrespective of meals were reversed totally (0.166 and −0.199, respectively). It was demonstrated that patients preferred injections in relation to meals and did not prefer injections irrespective of meals, and the possible reason was that patients' belief of injections in relation to meals could bring better blood glucose control.

The results of WTP calculation presented in this article generally demonstrated that patients were willing to pay for improved T2DM treatment, to gain additional benefits, like Jendle et al. stated in their study (31). Regarding the medication regimen, OAD was preferred to injections, and the WTP for OAD without injection was almost the same as WTP for avoiding injection two times a day in relation to meals, and three times

as high as WTP for injection once a day in relation to meals. The results showed that patients preferred treatment with no need for the blood glucose monitoring test. Regarding a weight change in small range (a gain of 3 kg or a loss of 3 kg/6 months), Chinese patients were willing to avoid it. For a greater degree of weight loss (a loss of 6 kg/6 months), patients started to have WTP, which might be the influence of social and cultural backgrounds. The two highest WTP demonstrated that patients paid much attention to the frequency of hypoglycemic events and blood glucose control, and they were not desirable for frequent frequency of hypoglycemic events and the instability of blood glucose level.

As for the limitations of this study, it may have a bias in the sampling. The sampling procedure was not random because, when the data collectors were unable to survey in one of the randomly visited hospitals or survey one of the randomly visited potential participants, they would randomly access another. Additionally, only two participants were surveyed in each hospital because the research resources were limited, and covering the variance between the participants in different cities was usually important in surveys in China. Therefore, the final sample of this study may not represent Chinese patients with T2DM. Despite its wide use in health economics, DCE still has drawbacks. DCE is a technique for measuring the stated preferences and, even though it resembles the real situations as much as possible, it is still different from the decision process in real-world situations. Patients' choices for hypothetical treatment may not be the same as actual choices. The conditional logit model assumes that the measured utility is equal across all respondents and choice questions, (23) and therefore it does not consider variations in the preferences that arise from differences in individual characteristics, such as age, education, gender, and health status among respondents (preference heterogeneity) (21). In the DCE, the cognitive burden may increase with increases in the number of choice sets, (46) so that in our study respondents exposed to 16 choice sets may have a higher response variance that may influence the final results. In addition, the questionnaire just selected the attributes that were frequently used in previous studies and did not consider the other possible factors that might affect treatment preferences. Also, the attributes used in this study were generated based on the literature, and evidence from patients or residents were not considered because evidences collected in the design period of this study were of low quality and applicability, the suggested attributes were usually too general, too specific, or similar to the attributes from the literature.

In this patient preference study, blood glucose controlled days are the most important attribute in the treatment choice for patients with T2DM in China, followed by the frequency of hypoglycemic events, medication regimen, weight change, and blood glucose monitoring. The results of this study can deepen the understanding of the preferences for patients with T2DM and to further assist in the development of diabetes treatment. Also, the results could be a boost of PRO use in clinical decisions for patients with T2DM in China, encouraging clinicians to take patient preferences for the treatment into consideration, which draws limited attention in China.

Preferences for different subgroups remain to be analyzed in future studies, and other attributes, such as heart function and gastrointestinal issues, may be taken into account as well.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of China Pharmaceutical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YH, QH, and XX contributed to study design, data analysis, interpretation, and manuscript drafting and review. AX and ML contributed to data collection and manuscript review. All authors approved the final version of the manuscript before its submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.782964/full#supplementary-material

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BRIEF RESEARCH REPORT
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Identifying Patients at Risk of Acute Kidney Injury Among Medicare Beneficiaries With Type 2 Diabetes Initiating SGLT2 Inhibitors: A Machine Learning Approach

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Introduction: To predict acute kidney injury (AKI) risk in patients with type 2 diabetes (T2D) prescribed sodium-glucose cotransporter two inhibitors (SGLT2i).

Methods: Using a 5% random sample of Medicare claims data, we identified 17,694 patients who filled ≥1 prescriptions for canagliflozin, dapagliflozin and empagliflozin in 2013–2016. The cohort was split randomly and equally into training and testing sets. We measured 65 predictor candidates using claims data from the year prior to SGLT2i initiation. We then applied three machine learning models, including random forests (RF), elastic net and least absolute shrinkage and selection operator (LASSO) for risk prediction.

Results: The incidence rate of AKI was 1.1% over a median 1.5 year follow up. Among three machine learning methods, RF produced the best prediction (C-statistic = 0.72), followed by LASSO and elastic net (both C-statistics = 0.69). Among individuals classified in the top 10% of the RF risk score (i.e., high risk group), the actual incidence rate of AKI was as high as 3.7%. In the logistic regression model including 14 important risk factors selected by LASSO, use of loop diuretics [adjusted odds ratio (95% confidence interval): 3.72 (2.44–5.76)] had the strongest association with AKI incidence.

Disscusion: Our machine learning model efficiently identified patients at risk of AKI among Medicare beneficiaries with T2D undergoing SGLT2i treatment.

Keywords: AKI (acute kidney injury), SGLT2i, machine learning (ML), type 2 dabetes, medicare

INTRODUCTION

Type 2 diabetes (T2D) affects over 400 million people globally. (Chen et al., 2011). The management of T2D is complex and challenging since it involves the prevention of organ damage and complications such as cardiovascular and kidney events. (Nathan, 1993; Zheng et al., 2018). Sodium glucose cotransporter two inhibitors (SGLT2i) have shown promise in preventing cardiovascular disease (CVD) and renal function decline in patients with T2D (Birkeland et al., 2017; Zaccardi et al., 2016) Conversely, SGLT2i agents have been associated with increased risk of acute kidney injury (AKI), likely attributed to hypovolemia attributable to its diuretic effect. (Nadkarni et al., 2017). AKI is a concerning adverse effect because it can increase the risk of end-stage renal disease and death.

Previous safety studies have focused on examining the association between SGLT2i use and occurrence of AKI (Menne et al., 2019); however, little is known about which factors increase the risk of AKI while on SGLT2i therapy. Identifying patients at increased risk of AKI and using SGLT2i is necessary to individualize SGLT2i treatment and improve CVD and renal outcomes in T2D patients while minimizing risks. The development of a high-performance predictive model can aid clinicians in balancing risks vs. benefits when prescribing SGLT2is. To address this evidence gap, we developed a machine learning model to predict the risk of AKI among T2D patients undergoing SGLT2i treatment, and identified risk factors associated with incident AKI after SGLT2i initiation.

MATERIALS AND METHODS

Study Population and Follow-Up

The study used 2012–2016 claims data from a 5% random sample of Fee-for-Service Medicare beneficiaries. We first identified patients with T2D and those with at least one SGLT2i prescription (canagliflozin, dapagliflozin, or empagliflozin) filled between April 2013 and December 2016. T2D diagnosis was defined following the Center for Medicare and Medicaid Services (CMS) Chronic Condition Warehouse (CCW) definition, which traces back the first diagnosis to the first month of Medicare eligibility. (Service CfMaM (2020). Chr, 2020). The date of the first SGLT2i prescription filled during the study period was designated as index date. We excluded patients who did not have continuous Medicare Part D enrollment in the year prior to index date (i.e., baseline year) or who had filled a prescription for SGLT2i in the baseline year.

Patients were followed from index date until AKI incidence, therapy discontinuation (defined as a treatment gap ≥60 days), death, or the end of the study (31 December 2016). This study was approved by the institutional review board at the University of Pittsburgh as an exempt study because de-identified data were used in analyses.

Outcome

The outcome variable was an incident AKI event after index date, which was defined as having inpatient primary or secondary diagnosis of International Classification of Disease (ICD), Ninth Revision diagnosis codes 584, or 10th Revision primary diagnosis code N17. (D'Arienzo et al., 2019).

Predictors

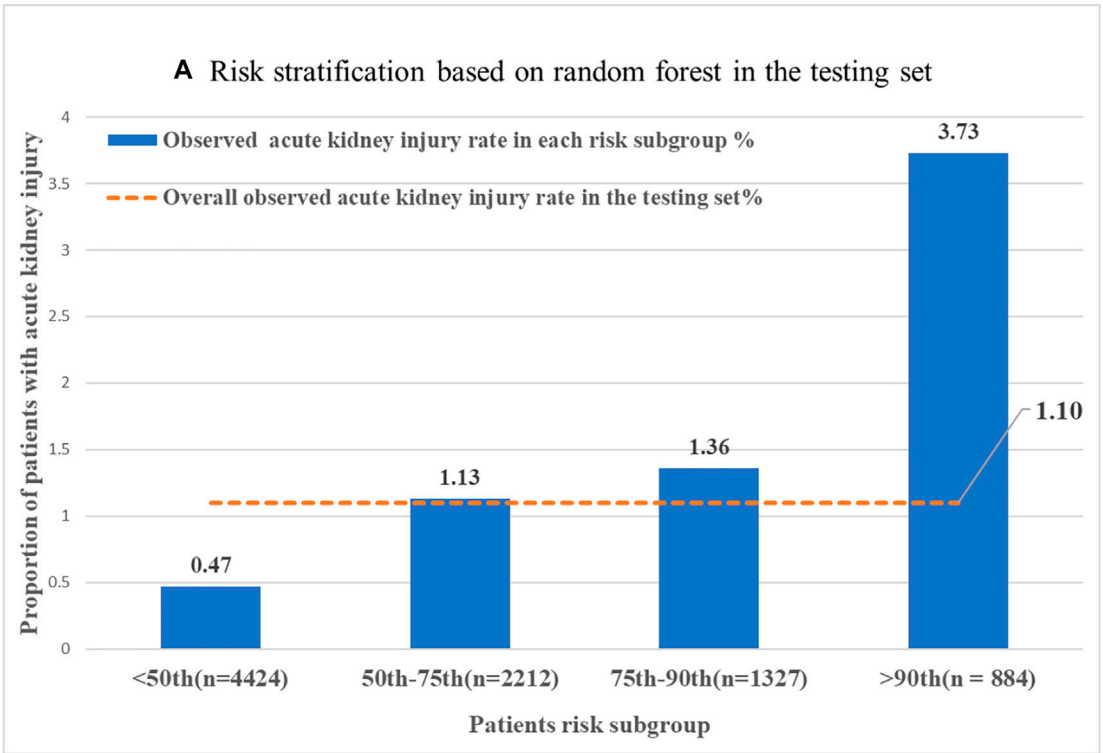
We compiled 65 predictor candidates using claims data from the baseline year, including information on sociodemographics, diabetes duration, comorbidities, and other medications (**Supplemental Table S1**). Sociodemographic characteristics included age, sex, race, region of residence, Medicaid eligibility, and receipt of low-income subsidy. Comorbidity information included history of AKI, acquired hypothyroidism, Alzheimer disease, ischemic heart disease, stroke or transient ischemic attack, atrial fibrillation, anemia, congestive heart failure, hyperlipidemia, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, lower extremity amputations, peripheral vascular disease, prostatic hyperplasia, rheumatoid arthritis, breast cancer, lung cancer and prostate cancer. Medication use included the use of other antidiabetic classes (i.e., metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase four inhibitors, glucagon-like peptide-1agonists, insulin, and others), angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), nonsteroidal anti-inflammatory drugs (NSAIDS), antiplatelet and loop diuretics. Predictors candidates were selected based on the risk factors associated with AKI in previous studies. (Nadkarni et al., 2017; Bhatraju et al., 2019; Kalisvaart et al., 2019; Menne et al., 2019).

Statistical Analyses

We split the sample randomly and equally into training (n = 8,847) and testing (n = 8,847) sets. We employed three machine learning approaches, including least absolute shrinkage and selection operator (LASSO), elastic net, and random forest (RF) to develop the AKI prediction model (**Supplemental Table S2**), which have been commonly used and shown success in predicting health outcomes. We used the training set to develop machine learning models and perform hyperparameter tuning and the testing set to evaluate the prediction performance.

C-statistics (or area under the receiver operating characteristic curves) including 95% confidence interval (CI) that were estimated by bootstrapping were calculated to assess the model's discrimination performance in the testing set. We plotted the observed AKI incidence rate across different risk subgroups (i.e., ≤50th, 50–75th, 75th–90th, and >90th percentile of the machine learning risk score) in the testing set to evaluate calibration performance.

To obtain the unbiased estimation of risk factors' odds ratios, we constructed a logistic regression model by including risk factors selected by LASSO (**Supplemental Table S3**). Analyses were performed using SAS, Version 9.4 (SAS Institute Inc.), and Python, Version 3.7 (Python Software Foundation).



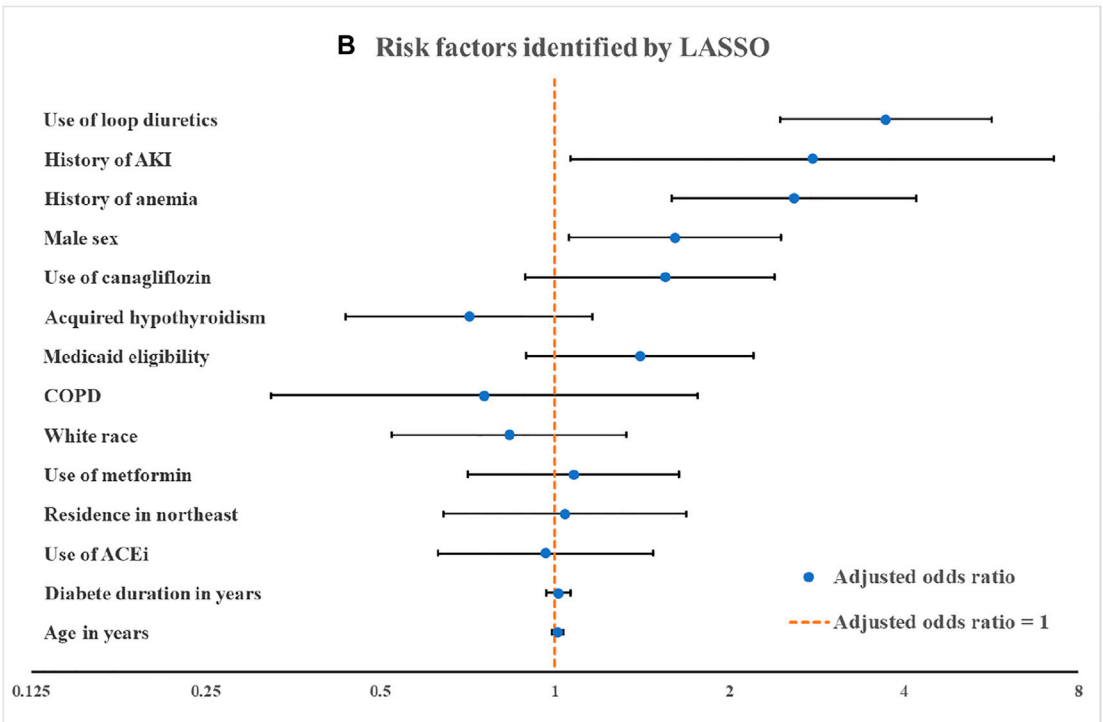


FIGURE 1 | Machine learning based risk stratification and important features. **(A)** Risk stratification by machine learning generated risk score: risk subgroup was categorized by the risk score that generated by random forest (i.e., ≤50th, 50–75th, 75–90th, >90th percentile of the random forest risk score). **(B)** Risk factors identified by LASSO. Adjusted odds ratios were obtained by regressing LASSO selected features against the AKI outcome a multiple logistic regression model. Note: The comparator for white race was non-white race, for residence in northwest was non residence in northwest. The comparator for use of canagliflozin was use of other SGLT2i including dapagliflozin and empagliflozin. Abbreviations: LASSO, Least absolute shrinkage and selection operator-type regularized regression. AKI, Acute kidney injury; COPD, chronic obstructive pulmonary disease; ACEi, Angiotensin-converting enzyme inhibitors.

RESULTS

Among 17,694 beneficiaries who initiated on SGLT2i, 194 (1.10%) developed AKI over a median follow-up period of 1.5 years. Patients in the training and testing sets shared comparable distributions of characteristics; both samples were approximately 48% male and 75% White (**Supplemental Table S4**).

The RF (C-statistic = 0.72, 95% CI 0.68–0.76) outperformed LASSO (C-statistic = 0.69, 95% CI 0.65–0.73) and elastic net (C-statistic = 0.69, 95% CI 0.65–0.73) in predicting AKI among T2D patients initiating SGLT2i. Using the risk score generated by the RF model, we categorized patients into four risk subgroups (**Figure 1A**). In the highest risk (i.e., top 10% of the risk score) and lowest risk (i.e., bottom 50% of the risk score) groups, the observed AKI incidence rates were 3.73% and 0.47%, respectively.

We identified risk factors using LASSO because of the interpretability of predictors in linear-based algorithms. Among 14 important features selected by LASSO (**Figure 1B**), use of loop diuretics [adjusted odds ratio (aOR): 3.72, 95% CI 2.45–5.6] and history of AKI (aOR: 2.78, 95% CI 1.06–7.3) had the strongest association with AKI incidence (**Figure 1B**), followed by anemia (aOR: 2.56, 95% CI 1.59–4.20) and male sex (aOR: 1.61, 95% CI 1.06–2.47).

DISCUSSION

Using real-world data, this study successfully developed and validated a machine learning model to identify T2D patients who were at high risk of AKI after SGLT2i initiation. The tree-based machine learning algorithm, RF, had reasonably good predictive utility and efficiently classified individuals into different risk subgroups. Although the predictive performance of LASSO––the linear-based algorithm––was slightly inferior to RF, it identified important risk factors associated with the development of AKI. The most important predictor was the use of loop diuretics which was associated with an almost four-fold increase in the odds of developing AKI among T2D patients taking SGLT2i.

To the best of our knowledge, our study was the first to identify an increased risk from loop diuretics among SGLT2i users. Traditionally, loop diuretics had been used to relieve symptoms of heart failure. The concomitant use of SGLT2i and loop diuretics may become common, given the remarkable reduction effect from SGLT2i in HF-associated negative outcomes. (Zaccardi et al., 2016; Wilcox et al., 2018). However, the synergistic effect of loop diuretics and SGLT2i in volume depletion might result in hypovolemia and systemic hypoperfusion, and further lead to reduced renal blood flow and AKI. (Wilcox et al., 2018; Mordi et al., 2020; Goyal et al., 2021). Future studies are needed to examine the safety profile of the combined use of loop diuretics and SGLT2 inhibitors among real-world patients.

To the best of our knowledge, our study is the first to use machine learning methods to predict AKI risk among real-world patients treated with SGLT2i. Previous AKI prediction models mainly focused on patients in critical and perioperative care. (Adhikari et al., 2019; Bhatraju et al., 2019; Kalisvaart et al., 2019; Gameiro et al., 2020). Our examination of patients is SGLT2is of major relevance due to the exponential uptake of SGLT2is in the recent years, driven by their distinctive cardiorenal benefits. (Zaccardi et al., 2016; Birkeland et al., 2017). Employing machine learning algorithms and administrative health care data to predict such rare, but serious, adverse events can provide opportunities for optimizing clinical decision making and individualized patient care. A risk prediction tool might be developed and implemented at the point of care to assist with therapeutic decisions and reduce preventable drug-related adverse outcomes. Nevertheless, future studies are needed to improve the performance of the model. Using claims data, we were not able to incorporate important predictors for SGLT2i users in the model such as serum creatinine level, hemoglobin A1c level. Our model performance can be further enhanced by using other more robust databases such as electronic health records databases. Furthermore, our model need to be updated for data that are more current considering the up taking trend of SGLT2i use. Lags in claim data is a hurdle that must be addressed prior to the implementation of the model.

The current study is subject to limitations. First, using claims data, we were unable to include some of the important clinical information used to predict AKI outcomes, such as estimated glomerular filtration rate (eGFR) and blood pressure. Second, our model was developed among new users of SGLT2i and predicted AKI risk within 1.5 years of follow-up. Future studies are needed to update the current model by using advanced methods and more robust linked data to dynamically predict AKI over the course of SGLT2i treatment. Third, external validation is needed for the current prediction model. Fourth; our findings may not be generalizable to other populations and settings, considering that the study was conducted among older adults with T2D based on Fee-for-Service Medicare claims data.

CONCLUSION

We successfully developed a machine learning model to predict AKI risk among T2D patients under SGLT2i treatment. Important risk factors––including use of loop diuretics, a history of AKI, and anemia––were identified as being associated with AKI development. Our data revealed relevant unmet needs that future studies can address through the implementation of machine learning-based alert tools aimed to improve early identification of rare, but serious, drug-related adverse events to support clinical, therapeutic decision-making and maximize treatment benefits.

DATA AVAILABILITY STATEMENT

The data analyzed in this study was obtained from Center for Medicare and Medicaid Services, the following licenses/restrictions apply: the data is not publicly available due to user agreement restrictions. Requests to access these datasets should be directed to Jingchuan Guo, juoj1@cop.ufl.edu.

ETHICS STATEMENT

Ethical review and approval was not required for the study of human participants in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

LY, IH and JG contributed to the conception and design of the study. NG performed data extraction and data management. SV, SK, and JB contributed to the design and method of the study. LY performed the statistical analysis. LY completed the first draft of this manuscript. NG, IH, SV, SK, JB, and JG wrote sections of this manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.834743/full#supplementary-material

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ORIGINAL RESEARCH
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Medication Regimen Complexity and Medication Burden Among Patients With Type 2 Diabetes Mellitus: A Retrospective Analysis

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Introduction: Most type 2 diabetes mellitus (T2DM) patients with chronic conditions require multiple medications to achieve and maintain good glycemic control.

Objective: This study assessed medication burden, regimen complexity, and adherence among T2DM patients and evaluate its association with glycemic control.

Method: We analyzed data of 2,696 T2DM patients at public health clinics in Malaysia from January 2018 until May 2019. Medication burden was based on medication count, regimen complexity was measured using the validated Medication Regimen Complexity Index (MRCI) tool, and adherence was measured using proportion of days covered (PDC) formula. Logistic regression models were used to compute unadjusted and adjusted odds ratio (aOR) with 95% confidence interval (CI) for association between the medication parameters and glycemic control (HbA1c ≤ 7.0%) over a 90-day period.

Results: The cohort mean age was 60.4 years old (±10.8) and 62.9% were female. Overall, the average medication count was 4.8 with MRCI score of 15.1. Mean adherence score (PDC) was 90%. High medication count and MRCI scores were associated with lower odds of achieving good glycemic control (aOR 0.88; 95% CI 0.82, 0.94 and aOR 0.89; 95% CI 0.87, 0.92, respectively) while inverse association was observed between adherence and HbA1c level (aOR 2.7, 95% CI 1.66, 5.19). Similar findings were observed for diabetes-specific measures.

Conclusions: High medication count, high regimen complexity, and low medication adherence were associated with poor glycemic control over the 3-month follow-up period. These parameters could be used to identify patients with complex pharmacotherapy regimens so that targets for intervention can be taken to achieve optimum outcomes and ease of self-care.

Keywords: medication regimen complexity, MRCI, medication burden, glycemic control, type 2 diabetes mellitus, polypharmacy, medication adherence, primary care

INTRODUCTION

Diabetes is a chronic illness that requires long-term medical care and patients are usually prescribed medications when attempts at lifestyle modifications alone fail to achieve or maintain adequate glycemic control. Patients with type 2 diabetes mellitus (T2DM) often requires more than one medication, which grows in complexity as the disease progresses and complications arise (Peron et al., 2015). The prevalence of multiple comorbidities among patients with established T2DM also increases the need for more medications and further complicates the treatment regimen. Besides medication count, other contributing attributes to the complexity of a medication regimen including dosage forms, dosing frequencies, complicated schedules, and special administration directions present challenges for patients with T2DM (Advinha et al., 2014). Studies have reported that complex treatment regimens are associated with worse outcomes, including medication non-adherence, poor control of medical conditions, and increased health resources utilization (Claxton et al., 2001; Ingersoll and Cohen, 2008; Pollack et al., 2010; Pantuzza et al., 2017; Ayele et al., 2019).

In Malaysia, the number of patients with T2DM is steadily increasing; the National Health and Morbidity Survey 2019 estimated that four million adult population had diabetes (Institute for Public Health, 2020). Previous data suggest that on average, patients with chronic condition take five medications per day (Hasan et al., 2017). Among patients with T2DM who attended primary care clinics in Malaysia, 60% reported taking more than three medications (Ahmad et al., 2013). Of note, it was reported that less than 25% of the patients with T2DM achieved the targeted HbA1c levels despite the evidence of improving processes of diabetes care in Malaysia (Mafauzy et al., 2016). One of the possible contributing factors is the medication burden imposed on the patients which resulted in poor adherence and subsequently suboptimal glycemic control (Sav et al., 2015). This has become the main focus in the development of diabetes management strategies, which included simplification of dosing regimens to promote better medication adherence among patients with T2DM (Nieuwlaat et al., 2014). A better understanding of treatment profiles is therefore urgently needed, before proper interventions can be tailored to improve the medication-taking behavior of T2DM patients.

Medication regimen complexity can be quantified using a validated tool, the Medication Regimen Complexity Index (MRCI) (George et al., 2004). The complexity level is based on the medication attributes of the regimen such as the number of medications, prescribed dosage forms, dosage frequency and administration instructions. The MRCI tool has demonstrated good evidence in classifying medication regimen complexity over a simple medication count (Mansur et al., 2012), by discriminating between regimens with the same number of medications but of different complexity. This tool was subsequently expanded and validated to include not only disease-specific prescription medications but also other prescription and over-the-counter (OTC) medications (Libby et al., 2013). The expanded tool, which is referred to as patient-level MRCI, provides a better perspective when patients are at greatest risk for failing to achieve desired outcomes.

To the best of our knowledge, detailed assessment of medication regimen complexity on T2DM has not been evaluated in the primary care settings in Malaysia. Understanding the association between these parameters and glycemic control may help to inform future strategies for developing interventions to improve therapeutic outcomes. The objective of this study was to determine medication burden, regimen complexity, and medication adherence among patients with T2DM and evaluate its effect on the level of glycemic control.

METHODS

Ethical approval was granted by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-17-267-34768) in compliance with the Declaration of Helsinki. Waiver of consent was also obtained. Medical records were reviewed retrospectively and all data was anonymized before use in the analysis.

Study Design and Setting

This cohort study was a retrospective analysis of data from a larger study—"The EnPHC interventions and evaluation study (EnPHC-Eva: Facility)". Pharmacy database from public primary care clinics in Malaysia was also utilized.

Primary care services in Malaysia are provided by a dual healthcare system: government-funded public health clinics and private clinics that operate on a fee-for-service model. Care for chronic diseases is largely concentrated in public health clinics while encounters in private clinics are mostly for acute and minor conditions (Khoo et al., 2015; Sivasampu et al., 2016). Workforce in public clinics encompasses a diverse skill mix including doctors, nurses, pharmacists, assistant medical officers, and other allied health professionals whereas the majority of private clinics are single medical practitioner practices. In public clinics, each clinic has an outpatient pharmacy that supplies and maintain records of medication supply for all patients seen at the respective clinics. Generally, the prescription is valid for the duration until the next scheduled appointment with the doctor. Patients visit the clinics' pharmacy directly for any prescription refills and the maximum period of each supply is usually limited to 1 month. For late refills, medications can only be dispensed if the prescription is still valid. Patients seeking care at public clinics may also request doctors to prescribe for them to get medications at the private pharmacies, but the proportion is low due to the additional cost incurred.

Data Sources

Patient and outcome data were obtained from the EnPHC cohort that includes patient demographic and diagnosis at baseline, as well as laboratory parameters collected during subsequent follow-up(s). Details on medication were retrieved from the pharmacy

dispensing records. The two databases were linked using a unique patient identifier. Details of the databases are described below.

The EnPHC Interventions and Evaluation Study (EnPHC-Eva: Facility)

The project "Evaluation of 'Enhanced Primary Health Care (EnPHC)' interventions in public health clinics was a quasi-experimental controlled study to assess the effectiveness of an intervention package on the process of care and intermediate clinical outcomes at 40 selected public primary care clinics in Malaysia. The clinics were selected by the study team based on their setup and size that reflects care services provided across public health clinics, along with budget and capacity to implement the EnPHC package. Details about the EnPHC project have been described and published elsewhere (Sivasampu et al., 2020). In summary, patients aged 30 years and older with a recorded diagnosis of T2DM or hypertension were sampled from the participating clinics. Their medical records were reviewed retrospectively and the following data were collected at several time points between November 2016 to June 2019: patient demographic (age, gender, ethnicity), risk factors (comorbidities, disease duration), physical examination (e.g., blood pressure (BP), body mass index), and laboratory investigations (e.g., HbA1c, lipid profile).

Pharmacy Dispensing Record

The Pharmacy Information System (PhIS) is an electronic medication management system implemented in public primary care clinics throughout Malaysia. The database contains details of medications supplied to patients including prescription date and duration, dispensed date and quantity, medication name, dosage, route, and frequency. Prescription and dispensing data are available from 1 January 2018 onwards.

Study Population

The present study selected patients with matched records from the two data sources for the period from 1 January 2018 until 31 May 2019. We included patients with T2DM, treated with at least one antidiabetic medication, and had at least one HbA1c reading recorded during this period. All medications prescribed and supplied to patients during the study period were assessed and medications for the treatment of chronic conditions were identified for inclusion in the analysis. Chronic medications were defined as medications with prescriptions filled for a supply duration of 90 days or more (U.S. National Center for Health Statistics, 2018). Patients were excluded if there was no data on medication(s) prescribed for the period before the last HbA1c measurement. The final cohort consisted of 2,696 patients.

Outcome Measures

Medications were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system recommended by the World Health Organization (WHO) (WHO Collaborating Centre for Drug Statistics Methodology, 2021). Medication regimens for all patients included in the analysis were assessed over 90 days preceding the latest HbA1c measurement. Analysis of medications was carried out at two levels: 1) diabetes-specific which included only antidiabetic medications, and 2) patient-level which included all chronic medications.

Medication Burden

Medication burden was quantified by simple medication count and calculated as the mean number of chronic medications dispensed per patient, per day. Based on the medication count, patients were grouped into the following categories: 1) one to two medications, 2) three to four medications, 3) five to six medications and 4) ≥ 7 medications.

Medication Regimen Complexity

Medication regimen complexity was computed using the MRCI tool (George et al., 2004). The validated tool consisted of three sections: dosage forms, dosing frequencies, and additional directions. MRCI score was calculated based on pre-assigned weights for these elements in which a higher MRCI score indicates a more complex medication regimen. Directions for use that were not recorded in the system (e.g. take with food) were identified from medication package insert or drug reference tool (Facts and Comparisons 2016).

Medication Adherence

Adherence to medications was measured by calculating the proportion of days covered (PDC) over a fixed time interval. PDC is defined as the number of days covered with medications divided by days of observation (Raebel et al., 2013; Pednekar et al., 2019) i.e.,

$$\text{PDC} = \frac{\text{Number of days}' \text{ covered}}{\text{Observation period}}$$

PDC was dichotomized using the convention threshold of 0.8 (Andrade et al., 2006). Patients were considered adherent if they have PDC ≥0.8 (80%).

Glycemic Control

The main outcome measure was the HbA1c level. Patients' latest readings of HbA1c were used to categorize them into two groups: controlled = HbA1c ≤ 7.0% and uncontrolled = HbA1c >7.0%. The level was selected based on guideline recommendations of HbA1c target ranges for the general population in Malaysia (Ministry of Health Malaysia, 2015).

Statistical Analysis

Patient demographics, clinical characteristics, and treatment characteristics were reported descriptively. Association between independent variables (medication burden, medication regimen complexity, and adherence) and dependent variable (glycemic control) were analyzed using binary logistic regression with a dichotomous outcome (HbA1c level ≤7.0% or >7.0%). In multivariable regression analysis, covariates included for adjustment were age, gender, ethnicity, presence of key

TABLE 1 | Demographic characteristic of study cohort from "EnPHC-Eva: Facility" Malaysia, 2018-2019 (N = 2,696).

Characteristics	n (%)
Age (years), mean (SD)	60.4 (10.8)
<65 years	1,744 (64.7)
≥65 years	952 (35.3)
Gender	
Male	1,000 (37.1)
Female	1,696 (62.9)
Ethnicity	
Malay	2,025 (75.1)
Chinese	368 (13.7)
Indian	278 (10.3)
Others	25 (0.9)
Location of primary care clinic	
Rural	1,330 (49.3)
Urban	1,366 (50.7)
BMI (kg/m^2), mean (SD) (N = 2,610)	28.4 (5.5)
BMI ≥27.5 kg/m^2	1,367 (52.4)
Comorbidity	
Hypertension	2,312 (85.8)
Hyperlipidaemia	2,011 (74.6)
Duration of diabetes (years), mean (SD)	7.1 (5.7)
Duration of hypertension (years), mean (SD) (N = 2,312)	7.7 (6.5)
Duration of hyperlipidaemia (years), mean (SD) (N = 2011)	5.0 (4.3)
Antidiabetic medication	
Oral anti-diabetic drugs	1,820 (67.5)
Oral anti-diabetic drugs + Insulin	876 (32.5)
Antihypertensive medication	
Free combination antihypertensive drugs	2,297 (99.4)
Fixed dose combination	15 (0.6)
Lipid lowering medication	
Statin	2,348 (87.1)
HbA1c (%), mean (SD)	8.3 (2.1)
Median (IQR)	7.8 (6.7, 9.6)
HbA1c ≤ 7.0%	931 (34.5)
HbA1c > 7.0%	1,765 (65.5)

**Denominator not equal to 2,696 due to missing data.*
Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; PDC, proportion of days covered; SD, standard deviation.

comorbidities (hypertension, hyperlipidemia), body mass index (BMI), duration since diabetes diagnosis, and location of clinic (urban vs. rural). Covariates included for adjustment in the multivariable model were identified based on univariable analysis and clinical importance. Analysis was carried out using a complex survey design to account for the clustering effect within clinics. Complete case analysis was performed for the regression. Multicollinearity of the covariates was checked.

Sensitivity analysis was conducted to assess the robustness of the results. In the first sensitivity analysis, the HbA1c level was analyzed as a continuous outcome variable and the association was measured using multivariate linear regression. The second sensitivity analysis used a higher HbA1c level of ≤7.5% to dichotomize the outcome of good glycemic control versus poor (HbA1c >7.5%) for measurement of association using logistic regression. The odds ratio (unadjusted and adjusted) and the corresponding 95% confidence intervals (CI) were reported. A *p*-value of <0.05 was considered statistically significant. All statistical analysis was performed using Stata statistical software version 15 (StataCorp, 2017).

RESULTS

A total of 2,696 patients who met the inclusion criteria were included in the final analysis. **Table 1** shows the characteristics of the study population. The mean age of the patients was 60.4 years (range: 30–93 years), 62.9% were females, and 75.1% were of Malay ethnicity. Approximately half of the patients were obese with BMI scores above 27.5 kg/m^2. Comorbidities of hypertension and hyperlipidemia were present in 85.8% and 74.6% of the patients, respectively. Almost one-third of the patients were treated with a combination of oral antidiabetics with insulin. Only 34.5% had HbA1c below 7.0%.

Table 2 describes treatment characteristics of the patients for three components: medication burden, regimen complexity, and adherence. On average, patients were taking 4.8 chronic

TABLE 2 | Treatment characteristics of study cohort from "EnPHC-Eva: Facility" Malaysia, 2018-2019 (N = 2,696).

Variable	n (%)
Medication burden	
Total number of medications per day, mean (SD)	4.8 (1.7)
Categories, by quantity	
1–2	221 (8.2)
3–4	942 (34.9)
5–6	1,081 (40.1)
≥7	452 (16.8)
Number of antidiabetic medications per day, mean (SD)	1.3 (0.7)
Percentage of total medication count, %	27.1
Categories, by quantity	
1	1,608 (59.6)
2	935 (34.7)
3–4	153 (5.7)
Medication regimen complexity	
Total patient-level MRCI score, mean (SD)	15.1 (4.9)
(i) Dosage form score, mean (SD)	2.0 (1.5)
Percentage of total pMRCI score, %	13.2
(ii) Dosing frequency score, mean (SD)	6.7 (2.4)
Percentage of total pMRCI score, %	44.4
(iii) Additional directions score, mean (SD)	6.4 (2.4)
Percentage of total pMRCI score, %	42.4
Diabetes-specific MRCI, mean (SD)	7.9 (3.0)
Percentage of total pMRCI score, (%)	52.9
(i) Dosage form score, mean (SD)	1.8 (1.2)
Percentage of total dMRCI score, %	22.8
(ii) Dosing frequency score, mean (SD)	3.2 (1.2)
Percentage of total dMRCI score, %	40.5
(iii) Additional directions score, mean (SD)	2.9 (1.3)
Percentage of total dMRCI score, %	36.7
Medication adherence	
Patient-level PDC, mean (SD)	0.90 (0.15)
Categories, by PDC level	
<80%	512 (19.0)
80–89%	403 (14.9)
≥90%	1,781 (66.1)
Diabetes-specific PDC, mean (SD)	0.91 (0.15)
Categories, by PDC level	
<80%	471 (17.5)
80–89%	311 (11.5)
≥90%	1,914 (71.0)

Abbreviations: dMRCI, diabetes-specific medication regimen complexity index; PDC, proportion days covered; pMRCI, patient-level medication regimen complexity index; SD, standard deviation.

TABLE 3 | Association between medication parameters and HbA1c level (≤7.0%) of study cohort from "EnPHC-Eva: Facility" Malaysia, 2018-2019.

	Unadjusted	Adjusted		
	OR (95% CI)	OR (95% CI)	*p*-value	R^2
Patient-level				
Medication count	0.92 (0.87, 0.96)	0.88 (0.82, 0.94)	<0.001	0.0862
MRCI score	0.91 (0.89, 0.92)	0.89 (0.87, 0.92)	<0.001	0.1126
Adherence (PDC)	1.91 (1.10, 3.31)	2.66 (1.66, 5.19)	0.004	0.0840
Diabetes-specific				
Medication count	0.54 (0.48, 0.61)	0.59 (0.52, 0.66)	<0.001	0.1003
MRCI score	0.68 (0.66, 0.71)	0.70 (0.67, 0.74)	<0.001	0.1900
Adherence (PDC)	1.11 (0.65, 1.89)	1.76 (0.86, 3.60)	0.123	0.0819

Note: Model was run separately for (i) medication count, (ii) MRCI, score, and (iii) adherence. Estimation using univariate (unadjusted) and multiple logistic regression adjusted for age (years), gender (male/female), ethnicity (Malay/Chinese/Indian/others), hypertension (no/yes), hyperlipidaemia (no/yes), body mass index (kg/m2), location of primary care clinic (rural/urban), duration of diabetes (years). p-value significant at <0.05. The variance inflation factors (VIFs) for all variables were less than two in all models. Abbreviations: OR, odds ratio; CI, confidence interval; MRCI, medication regimen complexity index; PDC, proportion days covered.

medications per day. There were 17% of patients with seven or more medications daily. Antidiabetic medication accounted for approximately 27.1% of the mean total medication burden, with the average antidiabetic medication burden of 1.3. The complexity of the medication regimen was presented as MRCI scores in **Table 2** for all chronic medications (patient-level) and antidiabetic medications (diabetes-specific). Breakdown of the individual components of the MRCI was also provided. The overall mean scores of patient-level MRCI and diabetes-specific MRCI were 15.1 and 7.9, respectively. Antidiabetic medications accounted for 52.3% of the overall patient-level MRCI scores. The main contributing attributes to the final score of medication regimen complexity were dosing frequency and the additional instructions given for taking the medications, followed by the dosage forms. In terms of medication adherence, the average PDC was 0.90 at the patient-level and 0.91 for diabetes-specific. Nonetheless, there were 19% of patients with PDC levels below 80% indicating poor adherence.

Table 3 depicts the association between the treatment profiles and good glycemic control (attainment of HbA1c ≤7.0%). Each model was run separately and adjusted for the covariates. For measurement at patient-level (chronic medications), increasing medication count (adjusted OR 0.88; 95% CI 0.82–0.94) and regimen complexity (adjusted OR 0.89: 95% CI 0.87–0.92) was associated with lower odds of achieving HbA1c below 7.0%. On the other hand, increasing adherence was associated with greater odds of achieving target HbA1c (adjusted OR 2.66; 95% CI 1.66–5.19). Similar findings were observed when the analysis was conducted for the diabetes-specific measures. However, the association between adherence and HbA1c level did not reach statistical significance for the diabetes-specific (adjusted OR 1.76; 95% CI 0.86–3.60). Estimates from sensitivity analyses were consistent with the main results (**Supplementary Table S1, S2**).

DISCUSSION

In this study, we used a validated MRCI tool to quantify the complexity of a medication regimen among patients with T2DM. We found that almost two-thirds of the patients had an average of at least five medications prescribed per day. The diabetes-specific MRCI accounted for 52.9% of the patient-level MRCI score. In our cohort of T2DM patients at public primary care clinics in Malaysia, high medication count, high regimen complexity, and low medication adherence were associated with poor glycemic control over the 3-month follow-up period.

On average, approximately two-thirds of the patients in this study were taking a minimum of five medications per day. This finding is not surprising as approximately 90% of patients with T2DM in our study had at least one other condition such as hypertension, hyperlipidemia or cardiovascular disorders which contributed to the additional medications. Despite the large proportion of patients with a high medication burden, a good medication adherence rate was observed in this study. Several reasons could account for this observation. First, it is possible that the adherence observed in this current study is still good until a certain threshold of medication burden is achieved before it starts to decline. Prior studies suggested that there is a limit to the number of medications a patient can consistently adhere to as prescribed (Shalansky and Levy, 2002; Kim et al., 2019). Second, the adherence measure (PDC) which we have calculated based on medication dispensing data is merely reporting on the rate of medication possession. This limitation may overestimate adherence to treatment for some patients. Finally, good adherence may be partly attributed to patients' health beliefs in effective disease management (Rosenstock, 2005). In this Health Belief Model, patients who believe that they are ill are likely to make additional efforts to take the medications as prescribed to maintain their health. Of note, medication adherence is a complex behavior. It can be influenced not only by patients' personal beliefs and knowledge about the necessity of their prescribed medication but also by patient characteristics and how patients make an effort to remember to take their medications (Ownby et al., 2006). Nevertheless, elevated medication burden also increases risk for medication interactions (Palleria et al., 2013) and potentially inappropriate medication use (Nothelle et al., 2017). Therefore, efforts to alleviate medication burden namely by the selection of medications that treat more than one underlying condition, combined indications with single medication or fixed-dose combination medications (FDC), when possible, should be considered.

The overall MRCI score in this study was comparable to that of a previous study specific to patients with T2DM with similar criteria where only those chronic medications filled for at least 90 days were considered in the analysis (Boye et al., 2020). The diabetes-specific MRCI accounted for 52.3% of the overall MRCI score in this present study. Similar results was found in prior studies (Libby et al., 2013; Rettig et al., 2013) where the MRCI score was found to be greater for the group with diabetes than for the group with hypertension despite no difference in the mean number of medications. This indicates that to a certain extent, the complexity components for antidiabetic medications contribute much more to regimen complexity than sheer medication count. Antidiabetic regimens can be a mixture of oral and injection; inclusion of insulin in the treatment regimen adds to the score of regimen complexity. The application of MRCI tool to quantify

pharmacotherapy complexity has been previously demonstrated; however, there are still inconclusive evidence on the appropriate cut-points of MRCI score to distinguish level of regimen complexity (Ferreira et al., 2015; Wimmer et al., 2016; Morillo-Verdugo et al., 2019). As such, meaningful comparisons across studies are difficult until the range of plausible MRCI is established.

The findings that the MRCI score was inversely associated with good glycemic control in the current study are consistent with those of previous reports specific to patients with T2DM (Pollack et al., 2010; Yeh et al., 2017; Ayele et al., 2019). However, it is important to take note that approximately 45% of the patient-level score was derived from non-antidiabetic medications such as antihypertensive medications and lipid-lowering agents. Despite the increase of the patient-level MRCI score by these medications, some of these medications may be associated with secondary effects on the glycemic levels. For instance, non-antidiabetic medications such as beta-blockers, salicylates and angiotensin-converting enzyme inhibitors have been reported to contribute to medication-induced hypoglycemia, even in individuals without diabetes (Vue and Setter, 2011). As expected, we found a positive association between good medication adherence and improvement in glycemic control. This is in keeping with those reported in several studies that greater adherence was associated with improved glycemic control (Schectman et al., 2002; Ho et al., 2006; Lin et al., 2017). One of the viable strategies that can be employed to reduce the regimen complexity is by reducing the frequency of the prescribed medications. It has been reported that simplification of medication dosing has a significant positive effect on adherence (Coleman et al., 2012; Weeda et al., 2016). However, increased medication burden may be unavoidable in most chronic conditions (Ong et al., 2020). Therefore, it is vital to have a regular review of patients' medication regimens to ensure that unnecessary and redundant medications are discontinued.

The findings of this study have to be considered within several limitations. First, this study focused on T2DM patients treated at public primary clinics and hence may not present the entire population of individuals with T2DM. However, a large proportion of diabetes patients seek treatment at public health facilities (Hussein et al., 2015; Sivasampu et al., 2016) and the population included in the current study may reflect most of the target population, albeit not the whole. Second, the analysis did not consider over-the-counter medications, vitamins or supplements when examining patient medication regimens. These medications may or may not have the potential to contribute significantly to the overall complexity. Thus, the overall MRCI might be underestimated. Third, medication use was proxied by medication dispensing data. As such, we were unable to confirm whether patients were taking the medications when a prescription was filled. Further, refilling a prescription on time does not necessarily mean that a patient is taking the drug correctly. This may overestimate adherence to treatment for some patients. Another limitation was that only one HbA1c measurement was used for the assessment of the relationship between medication regimen complexity measure and medication adherence. Nevertheless, we are confident with the findings because most of the study findings are consistent with many other related studies.

CONCLUSION

High medication count and regimen complexity were associated with lower odds of attaining good glycemic control while inverse association was observed between medication adherence and HbA1c level. These findings also suggest that medication adherence is likely the mediator in the association between regimen complexity and glycemic control. Our study showed that MRCI can be utilized as an objective proxy in addressing the complexity inherent within a medication prescription. Thus, it can be used to help with clinical decision support by identifying patients with complex pharmacotherapy regimens who can then be evaluated further before remedial action can be taken. This includes medication regimen simplification, reducing pill burden, medical reminder devices, closer clinical monitoring and clinical interventions if required as well as boosting patients' understanding of prescribed medications to improve adherence and achieve optimum outcomes in patients with T2DM and ease of self-care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia and complies with the Declaration of Helsinki. This included a waiver of informed consent. All medical records were reviewed retrospectively and data were anonymized before being used in the analysis.

AUTHOR CONTRIBUTIONS

NA: Conceptualization, Methodology, Formal analysis, Visualization, Writing—review and editing. ML: Conceptualization, Methodology, Formal Analysis, Writing—original draft, Writing-review and editing. ST: Data curation, Writing—review and editing. NH: Data curation, Writing—review and editing. SS: Conceptualization, Methodology, Writing—review and editing, Project Supervisor, Funding acquisition.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.808190/full#supplementary-material

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Predictive Effect of Triglyceride Glucose–Related Parameters, Obesity Indices, and Lipid Ratios for Diabetes in a Chinese Population: A Prospective Cohort Study

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Objective: The purpose of this study was to evaluate the association between triglyceride glucose (TyG) index and new-onset diabetes under different glycemic states and to compare the predictive value of TyG–related parameters, obesity indices, and lipid ratios for new-onset diabetes.

Methods: Data were collected from the China Health and Retirement Longitudinal Study (CHARLS), consisting of 6,258 participants aged ≥45 years. Participants were grouped according to their glycemic states. Cox proportional hazards models and restricted cubic spline regression were used to explore the association between TyG index and diabetes. Cox proportional hazard models were applied to confirm the predictive value of the optimal marker. Receiver operating characteristic (ROC) curves were used to compare the predictive value.

Results: TyG index was positively correlated with the risk of diabetes (hazard ratio (HR), 1.75; 95% confidence interval (CI), 1.56–1.97), and the linear association existed ($p < 0.001$). The highest correlation with diabetes was visceral adiposity index (VAI) (HR, 2.04; 95% CI, 1.44–2.90) in normal fasting glucose (NFG) group and TyG-body mass index (TyG-BMI) (HR, 2.53; 95% CI, 1.97–3.26) in impaired fasting glucose (IFG) group. The largest area under curve (AUC) was observed in TyG-waist-to-height ratio (TyG-WHtR) in the NFG group (AUC, 0.613; 95% CI, 0.527–0.700), and TyG-BMI had the highest AUC in the IFG group (AUC, 0.643; 95% CI, 0.601–0.685).

Conclusion: The association between TyG index and new-onset diabetes was positive and linear. TyG-WHtR was a clinically effective marker for identifying the risks of diabetes in the NFG group and TyG-BMI was an effective marker to predict diabetes in the IFG group.

Keywords: diabetes mellitus, triglyceride glucose index, obesity, lipid ratios, CHARLS

INTRODUCTION

The increasing prevalence of diabetes has become a major public health problem worldwide, especially in developing countries (1). According to the latest diabetes map released by the International Diabetes Federation (IDF) in 2021, the number of people with diabetes worldwide will grow to 783 million by 2045, and China's diabetes population has reached 140 million in 2021, ranking first in the world (2). Effective screening strategy is essential for identifying high-risk groups and reducing the incidence rate of diabetes.

The occurrence of diabetes can be predicted by relevant indicators (3–5). Insulin resistance (IR) plays an important role in the pathogenesis of diabetes and other metabolic-related diseases, which has already appeared before diabetes diagnosis (6, 7). Visceral obesity and ectopic fat deposition associated with IR lead to dyslipidemia and inflammation (8), which accelerated the development of diabetes. IR could be diagnosed by hyperinsulinemic-euglycemic clamp test (9) and homeostasis model assessment of IR (HOMA-IR) (10). However, it was inefficient for whole population screening due to the complex and expensive test process. Therefore, new markers or risk factors were needed to identify people at high risk of diabetes in order to implement prevention measures in the population.

In recent years, several studies have proposed new indicators for predicting diabetes, such as visceral adiposity index (VAI), a model based on anthropometry and laboratory parameters, and lipid accumulation product (LAP), based on the combination of TG and WC, which can be used to predict metabolic syndrome (11, 12). Triglyceride glucose (TyG) index and its related parameters were shown to be related to diabetes (13). However, the association between TyG index at different levels and diabetes was still inconsistent. A cohort study pointed out that there was a nonlinear relationship between the TyG index and incident T2DM (4). Studies have also indicated that total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG)/HDL-C can detect IR more effectively than simple lipid method (14). Some studies evaluated and compared the predictive value of TyG index, VAI, and LAP for new-onset diabetes (15–17), as well as the accuracy of the predictive value of various physical measurement indicators (3), but the conclusions of these studies were different for the best predictor of new-onset diabetes. No previous study specifically and comprehensively compared the accuracy of TyG-related parameters and these indicators in predicting the onset of diabetes, which should be verified in different ethnic groups. A study in China found that the incidence of diabetes in subjects with impaired fasting glucose (IFG) was more than six times higher than subjects with normal fasting glucose (NFG) (18). Therefore, the baseline blood glucose status of the population might also affect the accuracy of these indicators in predicting new-onset diabetes.

The aim of this study was to evaluate the correlation between TyG index and the risk of diabetes and to compare the predictive ability of TyG, TyG-body mass index (TyG-BMI), TyG-waist circumference (TyG-WC), TyG-waist-to-height ratio (TyG-WHtR), VAI, LAP, TG/HDL-C, and TC/HDL-C for the risk of new-onset diabetes under different glycemic states at follow-up in middle-aged and elderly Chinese population.

MATERIALS AND METHODS

Study Population

The data used in this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS), which was a longitudinal data of middle-aged and elderly people in China. The baseline wave of the study was conducted between June 2011 and March 2012, covered 28 provinces, 17,708 participants, with a response rate of 80.5%. Information on demographic, socioeconomic status, and health status of participants was collected using computer-assisted personal interview (CAPI) techniques. Follow-up surveys were conducted every 2 to 3 years, and so far, a second (2013), third (2015), and fourth (2018) wave have been conducted, of which blood samples were only collected from the baseline and third wave. The population that we included was no diabetes at baseline and followed up at least once. A total of 6,258 participants were included after removing the subjects with missing information on TG, TC, fasting blood glucose (FBG), hemoglobin A1c (HbA1c), HDL-C, and LDL-C at baseline or missing basic demographic characteristics and age <45 years (**Figure 1**).

All respondents were required to sign informed consent, and the ethical approval for data collection in CHARLS was approved by The Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). The use of CHARLS data obtained ethical approval from the Human Research Ethics Committee of the University of Newcastle (H-2015-0290).

Definition of Diabetes

Diabetes was defined as having FBG >125 mg/dl, HbA1c >6.5%, previous diagnosis of new-onset diabetes, or use of antidiabetic medications. IFG was defined as FBG of 100–125 mg/dl or HbA1c of 5.7%–6.4%. NFG was defined as without diabetes or prediabetes.

Anthropometric Measurements and Serum Biochemical Parameters

Anthropometric measurements were performed by trained staff. Weight was quantified without shoes to the nearest 0.1 kg, vertical height meter was used to measure the height, and the measurement was accurate to 0.1 cm. Waist circumference was measured horizontally around the subject at the umbilical position and to the nearest 0.1 cm. Venous blood was collected on an empty stomach and transported by a cold-chain transport company to the Chinese Center for Disease Control and Prevention in Beijing. FBG, HbA1c, TG, TC, and HDL-C were measured by trained staff. The obesity- and TyG-related indices were calculated using the following formula:

(1) WHtR = WC/height.

With WC in centimeters, and height in centimeters (19).

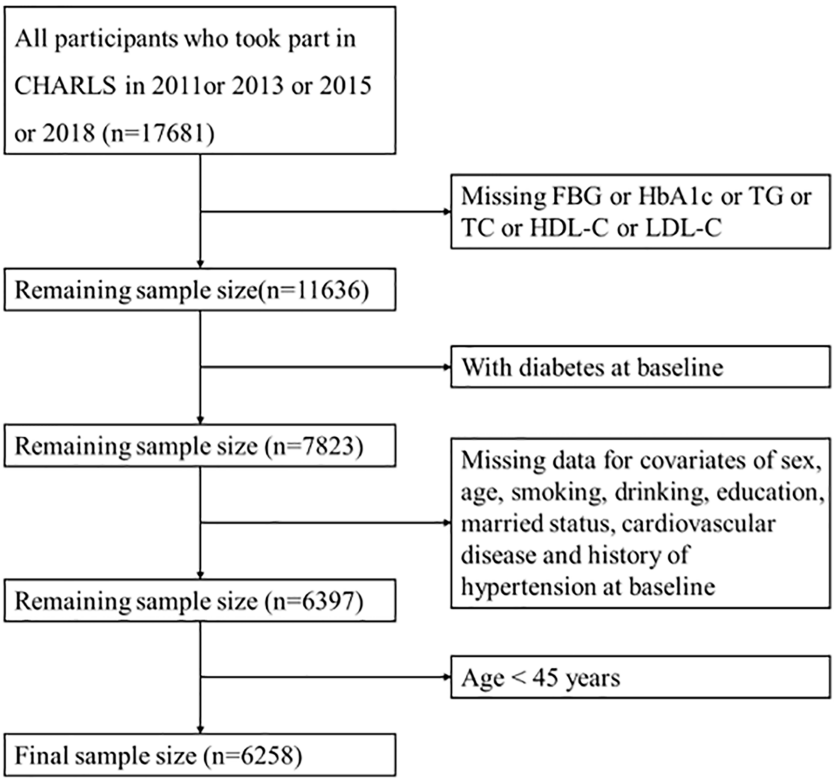

FIGURE 1 | Flow chart of study participants.

(2) VAI (men) = [WC/39.68 + (1.88 × BMI)] × (TG/1.03) × (1.31/HDL-C).

VAI (women) = [WC/36.58 + (1.89 × BMI)] × (TG/0.81) × (1.52/HDL-C).

With WC in centimeters, BMI in kilograms per square meter, TG and HDL-C both in millimoles per liter (20).

(3) LAP (men) = [WC − 65] × TG.

LAP (women) = [WC − 58] × TG.

With WC in centimeters and TG in millimoles per liter (21).

(4) TyG = Ln [(TG × FBG)/2].

With TG and FBG both in milligrams per deciliter (22).

(5) TyG-BMI = TyG × BMI. TyG-WC = TyG × WC. TyG-WHtR = TyG × WHtR (23).

Other Covariates

Through face-to-face questionnaire, the participants' sex, age, smoking, drinking, educational level, marital status, history of hypertension, cardiovascular disease, and other information were obtained.

Statistical Analysis

Data for quantitative variables were expressed as mean ± standard deviation (SD), and Student's *t*-test was used for comparison between the two groups. Data for qualitative variables were expressed as numbers (percentage) and were compared using Pearson's Chi-square test. Grouped by glycemic status at baseline, the cumulative incidence of each group was estimated by Kaplan–Meier method and compared by log-rank test. Participants were divided into four groups (Q1, Q2, Q3, Q4) based on the quartile of TyG, with quartile 1 as the reference group. Cox proportional hazards models were used to evaluate the association between the TyG index and new-onset diabetes. Model 2 was adjusted for age. Model 3 was adjusted for variables in model 2 plus drinking, education, hypertension, and cardiovascular disease. The dose–response association between the TyG index and the risk of diabetes was examined by restricted cubic spline model after adjustment for potential confounding factors. In order to compare the diagnostic value of different indicators for new-onset diabetes, four categories of TyG-BMI, TyG-WC, TyG-WHtR, VAI, LAP, TG/HDL-C, and TC/HDL-C were used as independent variables to calculate hazard ratio (HR) and 95% confidence interval (CI). The area under the receiver operating characteristic (ROC) curve (AUC) was used to test the predictive power of TyG, TyG-BMI, TyG-WC, TyG-WHtR, VAI, LAP, TG/HDL-C, and TC/HDL-C at baseline for the risk of emerging diabetes at follow-up. $p < 0.05$ was considered statistically significant. R Version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analysis.

RESULTS

Baseline Characteristics of Study Participants

A total of 6,258 participants were included in the study, of whom 858 developed diabetes at follow-up. **Table 1** summarized the baseline characteristics of participants based on glycemic status and diabetes status at follow-up. The average age of the whole cohort was 58.51 years old and men accounted for 45.2%. In different glycemic status groups, compared with people without diabetes, participants with diabetes were older, had higher levels of TG, HDL-C, TyG, TyG-BMI, TyG-WC, TyG-WHtR, VAI, LAP, TG/HDL-C, and TC/HDL-C ($p < 0.05$), and were more likely to have hypertension ($p < 0.001$). In participants with normal blood glucose at baseline, no diabetes group had higher education level than the diabetes group ($p = 0.022$). In participants with impaired fasting glucose at baseline, the diabetes group was more likely to have cardiovascular disease ($p = 0.003$). During follow-up, the incidence of diabetes was 9.4% in the NFG and 17.6% in the IFG. As shown in **Figure 2**, Kaplan–Meier curves showed significant differences in the cumulative incidence of diabetes between baseline glucose states (log-rank test, $p < 0.001$), and those with higher glucose had a greater risk of diabetes over time.

TABLE 1 | Demographic and clinical characteristics of the participants by glycemic status and diabetes status at follow-up.

	Total (*n* = 6,258)	NFG (*n* = 2,970)			IFG (*n* = 3,288)		
		Without diabetes (*n* = 2,691)	With diabetes (*n* = 279)	*p*-Value	Without diabetes (*n* = 2,709)	With diabetes (*n* = 579)	*p*-Value
Age	58.51 ± 8.80	57.75 ± 8.82	59.49 ± 9.14	0.002	58.89 ± 8.72	59.80 ± 8.59	0.022
Sex				0.597			0.122
Men	2,831 (45.2)	1,219 (45.3)	131 (47.0)		1,237 (45.7)	244 (42.1)	
Women	3,427 (54.8)	1,472 (54.7)	148 (53.0)		1,472 (54.3)	335 (57.9)	
Drinking				0.497			0.083
Yes	2,057 (32.9)	903 (33.6)	88 (31.5)		896 (33.1)	170 (29.4)	
No	4,201 (67.1)	1,788 (66.4)	191 (68.5)		1,813 (66.9)	409 (70.6)	
Smoking				0.772			0.811
Yes	2,381 (38.0)	1,056 (39.2)	107 (38.4)		1,001 (37.0)	217 (37.5)	
No	3,877 (62.0)	1,635 (60.8)	172 (61.6)		1,708 (63.0)	362 (62.5)	
Hypertension				<0.001			<0.001
Yes	1,349 (21.6)	491 (18.2)	77 (27.6)		588 (21.7)	193 (33.3)	
No	4,909 (78.4)	2,200 (81.8)	202 (72.4)		2,121 (78.3)	386 (66.7)	
Cardiovascular disease				0.303			0.003
Yes	662 (10.6)	257 (9.6)	32 (11.5)		287 (10.6)	86 (14.9)	
No	5,596 (89.4)	2,434 (90.4)	247 (88.5)		2,422 (89.4)	493 (85.1)	
Education				0.022			0.298
Primary school or lower	4,380 (70.0)	1,852 (68.8)	211 (75.6)		1,898 (70.0)	419 (72.4)	
Secondary school	1,807 (28.9)	808 (30.0)	68 (24.4)		775 (28.6)	156 (26.9)	
Higher	71 (1.1)	31 (1.2)	0 (0.0)		36 (1.3)	4 (0.7)	
Married status				0.415			0.118
Unmarried	31 (0.5)	14 (0.5)	0 (0.0)		13 (0.5)	4 (0.7)	
Married	5,342 (85.4)	2,306 (85.7)	237 (84.9)		2,322 (85.7)	477 (82.4)	
Widowed/divorced/separated	885 (14.1)	371 (13.8)	42 (15.1)		374 (13.8)	98 (16.9)	
BMI (kg/m^2)	23.41 ± 3.83	22.95 ± 3.67	23.71 ± 4.35	0.005	23.55 ± 3.82	24.83 ± 3.91	<0.001
WC (cm)	83.71 ± 12.41	82.16 ± 12.23	84.86 ± 13.00	0.001	84.20 ± 12.25	88.07 ± 12.59	<0.001
WHtR	0.53 ± 0.08	0.52 ± 0.08	0.54 ± 0.09	0.001	0.53 ± 0.08	0.56 ± 0.08	<0.001
HDL-C (mmol/l)	1.35 ± 0.39	1.37 ± 0.37	1.32 ± 0.40	0.026	1.34 ± 0.40	v1.25 ± 0.40	<0.001
LDL-C (mmol/l)	3.04 ± 0.88	2.96 ± 0.80	2.98 ± 0.87	0.664	3.10 ± 0.94	3.18 ± 0.88	0.076
TC (mmol/l)	4.99 ± 0.97	4.84 ± 0.89	4.92 ± 0.96	0.160	5.10 ± 1.02	5.18 ± 0.94	0.076
FBG (mg/dl)	100.00 ± 11.65	90.89 ± 8.18	90.67 ± 10.46	0.732	107.78 ± 7.10	110.24 ± 7.36	<0.001
TG (mmol/l)	1.37 ± 0.85	1.19 ± 0.62	1.40 ± 0.82	<0.001	1.48 ± 0.96	1.67 ± 1.06	<0.001
TyG	8.56 ± 0.55	8.36 ± 0.49	8.50 ± 0.51	<0.001	8.70 ± 0.55	8.85 ± 0.55	<0.001
TyG-BMI	201.06 ± 38.59	192.29 ± 35.28	201.91 ± 40.03	<0.001	205.55 ± 38.93	220.42 ± 40.47	<0.001
TyG-WC	718.33 ± 126.22	688.06 ± 117.15	722.63 ± 125.29	<0.001	734.38 ± 126.13	781.46 ± 131.60	<0.001
TyG-WHtR	4.56 ± 0.82	4.36 ± 0.76	4.58 ± 0.83	<0.001	4.66 ± 0.82	4.96 ± 0.84	<0.001
VAI	94.92 ± 109.04	75.58 ± 70.44	94.99 ± 83.28	<0.001	105.14 ± 125.89	136.82 ± 155.98	<0.001
LAP	33.24 ± 33.39	26.62 ± 25.13	34.67 ± 32.49	<0.001	36.39 ± 36.79	48.49 ± 42.65	<0.001
TG/HDL-C	1.22 ± 1.23	1.00 ± 0.78	1.25 ± 1.08	<0.001	1.34 ± 1.43	1.63 ± 1.67	<0.001
TC/HDL-C	3.97 ± 1.32	3.74 ± 1.10	4.01 ± 1.33	<0.001	4.09 ± 1.38	4.49 ± 1.48	<0.001

NFG, normal fasting glucose; IFG, impaired fasting glucose; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; FBG, fasting blood glucose; TG, triglyceride; TyG, triglyceride glucose; TyG-BMI, TyG related to BMI; TyG-WC, TyG related to WC; TyG-WHtR, TyG related to WHtR; VAI, visceral adiposity index; LAP, lipid accumulation product.

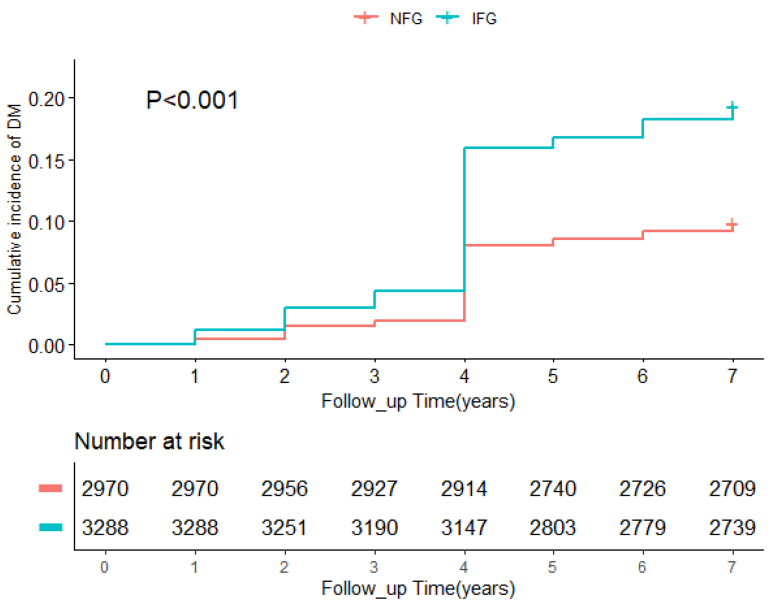

FIGURE 2 | Kaplan–Meier analysis showing cumulative incidence of diabetes.

Relation Between TyG Index and Incident Diabetes

The univariate and multivariate analyses of TyG index with the incidence of diabetes are shown in **Table 2**. After adjusting for age, drinking, education, hypertension, and cardiovascular disease, TyG index was positively correlated with the risk of diabetes (HR, 1.75; 95% CI, 1.56–1.97) in the whole population, which was the same as the NFG and IFG groups. In order to verify the influence of different

TABLE 2 | Cox proportional hazard models for the association between TyG index and incident diabetes.

	Incident diabetes						Nonlinear *p*-value
	Crude model 1		Model 2		Model 3		
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	
Total							
TyG (continuous)	1.80 (1.61, 2.02)	<0.001	1.83 (1.63, 2.05)	<0.001	1.75 (1.56, 1.97)	<0.001	0.221
TyG (quartile)							
Q1	1		1		1		
Q2	1.16 (0.93, 1.46)	0.203	1.16 (0.92, 1.46)	0.202	1.13 (0.90, 1.42)	0.290	
Q3	1.93 (1.57, 2.37)	<0.001	1.93 (1.57, 2.37)	<0.001	1.82 (1.48, 2.24)	<0.001	
Q4	2.31 (1.89, 2.82)	<0.001	2.33 (1.91, 2.85)	<0.001	2.18 (1.78, 2.66)	<0.001	
NFG							
TyG (continuous)	1.74 (1.37, 2.20)	<0.001	1.75 (1.38, 2.21)	<0.001	1.69 (1.33, 2.15)	<0.001	0.665
TyG (quartile)							
Q1	1		1		1		
Q2	1.04 (0.72, 1.51)	0.826	1.03 (0.71, 1.50)	0.868	1.02 (0.71, 1.49)	0.889	
Q3	1.32 (0.93, 1.88)	0.117	1.32 (0.93, 1.87)	0.123	1.29 (0.91, 1.84)	0.150	
Q4	1.78 (1.28, 2.49)	<0.001	1.78 (1.28, 2.48)	<0.001	1.71 (1.22, 2.39)	0.002	
IFG							
TyG (continuous)	1.52 (1.32, 1.75)	<0.001	1.55 (1.34, 1.78)	<0.001	1.48 (1.28, 1.71)	<0.001	0.057
TyG (quartile)							
Q1	1		1		1		
Q2	1.26 (0.97, 1.64)	0.088	1.26 (0.96, 1.63)	0.091	1.21 (0.93, 1.58)	0.154	
Q3	1.69 (1.32, 2.17)	<0.001	1.70 (1.33, 2.18)	<0.001	1.60 (1.25, 2.05)	<0.001	
Q4	2.00 (1.62, 2.62)	<0.001	2.04 (1.60, 2.60)	<0.001	1.89 (1.48, 2.41)	<0.001	

HR, hazard ratio; CI, confidence interval; TyG, triglyceride glucose; NFG, normal fasting glucose; IFG, impaired fasting glucose.
Model 2 adjusted for age. Model 3 adjusted for age, drinking, education, hypertension, and cardiovascular disease.

TyG levels on diabetes, we classified TyG index into quartiles. Compared with the lowest quartile, Q3 (HR, 1.93; 95% CI, 1.57–2.37) and Q4 (HR, 2.31; 95% CI, 1.89–2.82) had a significantly higher risk of developing diabetes. After adjusting for the potential confounding factors, the correlation still existed. The risk of diabetes in the highest quartile in the different glycemic status groups was 1.78 (95% CI: 1.28–2.49) and 2.00 (95% CI: 1.62–2.62). After adjusting for covariates, the statistical significance remained. In the restricted cubic spline regression model, the association between TyG index and the risk of diabetes was linear (nonlinear *p*-value >0.05) (**Table 2** and **Figure 3**).

Associations of Indicators With Incident Diabetes

After stratification by glycemic status and adjusting for the influence of potential confounding factors, the results are shown in **Tables 3**, **4**. In the NFG group, compared with the lowest four percentiles, the Q4 of TyG-BMI, TyG-WC, TyG-WHtR, VAI, LAP, TG/HDL-C, and TC/HDL-C was correlated with the incidence of diabetes ($p < 0.05$), and VAI (HR, 2.04; 95% CI, 1.44–2.90) had the highest influence on the risk of diabetes. In the IFG group, compared with the lowest four percentiles, the Q3 and Q4 of TyG-BMI, TyG-WC, TyG-WHtR, VAI, LAP, TG/HDL-C, and TC/HDL-C were correlated with the incidence of diabetes($p < 0.05$), and TyG-BMI (HR, 2.53; 95% CI, 1.97–3.26) had the highest influence on the risk of diabetes.

The Predictive Value of Each Index for Diabetes

ROC curves for different indices are presented in **Figure 4**. The cutoff value and AUC with sensitivity, specificity, and Youden index are presented in **Table 5**. In the whole study population, TyG-WHtR had the highest AUC (AUC, 0.658; 95% CI, 0.619–0.696), followed by TyG-BMI (AUC, 0.644; 95% CI, 0.605–0.682) and TyG-WC (AUC, 0.642; 95% CI, 0.603–0.682). The optimal cutoff of TyG-WHtR, TyG-BMI, and TyG-WC were 4.99, 209.89, and 764.61. After stratifying based on the level of blood glucose, TyG-WHtR (AUC, 0.613; 95% CI, 0.527–0.700) had the highest diagnostic value in the NFG group, followed by LAP (AUC, 0.601; 95% CI, 0.528–0.684) and TyG-WC (AUC, 0.585; 95% CI, 0.499–0.671). However, in the IFG group, TyG-BMI (AUC, 0.643; 95% CI, 0.601–0.685) had the highest diagnostic value for diabetes, followed by TyG-WHtR (AUC, 0.639; 95% CI, 0.596–0.682) and TyG-WC (AUC, 0.630; 95% CI, 0.586–0.674).

Subgroup Analyses

Table 6 shows the results stratified by age. The predictive value of TyG-WHtR for new-onset diabetes was highest among participants aged <65 years. The predictive value of all indicators for new-onset diabetes was generally low in the NFG participants aged ≥65 years. TyG-BMI had the highest predictive value for new-onset diabetes among participants aged ≥65 years in the IFG group.

DISCUSSION

In this cohort study, we explored the association between TyG index and new-onset diabetes in different glycemic status and directly compared the predictive value of TyG, TyG-BMI, TyG-WC, TyG-WHtR, VAI, LAP, TG/HDL-C, and TC/HDL-C

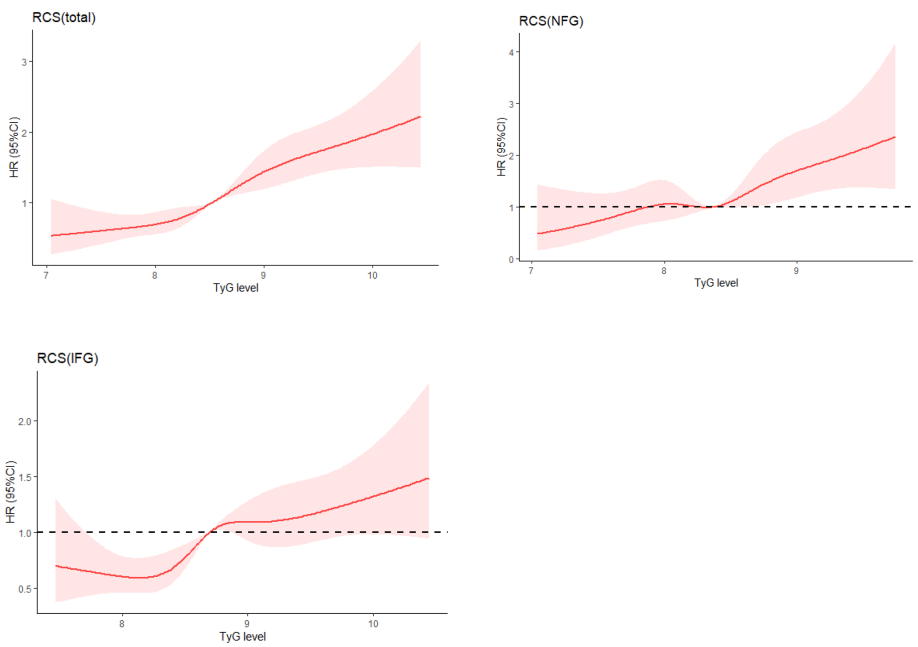

FIGURE 3 | Adjusted cubic spline model of the association between triglyceride glucose index and risk of new-onset diabetes. NFG, normal fasting glucose; IFG, impaired fasting glucose; TyG, triglyceride glucose.

TABLE 3 | Adjusted HR and 95% CI in quartiles of each index in the NFG group.

NFG (*N* = 2,970)	Incident diabetes					
	Crude model 1		Model 2		Model 3	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
TyG-BMI						
Q1	1		1		1	
Q2	0.99 (0.69, 1.43)	0.971	1.05 (0.72, 1.51)	0.810	1.03 (0.71, 1.49)	0.882
Q3	1.14 (0.80, 1.63)	0.468	1.26 (0.88, 1.81)	0.204	1.23 (0.85, 1.76)	0.269
Q4	1.81 (1.31, 2.50)	<0.001	1.97 (1.42, 2.73)	<0.001	1.84 (1.31, 2.59)	<0.001
TyG-WC						
Q1	1		1		1	
Q2	0.86 (0.59, 1.25)	0.427	0.88 (0.60, 1.28)	0.491	0.87 (0.60, 1.27)	0.483
Q3	1.09 (0.77, 1.56)	0.623	1.12 (0.78, 1.59)	0.543	1.10 (0.77, 1.57)	0.600
Q4	1.88 (1.37, 2.59)	<0.001	1.91 (1.39, 2.62)	<0.001	1.82 (1.31, 2.52)	<0.001
TyG-WHtR						
Q1	1		1		1	
Q2	0.96 (0.66, 1.38)	0.796	0.96 (0.67, 1.39)	0.846	0.94 (0.65, 1.36)	0.758
Q3	1.16 (0.81, 1.65)	0.411	1.16 (0.82, 1.65)	0.405	1.11 (0.77, 1.58)	0.574
Q4	1.77 (1.28, 2.45)	<0.001	1.74 (1.26, 2.40)	<0.001	1.61 (1.15, 2.25)	0.006
VAI						
Q1	1		1		1	
Q2	1.21 (0.83, 1.76)	0.325	1.25 (0.86, 1.82)	0.241	1.25 (0.86, 1.82)	0.249
Q3	1.42 (0.98, 2.04)	0.061	1.49 (1.04, 2.15)	0.032	1.46 (1.01, 2.10)	0.046
Q4	2.05 (1.46, 2.88)	<0.001	2.15 (1.53, 3.03)	<0.001	2.04 (1.44, 2.90)	<0.001
LAP						
Q1	1		1		1	
Q2	0.69 (0.47, 1.01)	0.056	0.71 (0.48, 1.04)	0.075	0.70 (0.47, 1.02)	0.062
Q3	1.04 (0.74, 1.47)	0.809	1.07 (0.76, 1.51)	0.701	1.03 (0.73, 1.46)	0.857
Q4	1.65 (1.21, 2.26)	0.002	1.69 (1.23, 2.30)	0.001	1.57 (1.13, 2.17)	0.007
TG/HDL-C						
Q1	1		1		1	
Q2	1.06 (0.74, 1.53)	0.748	1.07 (0.74, 1.54)	0.728	1.07 (0.74, 1.54)	0.717
Q3	1.32 (0.93, 1.87)	0.125	1.33 (0.93, 1.88)	0.116	1.31 (0.92, 1.86)	0.138
Q4	1.71 (1.22, 2.38)	0.002	1.73 (1.24, 2.42)	0.001	1.67 (1.19, 2.33)	0.003
TC/HDL-C						
Q1	1		1		1	
Q2	0.99 (0.69, 1.42)	0.967	0.99 (0.69, 1.42)	0.946	0.98 (0.68, 1.40)	0.894
Q3	1.27 (0.90, 1.78)	0.169	1.29 (0.92, 1.81)	0.146	1.26 (0.90, 1.78)	0.180
Q4	1.46 (1.05, 2.03)	0.026	1.45 (1.05, 2.02)	0.026	1.41 (1.01, 1.96)	0.045

HR, hazard ratio; CI, confidence interval; NFG, normal fasting glucose; TyG-BMI, triglyceride glucose related to body mass index; TyG-WC, TyG related to waist circumference; TyG-WHtR, TyG related to waist-to-height ratio; VAI, visceral adiposity index; LAP, lipid accumulation product; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; TC/HDL-C, total cholesterol to high-density lipoprotein cholesterol ratio.

Model 2 adjusted for age. Model 3 adjusted for age, drinking, education, hypertension, and cardiovascular disease.

indicators in new-onset diabetes. Overall, we found that a positive correlation between TyG index and the risk of diabetes existed, and the relationship was linear. In addition, all indices exhibited the capability to identify individuals with diabetes (AUC >0.5 for all), and TyG-WHtR was superior to other indicators for predicting diabetes in the whole subjects and NFG subgroup. However, in the IFG subgroup, TyG-BMI had higher predictive ability for diabetes than other indicators.

The increase of glucose concentration can elevate the level of reactive oxygen species, and then produce toxic effects on β cells (24). The increase of TG level in blood was negatively correlated with insulin secretion (25) and would lead to ectopic fat deposition in the body and the increase of triglyceride level in muscle cells, resulting in IR (26). Also, excessive TG in pancreatic islet cells can disrupt β-cell function (27). TyG index incorporated the compound effect of both, which was a simple index to detect IR. Previous studies indicated that the risk of diabetes was elevated with the increase of TyG level (divided into four quantiles) (13). However, some studies showed that there was a nonlinear association between them (4, 28). The association between TyG index and the risk of diabetes in our study was positively and linear. The reason was that the subjects of our study were middle aged and elderly, whose TyG index was generally high. This was also consistent with previous studies suggesting that high TyG index was relevant to future risk of diabetes in different races (29, 30). The results of the IFG group were similar to the whole subjects. However, in the NFG group, the correlation between TyG index and diabetes only existed when the TyG index was high. Compared with group NFG, impaired fasting glucose was more likely to be related with IR, which explained the higher correlation between TyG index and new-onset diabetes in IFG group (31). In this context, the TyG

TABLE 4 | Adjusted HR and 95% CI in quartiles of each index in the IFG group.

IFG (*N* = 3,288)	Incident diabetes					
	Crude model 1		Model 2		Model 3	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
TyG-BMI						
Q1	1		1		1	
Q2	1.28 (0.98, 1.67)	0.076	1.35 (1.03, 1.77)	0.030	1.33 (1.02, 1.75)	0.039
Q3	1.58 (1.22, 2.05)	<0.001	1.69 (1.30, 2.20)	<0.001	1.59 (1.22, 2.08)	<0.001
Q4	2.56 (2.01, 3.25)	<0.001	2.80 (2.19, 3.58)	<0.001	2.53 (1.97, 3.26)	<0.001
TyG-WC						
Q1	1		1		1	
Q2	1.31 (0.99, 1.72)	0.054	1.31 (0.99, 1.72)	0.054	1.29 (0.98, 1.70)	0.066
Q3	1.77 (1.36, 2.29)	<0.001	1.80 (1.39, 2.33)	<0.001	1.70 (1.31, 2.21)	<0.001
Q4	2.65 (2.08, 3.39)	<0.001	2.69 (2.10, 3.43)	<0.001	2.45 (1.91, 3.15)	<0.001
TyG-WHtR						
Q1	1		1		1	
Q2	1.29 (0.98, 1.70)	0.065	1.30 (0.99, 1.70)	0.058	1.28 (0.97, 1.68)	0.076
Q3	1.76 (1.37, 2.28)	<0.001	1.78 (1.38, 2.30)	<0.001	1.68 (1.30, 2.17)	<0.001
Q4	2.52 (1.98, 3.21)	<0.001	2.52 (1.97, 3.21)	<0.001	2.27 (1.77, 2.92)	<0.001
VAI						
Q1	1		1		1	
Q2	1.34 (1.03, 1.75)	0.028	1.36 (1.04, 1.77)	0.023	1.31 (1.01, 1.71)	0.045
Q3	1.70 (1.32, 2.18)	<0.001	1.74 (1.35, 2.23)	<0.001	1.62 (1.25, 2.09)	<0.001
Q4	2.13 (1.67, 2.71)	<0.001	2.22 (1.74, 2.84)	<0.001	2.01 (1.56, 2.58)	<0.001
LAP						
Q1	1		1		1	
Q2	1.08 (0.82, 1.42)	0.594	1.09 (0.83, 1.44)	0.523	1.05 (0.80, 1.38)	0.734
Q3	1.94 (1.52, 2.49)	<0.001	1.98 (1.55, 2.54)	<0.001	1.84 (1.44, 2.37)	<0.001
Q4	2.19 (1.72, 2.79)	<0.001	2.25 (1.77, 2.87)	<0.001	2.02 (1.57, 2.59)	<0.001
TG/HDL-C						
Q1	1		1		1	
Q2	1.19 (0.92, 1.55)	0.182	1.20 (0.93, 1.56)	0.162	1.17 (0.90, 1.52)	0.239
Q3	1.64 (1.29, 2.10)	<0.001	1.67 (1.30, 2.13)	<0.001	1.55 (1.22, 1.99)	<0.001
Q4	1.93 (1.52, 2.45)	<0.001	1.99 (1.57, 2.52)	<0.001	1.83 (1.44, 2.33)	<0.001
TC/HDL-C						
Q1	1		1		1	
Q2	1.16 (0.90, 1.51)	0.259	1.17 (0.90, 1.52)	0.234	1.13 (0.87, 1.47)	0.349
Q3	1.50 (1.17, 1.92)	<0.001	1.52 (1.19, 1.94)	<0.001	1.43 (1.11, 1.83)	0.004
Q4	1.97 (1.56, 2.49)	<0.001	2.00 (1.58, 2.53)	<0.001	1.86 (1.46, 2.35)	<0.001

HR, hazard ratio; CI, confidence interval; IFG, impaired fasting glucose; TyG-BMI, triglyceride glucose related to body mass index; TyG-WC, TyG related to waist circumference; TyG-WHtR, TyG related to waist-to-height ratio; VAI, visceral adiposity index; LAP, lipid accumulation product; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; TC/HDL-C, total cholesterol to high-density lipoprotein cholesterol ratio.

Model 2 adjusted for age. Model 3 adjusted for age, drinking, education, hypertension, and cardiovascular disease.

index could be considered a potential and reliable prognosticator for the incidence of diabetes for broad clinical usage.

However, some studies showed that obesity and lipid indicators were also good predictors of new-onset diabetes (3, 5, 17). The association between obesity and diabetes was mentioned in several studies (32, 33). Compared with general obesity and subcutaneous fat, visceral fat accumulation had a significant negative effect on blood glucose control by reducing peripheral insulin sensitivity and enhancing gluconeogenesis, which was closely related to IR (34). Visceral fat accumulation might also induce the secretion of adipocytokines. Oversecretion of proinflammatory adipocytokines and hyposecretion of defensive adipocytokines might be the main mechanism of IR and T2DM (35). Some simple anthropometric parameters were used as surrogate indicators of visceral fat, such as WC and WHtR, but these classic indicators could not take metabolic measures into account.

Our study indicated that the predictive value of TyG-related parameters combined with anthropometric parameters was superior to TyG index in new-onset diabetes. TyG-related parameters were useful clinical substitutes for predicting new-onset diabetes. Because they combined TG, FBG, and obesity indicators, the role of which in identifying IR was validated in previous studies (5). The utility of TyG index in evaluating IR was pointed out in a number of studies (36, 37). However, there were still controversy about the predictive value of TyG index and TyG-related parameters. A study in Chinese elderly population found that TyG index had higher predictive ability than TyG-related parameters (23). However, TyG-BMI and TyG-WC were significantly better than TyG index in predicting the risk of T2DM in Korean population (5), which was consistent with our conclusion.

Another important result of our study was that TyG-WHtR was superior to other TyG-related parameters in identifying the

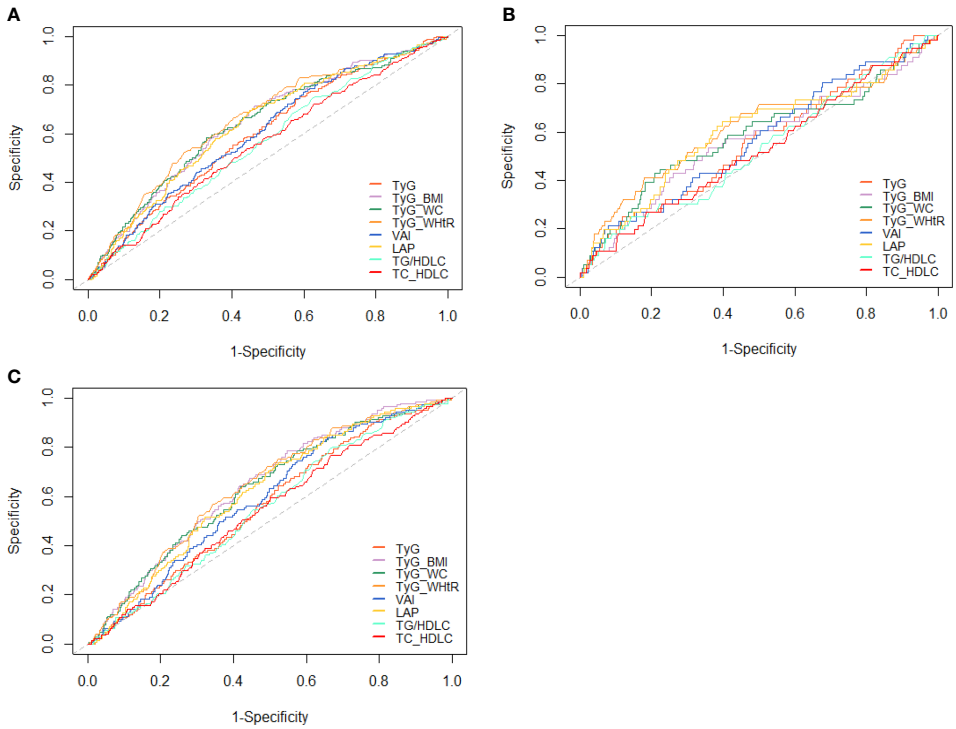

FIGURE 4 | ROC curves for each index as predictors of diabetes. **(A)** Whole cohort, **(B)** NFG, and **(C)** IFG. ROC, receiver-operating characteristic; TyG, triglyceride glucose; TyG-BMI, TyG related to body mass index; TyG-WC, TyG related to waist circumference; TyG-WHtR, TyG related to waist-to-height ratio; VAI, visceral adiposity index; LAP, lipid accumulation product; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; TC/HDL-C, total cholesterol to high-density lipoprotein cholesterol ratio.

risk of early diabetes in the NFG group. A cohort study in Iran showed that WHtR was a better predictor than BMI and WC (38). A systematic review and meta-analysis (39) also showed a stronger association between WHtR and T2DM than BMI. This maybe because WHtR reflected the effect of visceral fat better than WC. Because metabolic risk was different in people with the same WC but different heights, and height was usually inversely associated with cardiometabolic morbidity and mortality (40). IFG refers to liver IR and early insulin secretion defects, along with impaired β-cell function (41, 42). Early identification of high-risk groups of diabetes is crucial in the occurrence of IFG. Our data showed that in the IFG group, TyG-BMI had the highest predictive value for new-onset diabetes. In our study, TyG-BMI predicted that new-onset diabetes was more effective than TyG-WC and TyG-WHtR in IFG group, probably because the population had high levels of systemic obesity. Abdominal fat includes subcutaneous fat and visceral fat, and visceral fat plays an important role in the pathogenesis of IR. However, WC cannot separate subcutaneous adipose tissue from visceral adipose tissue, so abdominal obesity cannot be accurately measured (5), leading to inaccurate measurement results of WHtR. In another study, the intraobserver and interobserver variability of waist circumference was higher than that of body mass index (43), and the accuracy of WC measurement was affected by its measurement location (44).

VAI and LAP were comprehensive measures that combined lipid variables with obesity status and were predictors of diabetes mellitus (45). Our study found that in the whole population and IFG group, the predictive value of VAI and LAP for diabetes was weaker than that of TyG-related parameters but higher than that of lipids. However, it was worth noting that the predictive value of LAP for diabetes was only next to TyG-WHtR in NFG group, and VAI had the most significant correlation with new-onset diabetes. The possible explanation was that the NFG population had better glycemic regulation than IFG population, so the effect of glycotoxicity on NFG people was slight. Therefore, VAI, which represented obesity status and lipid level, was closely associated with diabetes in NFG population. Furthermore, our study found that although there was a strong association between lipid ratio and new-onset diabetes, the predictive ability of both to new-onset diabetes was lower than other indicators. There was evidence showing that lipid ratios, such as TG/HDL-C and TC/HDL-C, were more effective than single lipid measurements in detecting IR (14). Also, a cohort study in China demonstrated that TyG, VAI, and LAP were mostly superior than TG/HDL-C in predicting T2DM (15).

The main strength of our research is that we are the first to analyze the predictive value of TyG-related parameters, visceral obesity index, and lipid ratio for new-onset diabetes under different glycemic states. The conclusion of this study has an

TABLE 5 | Sensitivity, specificity, Youden index, cutoff points, and AUC (95% CI) for each index in predicting diabetes risk among adults in China.

	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Youden index
Total					
TyG	8.41	0.597 (0.559, 0.636)	74.11	41.91	16.02
TyG-BMI	209.89	0.644 (0.605, 0.682)	58.88	64.43	23.31
TyG-WC	764.61	0.642 (0.603, 0.682)	57.87	67.15	25.02
TyG-WHtR	4.99	0.658 (0.619, 0.696)	52.28	72.86	25.14
VAI	77.02	0.603 (0.565, 0.641)	52.28	59.17	11.45
LAP	32.75	0.635 (0.597, 0.674)	59.39	62.61	22.00
TG/HDL-C	0.98	0.565 (0.526, 0.604)	50.25	56.76	7.01
TC/HDL-C	3.95	0.557 (0.517, 0.597)	52.28	57.22	9.50
NFG					
TyG	8.47	0.558 (0.481, 0.635)	46.43	59.33	5.76
TyG-BMI	211.42	0.565 (0.481, 0.648)	42.86	73.99	16.85
TyG-WC	783.71	0.585 (0.499, 0.671)	39.29	81.13	20.42
TyG-WHtR	4.54	0.613 (0.527, 0.700)	60.71	60.60	21.31
VAI	77.79	0.568 (0.491, 0.644)	42.86	66.30	9.16
LAP	31.13	0.601 (0.528, 0.684)	51.79	67.91	19.70
TG/HDL-C	0.69	0.532 (0.454, 0.610)	62.50	41.63	4.13
TC/HDL-C	3.45	0.526 (0.448, 0.605)	55.36	45.68	1.04
IFG					
TyG	8.56	0.562 (0.517, 0.606)	69.50	40.86	10.36
TyG-BMI	222.56	0.643 (0.601, 0.685)	51.06	68.26	19.32
TyG-WC	764.61	0.630 (0.586, 0.674)	63.12	58.31	21.43
TyG-WHtR	4.99	0.639 (0.596, 0.682)	56.74	65.14	21.88
VAI	67.49	0.590 (0.547, 0.633)	65.25	47.89	13.14
LAP	29.36	0.619 (0.576, 0.662)	69.50	51.00	20.50
TG/HDL-C	0.99	0.552 (0.507, 0.596)	56.03	51.35	7.38
TC/HDL-C	3.89	0.544 (0.497, 0.590)	59.57	49.19	8.76

AUC, area under curve; CI, confidence interval; NFG, normal fasting glucose; IFG, impaired fasting glucose; TyG, triglyceride glucose; TyG-BMI, TyG related to body mass index; TyG-WC, TyG related to waist circumference; TyG-WHtR, TyG related to waist-to-height ratio; VAI, visceral adiposity index; LAP, lipid accumulation product; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; TC/HDL-C, total cholesterol to high-density lipoprotein cholesterol ratio.

important guiding role for clinicians to identify high-risk groups and predict the occurrence of diabetes in the future. Moreover, this is a prospective study with long-term follow-up in middle-aged and elderly Chinese population. Several limitations may exist in this study. First of all, the study population is only composed of middle-aged and elderly people. It is necessary to be cautious to extend the research results to other populations. Secondly, we did not use the 2-h oral glucose tolerance test to

TABLE 6 | Sensitivity, specificity, and AUC (95%CI) for each index in predicting diabetes risk by age.

	NFG			IFG		
	AUC (95% CI)	Sensitivity (%)	Specificity (%)	AUC (95% CI)	Sensitivity (%)	Specificity (%)
Age <65						
TyG	0.598 (0.511, 0.686)	30.95	87.73	0.541 (0.493, 0.589)	82.20	29.18
TyG-BMI	0.605 (0.513, 0.687)	59.52	64.45	0.623 (0.574, 0.671)	77.97	41.28
TyG-WC	0.627 (0.531, 0.722)	47.62	77.77	0.618 (0.568, 0.668)	44.92	74.07
TyG-WHtR	0.671 (0.578, 0.765)	73.81	58.8	0.628 (0.580, 0.676)	58.47	62.58
VAI	0.590 (0.505, 0.675)	76.19	39.10	0.560 (0.513, 0.608)	83.90	31.51
LAP	0.644 (0.552, 0.735)	69.05	61.50	0.601 (0.554, 0.649)	72.88	46.57
TG/HDL-C	0.539 (0.447, 0.631)	28.57	85.45	0.525 (0.477, 0.574)	78.81	31.92
TC/HDL-C	0.524 (0.434, 0.615)	19.05	89.61	0.517 (0.467, 0.568)	74.58	32.05
Age ≥65						
TyG	0.438 (0.292, 0.584)	7.14	99.83	0.641 (0.528, 0.754)	69.57	60.00
TyG-BMI	0.458 (0.285, 0.630)	42.86	69.18	0.710 (0.619, 0.801)	82.61	61.69
TyG-WC	0.465 (0.291, 0.639)	35.71	79.28	0.680 (0.588, 0.771)	91.30	47.75
TyG-WHtR	0.441 (0.263, 0.619)	21.43	87.50	0.695 (0.599, 0.792)	65.22	70.00
VAI	0.511 (0.350, 0.672)	42.86	72.43	0.705 (0.606, 0.804)	82.61	53.52
LAP	0.478 (0.313, 0.643)	35.71	75.86	0.684 (0.585, 0.783)	60.87	74.37
TG/HDL-C	0.519 (0.378, 0.660)	92.86	21.75	0.660 (0.552, 0.767)	69.57	60.28
TC/HDL-C	0.529 (0.374, 0.685)	35.71	80.31	0.658 (0.547, 0.769)	56.52	74.23

NFG, normal fasting glucose; IFG, impaired fasting glucose; AUC, area under curve; CI, confidence interval; TyG, triglyceride glucose; TyG-BMI, TyG related to body mass index; TyG-WC, TyG related to waist circumference; TyG-WHtR, TyG related to waist-to-height ratio; VAI, visceral adiposity index; LAP, lipid accumulation product; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; TC/HDL-C, total cholesterol to high-density lipoprotein cholesterol ratio.

detect cases of diabetes, so the incidence might have been underestimated. Finally, we could not evaluate the HOMA-IR in our study.

CONCLUSION

The association between TyG index and new-onset diabetes was positive and linear. For predicting diabetes, TyG-WHtR was a valuable marker for predicting the risk of new-onset diabetes in the NFG group and the whole population. The predictive value of TyG-BMI was higher in the NFG group. We suggest that this index should be used in clinical practice or epidemiological investigation for early detection of diabetes.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. These data can be found here: http://charls.pku.edu.cn/.

ETHICS STATEMENT

All respondents were required to sign informed consent, and the ethical approval for data collection in CHARLS was approved by The Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). The use of CHARLS data obtained ethical approval from the Human Research Ethics Committee of the University of Newcastle (H-2015-0290).

AUTHOR CONTRIBUTIONS

XL, BL and MS made the study design. MS, SY, and YW conducted the study. XL, RG, and NY analyzed the data and wrote the manuscript. LW, WH, and YY attended the manuscript revision. All authors agreed with the final manuscript.

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REVIEW
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Endogenous Protective Factors and Potential Therapeutic Agents for Diabetes-Associated Atherosclerosis

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The complications of macrovascular atherosclerosis are the leading cause of disability and mortality in patients with diabetes. It is generally believed that the pathogenesis of diabetic vascular complications is initiated by the imbalance between injury and endogenous protective factors. Multiple endogenous protective factors secreted by endothelium, liver, skeletal muscle and other tissues are recognized of their importance in combating injury factors and maintaining the homeostasis of vasculatures in diabetes. Among them, glucagon-like peptide-1 based drugs were clinically proven to be effective and recommended as the first-line medicine for the treatment of type 2 diabetic patients with high risks or established arteriosclerotic cardiovascular disease (CVD). Some molecules such as irisin and lipoxins have recently been perceived as new protective factors on diabetic atherosclerosis, while the protective role of HDL has been reinterpreted since the failure of several clinical trials to raise HDL therapy on cardiovascular events. The current review aims to summarize systemic endogenous protective factors for diabetes-associated atherosclerosis and discuss their mechanisms and potential therapeutic strategy or their analogues. In particular, we focus on the existing barriers or obstacles that need to be overcome in developing new therapeutic approaches for macrovascular complications of diabetes.

Keywords: endogenous protective factors, analogues, diabetes mellitus, atherosclerosis, therapy

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INTRODUCTION

Atherosclerosis-related vascular complications are the main cause of reduced life quality and expectancy in diabetics. Atherosclerosis is known as chronic inflammatory diseases involving a variety of cells and pathogenesis, which is characterized by endothelial dysfunction, foam cell formation, the accumulation of lipids and eventually leads to lesion development (1). In diabetes, hyperglycemia is one of the main causes of atherosclerosis, but it is often combined with other risk factors, namely, dyslipidemia and hypertension to aggravate vascular injury synergistically. It is indistinguishable at histological examination of atherosclerotic lesions in patients with hyperglycemia to those with other risk factors like hypercholesterolemia or smoking (2). However, as reported, diabetic patients are four to five times more likely to develop cardiovascular diseases or stroke than individuals without diabetes (3). This obvious discrepancy may be owing to unique pathophysiological mechanisms of diabetes-associated atherosclerosis. It is

generally believed that the pathogenesis of diabetic vascular complications is initiated by the imbalance between injury and endogenous protective factors. Among them, multiple mechanisms of destructive factors have been extensively studied to mediate the adverse effects on vascular tissues of hyperglycemia (4, 5). These include overproduction of reactive oxygen species (ROS) (6), formation of advanced glycation end products (AGEs) (7), activation of proinflammatory pathways, and increased expression of adhesion molecules. By contrast, very few studies have focused on the endogenous protective factors that exist to neutralize toxic AGEs, oxidative stress, and inflammation actions. The 50-Year Medalist Study showed diabetic patients with long-term poor glycemic did not correlate with vascular complications, and the effects of strict blood glucose control on cardiovascular disease (CVD) are marginal, suggesting the existence of endogenous protective factors can neutralize toxic effects of hyperglycemia and counteract mechanisms responsible for complication progression (8, 9). However, to our knowledge, most of these studies and reviews focus on protective factors on microvascular complications especially diabetic retinopathy and diabetic nephropathy, while systemic reviews update about endogenous protective factors on diabetic atherosclerosis or macrovascular complications are relatively lacked. Herein, we review the endogenous protective factors and potential therapeutic analogues that were proven to be effective at least in animal models with diabetic atherosclerosis.

NO and eNOS

Endothelial dysfunction, characterized by the lowered bioavailability of nitric oxide (NO), is recognized to be the first step of atherosclerosis and cardiovascular disease (10). Oxidative stress or increased ROS formation in the vascular wall is a significant driver to reduce bioactive NO in underpinning diabetic vascular complications (11). Endothelial NO protects against atherosclerosis by mediating vasodilation, inhibiting platelet adhesion, leukocyte chemotaxis, and cellular proliferation of vascular smooth muscle cells, thus promoting endothelial cell barrier integrity (12). Atheroprotective NO is mainly produced by enzyme endothelial nitric oxide synthase (eNOS), which is a dimeric NOS isoform specifically expressed in endothelial cells and known as an endothelial protective factor in atherosclerosis while the inducible nitric oxide synthase (iNOS), another NOS isoform induced by cytokines and other agents expressed in almost any cell type, shown to be proatherogenic (13). eNOS is constitutively expressed in the caveolae and maintains its basal activity by interacting with Caveolin-1 (Cav-1), the main coat protein of caveolae. The regulation of eNOS is much complicated in atherosclerosis. On one hand, eNOS can be activated by phosphorylation of the enzyme response to various factors, such as increased shear stress or insulin stimulation, then coupled with cofactor (BH4) or substrate (L-arginine), leading to the production of protective NO. On the other hand, uncoupling eNOS in disease settings can be a source of superoxide, resulting in NO inactivation. In diabetes and its related atherosclerosis, hyperglycemia negatively regulated eNOS phosphorylation, causing eNOS uncoupling and reduced bioactive NO by increasing AGEs formation and activating Protein kinase C (PKC) pathway (14–16). Thus, the NO bioavailability depends on the expression level of eNOS, but more importantly, the eNOS activity.

Multiple conventional drugs such as statins or angiotension converting enzyme inhibitors (ACEi) can reduce vascular oxidative stress and increase bioactive NO in clinical or preclinical settings, but it remains elusive because all these drugs are pleiotropic or secondary effects rather than direct regulation of eNOS derived NO. CavNOxin is a Cav-1-derived peptide with T90, 91, F92 substituted to alanines. It has been identified to highly specific increase eNOS activity by preventing eNOS uncoupling (17, 18). As reported, CavNOxin could attenuate total aortic plaque up to 70% in diabetic apolipoprotein E knockout ($ApoE^{-/-}$) mice, a well-established model of experimental atherosclerosis, whereas mice lacking eNOS show resistance to CavNOxin treatment, suggesting endogenous eNOS activation can provide atheroprotection in diabetes (12). Beyond that, there are amounts of other small molecules, such as compounds AVE9488, AVE3085 and trans-resveratrol, enhancing eNOS expression and preventing eNOS uncoupling under pathophysiological conditions and also showing therapeutic potential *in vitro* studies (13). AVE9488 and AVE3085 were known as novel eNOS transcription enhancers. AVE9488 enhanced vascular content of the essential eNOS cofactor BH_4 and reversed eNOS uncoupling (19). Long-term treatment with AVE9488 improved cardiac remodeling and protected ischemia-reperfusion damage through increasing NO bioavailability (20). AVE3085 prevented endothelial dysfunction in arteries by regulating the expression of eNOS at different phosphorylation sites and also inhibition of arginase and iNOS (21). In addition, trans-resveratrol, a class of flavonoid compounds, has been demonstrated to increase endothelial NO production through diverse mechanisms, namely, upregulating of eNOS expression, stimulating of eNOS enzymatic activity, and preventing of eNOS uncoupling (22). Pharmacological interventions of them regulated eNOS/NO signaling pathway mainly through eNOS phosphorylation and protein-interactions. In this context, further in-depth studies are required to have a better understanding of how to improve eNOS-derived NO in patients with diabetes.

Lipoxins

Growing evidence suggests that chronic inflammation plays an important role in the pathophysiology of diabetes and diabetes-related vascular complications, therefore, the endogenous proresolution molecules and synthetic analogs targeting inflammation resolution are increasingly recognized as a therapeutic strategy to ameliorate diabetes, prevent its progression and vascular complications (23–26).

The omega-6 arachidonic acid (AA)-derived lipoxins [LXs], namely, LXA4 and LXB4 in mammals, are the first recognized endogenous lipid mediators that have dual anti-inflammatory and pro-resolution activities (27). They are produced by different biosynthetic pathways, involving the interaction of activated neutrophils within the epithelium, endothelium, and platelets (28).

Previous clinical data have shown that circulating levels of LXs or arachidonic acid (AA) are reduced in patients with obesity (29), diabetes and its complications (30), suggesting LXs maybe protective factors in metabolic disease and associated vascular complications. Borgesön et al. (31) reported that LXA4 and a benzo-LXA4 analogue reduced obesity-induced adipose inflammation by promoting a macrophage M1-to-M2 switch, modulating adipose autophagy. They demonstrated the Lipoxin-mediated protection was independent of adiponectin by using adiponectin$^{-/-}$ mice.

Recently, Brennan (32) reported that LXs could prevent and attenuate the development of atherosclerotic lesions in diabetic ApoE$^{-/-}$ mice but not in nondiabetic ApoE$^{-/-}$ mice. The mechanism involved the inhibition of the vascular smooth muscle cell proliferation and endothelial cell inflammation. They showed that metabolic parameters were not changed by LXs, suggesting that LXs-mediated protection was independent of glycemic control. Consistently with the animal experiments, LXA4 suppressed inflammatory cytokine release, namely, tumor necrosis factor-α and interleukin-1β in human carotid plaque explants. These data suggest that LX and its analogue therapy may offer a novel therapeutic approach in the context of diabetes-associated vascular complications (33).

Adiponectin

Adiponectin is a widely studied adipokine with anti-inflammatory, antioxidant, antiatherogenic, and insulin-sensitizing properties (34–36). Adiponectin exerts its biological role mainly by binding to its specific receptors, namely, adiponectin receptor 1 (AdipoR1), adiponectin receptor 2 (AdipoR2), and newly discovered T-cadherin (37). The receptors are abundantly expressed in cardiomyocytes, vascular smooth muscle cells, and endothelial cells and were supposed to be involved in atherosclerosis development (38–40).

Clinically, a large number of epidemiological studies suggested that the level of serum adiponectin in patients with obesity, type 2 diabetes, and atherosclerotic cardiovascular disease were significantly lower than that in normal subjects (41–43), while the low calorie diets, physical exercise, and bariatric surgery leading to weight loss may result in consistent increases of adiponectin levels (44). It was proved that hypoadiponectinemia could predict endothelial dysfunction in healthy men (45) and predict atherosclerosis in patients with end-stage renal disease (46). Further, adiponectin-deficient mice showed significantly increased neointimal thickening disordered endothelium-dependent vasodilation compared with wild-type mice (47–49). Moreover, adiponectin overexpression in the ApoE$^{-/-}$ mouse, can reduce the progression of fatty streak lesion through attenuating endothelial inflammatory response and macrophage to foam cell transformation (50). Based above, adiponectin is proposed as a predictive factor and a potential therapeutic target for atherosclerotic cardiovascular disease.

Adiponectin is known to exert vasoprotective actions through several mechanisms (51). A number of studies show that adiponectin could suppress the activation of pro-inflammatory and adhesion molecules, inhibit the monocyte/macrophage migration to the vascular wall and prevent the formation of foam cells (52–54). *In vitro* and *in vivo* studies indicated that adiponectin also reduced oxidative stress and high glucose-induced apoptosis, protected against endothelial dysfunction induced by OxLDL (55, 56). Furthermore, adiponectin can inhibit several atherogenic growth factors including platelet-derived growth factor to block the proliferation and migration of human aortic smooth muscle cells (57). In addition, adiponectin exerts the vascular protective function by directly enhancing the eNOS activity and improving the NO production depending on AdipoR1–AMPK signaling pathways (53, 58).

Several drugs (e.g., thiazolidinediones, angiotensin receptor blocker, sodium glucose cotransporter 2 inhibitors and incretins) have an effective influence on circulating adiponectin level through multiple mechanisms such as transcription regulation of adiponectin expression and pathways that enhance adipogenesis and insulin sensitivity (51). However, the actual clinical application of exogenous recombinant adiponectin is scarce due to the complexity of adiponectin multimers structure and its short half-life *in vivo* (59), and designing agonists to activate adiponectin receptor is suggested as an alternative strategy to maximize the beneficial effects of adiponectin. ADP355 and osmotin are two adipoR agonists among the numerous promising candidates in preclinical development. ADP355, an adiponectin-derived active peptide, was reported to ameliorate lipid metabolism and inhibit atherosclerosis in apoE$^{-/-}$ mice (60). Osmotin, an adiponectin homolog, that was found to function as an agonist for AdipoR1 (61) and infusion of osmotin could suppress the development of aortic atherosclerotic lesions in apoE$^{-/-}$ mice (62). In comparison, AdipoRon is a selective, orally active, synthetic small-molecule agonist, which can bind and activate AdipoR1 and AdipoR2, attenuated insulin resistance and glucose intolerance, improving lipid metabolism in high-fat diet mice (63). Oral administration of AdipoRon in C57BL/6J mice significantly suppressed arterial injury-induced neointimal hyperplasia by targeting VSMC proliferative signaling events (64), but there are lacking studies up to now to examine the role of AdipoRon on atherosclerosis in diabetes models. Further studies are needed to evaluate the clinical implications targeting to adiponectin or its receptors in the treatment of cardiometabolic diseases in diabetes.

Omentin

Omentin (also known as omentin-1 or intelectin-1) is a newly discovered adipokine with insulin-sensitizing, antioxidant, anti-inflammatory, and anti-atherosclerotic effects (65). It is preferentially secreted from the visceral fat stromal vascular cells, and also less expressed in endothelial cells, lung, heart, and placenta (66).

Recently, the level of omentin-1 was considered as a new biomarker of vascular endothelial function, especially for diabetic patients (67). Several cross-sectional studies reported that the concentration of omentin-1 decreased in patients with type 2 diabetes (T2DM) (68), coronary artery disease (CAD) (69, 70) or obese individuals with higher cardiovascular risk (71). Circulating omentin-1 level are negatively correlated with carotid intima-media thickness (IMT), arterial stiffness and carotid plaque in healthy men and type 2 diabetic patient (68, 72). Consistently, in apolipoprotein

E-deficient mice, omentin exhibited a significant reduction of the atherosclerotic areas by affecting the phenotypes of macrophages (73). On the contrary, a recent population-based cohort studies showed higher omentin concentrations were associated with a higher risk of primary cardiovascular events in diabetic patients even after adjusting for other cardiovascular risk factors including adiponectin (66). It appears possible that this association reflects a counterregulatory mechanism.

Liu et al. (74) found that omentin-1 protected against high glucose-induced vascular-endothelial dysfunction through its ability to inhibit reactive oxygen species (ROS) and increase NO production *via* activation of eNOS signaling pathway in isolated mouse aortas and mouse aortic endothelial cells (MAECs). Another evidence from diabetic rat studies indicated the protective effects of omentin against endothelial dysfunction through its actions on anti-inflammatory and antioxidant in perivascular adipose tissue (65). These studies suggested targeting circulating omentin levels may present therapeutic potential for cardiovascular diseases in diabetic patients.

HDLs and apoA-I

High-density lipoprotein cholesterol (HDLs) are complex polymolecular assemblies produced by the liver, jejunum and in serum. They are consisting of a hydrophobic lipid core (TGs and cholesterols) and an outer layer of phospholipids and apolipoproteins (mainly apoA-I), which facilitate reverse cholesterol transport (RCT) from peripheral tissues to liver.

In the past few decades, HDLs are recognized as a protective factor against vascular complications with diabetes mellitus (DM) due to its multiple functions encompassing anti-inflammatory, anti-oxidative, anti-thrombotic, and anti-diabetic properties (75, 76). A wealth of epidemiological and clinical studies indicated low HDL levels are independent risk factors for the development of atherosclerotic CVD or stroke with DM (77, 78). Similarly, alterations in plasma HDL and its related factors, LDL-C/HDL-C and TC/HDL-C ratio, showed a potential value in predicting glycemic control or cardiovascular function in diabetic patients (79, 80). A less favorable lipid profile could explain the success of lipid-modifying therapies, such as statins, in reducing adverse cardiovascular events. However, until now, HDL is still not considered a primary target of therapy in the latest national clinical guidelines on cholesterol management (81, 82). Although deficiency (83, 84) or overexpressing (85, 86) of high density lipoprotein or apolipoprotein A-I has clearly demonstrated a reduction or acceleration of atherosclerosis respectively in mice, several clinical studies aiming to raise HDL level therapies like CETP inhibitors or niacin have no significant benefits to cardiovascular events in patients with or without DM (87). An international double-blind randomized clinical showed infusion of recombinant HDL or apoA-I fail to regress plaque in coronary arteries of patients with acute coronary syndrome (88). One possible explanation of these negative results is that biological HDL could be adversely modified to be "dysfunctional HDL" by diabetes and atherosclerosis through the alteration of specific components and modifications of oxidation or glycation of HDL particles. This was supported by previous studies that HDL particle size and the distribution of HDL sub-classes were significantly altered in patients with coronary heart disease (CAD) complicated by DM compared with those in CAD without DM (89). Clinical data showed that highly elevated HDL did not always protect against cardiovascular disease, sometimes even diametrically opposed (90). Moreover, measures of HDL function such as cholesterol efflux capacity from macrophages is more effective in predicting the prevalence and incidence of CVD than measuring quantity of HDL cholesterol or apoA-I (91, 92). These results suggested that future development of novel therapies aiming HDL should focus on overcoming HDL dysfunction rather than improving the quantity of HDL. Indeed, development of HDL analogues and apoA-I mimetic peptides in view of overcoming the limits of the low efficiency of HDL in these processes do show some promise. Some novel apoA-I mimetic peptide, such as D-4F (93) and P12 (94), were believed to suppress atherosclerosis by promoting physiological HDL function *in vitro* studies or a murine model of diabetic atherosclerosis. Further clinical studies involving these compounds on vascular complications in diabetic patients are eagerly awaited.

Incretins (GLP-1 and GIP)

Incretins are a family of gut-derived peptide hormones which include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (95), which are respectively secreted from L cells of the distal intestine and the K cells of the proximal intestine in response to ingestions of various nutrients. They both stimulate insulin secretion in a glucose-dependent manner by binding with specific receptors, namely GLP-1 receptors (GLP-1R) and GIP receptors (GIPR) on β-pancreatic cells (96, 97).

In diabetes, the secretion of incretins, especially the GLP-1 after meal ingestion were significantly reduced compared with healthy individuals. Targeting this deficiency by using GLP-1-based drugs is a well-established approach in T2DM. Since GLP-1 is easily degraded by dipeptidyl peptidase-4 (DPP-4), DPP-resistant GLP-1 receptor agonists (GLP-1 RAs) were designed basing on either exendin-4 (drugs such as exenatide and lixisenatide) or human GLP-1 (drugs such as liraglutide, dulaglutide, and semaglutide), and therefore, have a prolonged half-life. DPP-4 inhibitors such as sitagliptin and sagliptin are also effective strategies by increasing the concentration of endogenous GLP-1. GLP-1 RAs exert glucoregulatory effects *via* glucose-dependent secretion of insulin, inhibition of glucagon release. Further, the presence of GLP-1R has been detected in a wide range of organs, namely, vessels, heart, brain, and gastrointestinal tract (98, 99). The extrapancreatic actions of GLP-1 include inhibition of gastric emptying, gastric acid secretion, and suppressing appetite, thereby fulfilling the definition of GLP-1 as an enterogastrone. GLP-1 RAs have been effective glucose-lowering drugs for a decade with weight loss, lower risk of hypoglycemia, and even cardiovascular benefits.

Indeed, numerous clinical studies have shown the cardiovascular protective effects of GLP-1 RAs on atherosclerosis, coronary arterial disease (CAD), and cerebrovascular disease (100). For example, in an $ApoE^{-/-}$ mouse model, liraglutide has shown to inhibit atherosclerotic plaque formation and enhanced plaque stability

and endothelial function (101). In T2DM patients, Rizzo and colleagues (102) reported 8 months treatment of liraglutide therapy leads to a reduction in carotid intima media thickness (cIMT), a surrogate marker for CVD risk, and this effete is independently of its effect on plasma glucose and lipids concentrations. In the cardiovascular outcomes trials of liraglutide (the LEADER study), liraglutide could further significantly reduce the risk of major cardiovascular adverse events by 13% in patients already received cardiovascular secondary prevention drugs (103). In these studies, the cardiovascular protective effects of GLP-1 RAs was independent of glycemic control (104, 105).

GLP-1/GLP-1RAs may mediate effects on cardiovascular outcomes through effects on other risk factors such as the decreasing blood pressure values, weight reduction and improvement of dyslipidemia and endothelial dysfunction. Accumulating evidence suggests that GLP-1/GLP-1RAs increases the production of endothelial nitric oxide (NO) (106), reduces endothelial dysfunction (107), inflammation and oxidative stress (108) and also inhibits the transformation from monocytes to foam cells (109). In addition, treatment with GLP-1RA also increased circulating adiponectin levels (110), which play a protective role in the cardiovascular system. Based on these findings and mechanisms, GLP-1RAs have now been recommended by the ESC/EASD (European Society of Cardiology/European Association for the Study of Diabetes) released guidelines as one of the first-line therapies in type 2 diabetic patients with high risks or established cardiovascular disease (111, 112).

Compared with GLP-1, no GIP receptor agonist is utilized clinically to date because the glucoregulatory effects of GIP shows to be weakened in individuals with diabetes (113, 114). In patients with hyperglycemia and liver cirrhosis, GIP can stimulate the secretion of glucagon, resulting in increased glucose levels (115, 116). Inhibition of physiological GIP has been shown to alleviate obesity and insulin resistance under high-fat diet conditions (117). Consistently, GIPR antagonist can enhance insulin sensitivity, improve glucose tolerance, and reduce weight gain (118, 119). These studies indicated that the GIP treatment might increase the risk of metabolic deterioration in diabetes. However, the concern for its safety leading the neglection for its function on cardiovascular health. Recently, infusion of GIP in pharmacological dose have been found to prevent accumulation of aortic plaque, macrophages and foam cells in diabetic apolipoprotein E-null mice (120). Anti-atherosclerosis function of GIP may lie in the mechanism of improving NO production in VECs and activation of AMPK, inhibiting cell proliferation in VSMCs, and inhibiting inflammatory effect of monocytes, macrophages, and adipocytes (121). These observations suggest that GIP under pharmacological concentration may induce anti-diabetic and antiatherogenic effects. More fundamental studies and preclinical trials such as dual agonists targeting for GIPR and GLP-1R are still ongoing.

L-Carnosine

L-carnosine (beta-alanyl-L-histidine) is an endogenous dipeptide composed of β-alanine and l-histidine and highly expressed in skeletal muscle, brain and less in cardiac muscles (122). It is synthesized endogenously by carnosine synthase in skeletal muscle cells, glial cells, and myocytes, and it also could be obtained from dietary sources such as meat and fish (123). L-carnosine is a quencher of the Reactive Carbonyl Species (RCS), which are derived from Advanced Glycation (AGEs) and lipoxidation end-products. Therefore, it not only plays a major role in inhibiting AGEs formation, but also prevents the activation of pro-oxidative and pro-inflammatory pathways secondary to its ability to trap RCS (124, 125).

Several studies have been conducted on the effect of carnosine on diabetes and its complications, thanks to its inhibitory effect on the production of AGEs and oxygen toxicity. As expected, this endogenous dipeptide is proved to reduce cholesterol and triglyceride levels and ameliorate the dyslipidemic blood profile in multiple animal models, namely, diabetic Balb/cA mice (126), finishing Pigs (127), and obese Zucker rats (128). Further, Brown et al. (122) reported L-carnosine supplementation in drinking water for 20 weeks reduced plasma triglycerides, changed plaque atherosclerotic composition, and suppressed atherosclerotic plaque instability in diabetic ApoE$^{-/-}$ mice. Consistently, *in vitro* studies revealed that L-carnosine was able to inhibit glycation of low-density lipoproteins and reduce the formation of foam cells when incubated with glycated LDLs (129). These findings may partly explain the modifications in plaque composition observed by Brown et al. However, since L-carnosine is rapidly inactivated by serum carnosinase in human, the search for carnosine derivatives that are resistant to hydrolysis by carnosinase enzymes maybe a more suitable strategy. Stefano Menini and his colleagues (130) showed the diabetic ApoE$^{-/-}$ mice treated with D-carnosine-octylester (DCO), a bioavailable pro-drug of the carnosinase-resistant D-carnosine, for 20 weeks resulted in a more stable plaque phenotype, and even further a reduced atherosclerotic lesion size compared to untreated animals. In more detail, DCO treatment for 11 weeks also afforded partial protection from diabetes-induced atherosclerosis. Interestingly, the protective effect of DCO was more effectively achieved by early treatment (treated with DCO from weeks 1 to 11) than by late treatment (treated with DCO from weeks 9 to 19) due to early inhibition of AGE formation. The phenotypes obtained by carnosine and DCO is regardless of lipidemic and glycemic status, suggesting the protective effect is independent of hypoglycemic and lipid-lowering effect. They also showed the molecular mechanisms underlying the protective effects by DCO was associated with reduced foam cell accumulation, inflammation and apoptosis and also with increased content of collagen and smooth muscle cells.

In human study, supplementation with a daily dose of 2 g carnosine improved glucose metabolism, preserved insulin sensitivity and secretion in overweight and obese individuals (131). There is an ongoing randomized controlled trial (RCT) focusing on carnosine on cardiometabolic health and cognitive function in patients with prediabetes and type 2 diabetes (132). If this trial proves to be effective, more well-designed clinical trials with larger samples are needed to confirm the potential roles of carnosine and its derivatives in the prevention and treatment of diabetes and diabetic cardiovascular disease.

Irisin

Irisin is a recently recognized cytokine that is produced by plasma membrane protein fibronectin type III domain-

containing protein 5 (FNDC5) cleavage. It is mainly secreted by skeletal muscle and released into the blood circulation during exercise, and known as a mediator for browning of subcutaneous white adipose tissue (WAT) and increased thermogenesis and alleviate insulin resistance (133, 134).

There have been a lot of studies investigating the association between circulating irisin with obesity (135–138) and diabetes mellitus (136, 139–145). Majority of studies in human and animals showed that lower circulating levels of irisin were associated with obesity (135, 137) and T2DM (136, 140–145), but so far with inconsistent and controversial results; the opposite trend was also found in subjects with obesity (136, 138), metabolic syndrome (146), and T2DM (147). It is still controversial whether disease condition increases or decreases circulating irisin levels. These discrepant findings may be due to the difference of study population, type of disease, and experimental design. Elevated irisin levels in those patients may act as a compensatory mechanism to combat metabolic disorders.

TABLE 1 | A list of endogenous protective factors and their serum level under diabetic condition and its macrovascular complication.

Endogenous protective factors	Serum level under diabetic condition	Serum level under diabetic macrovascular complication	Production/expression site
eNOS activity	↓	↓	endothelial cells
Adiponectin	↓	↓	adipose tissue
Omentin	↓	↓/↑	adipose tissue
HDLs/apoA-I	↓	↓	liver, jejunum and in serum
GLP-1	↓	↓	L cells of the distal intestine
Lipoxins	↓	↓	epithelium, endothelium, and platelets
L-carnosine[a]	–	–	skeletal muscle, brain, cardiac muscles
Irisin	↓/↑	↓	skeletal muscle and released into serum

–, unknown; ↓, decreased; ↑, increased; ↓/↑, decreased or increased results were observed with controversy.
[a]L-carnosine is rapidly inactivated by serum carnosinase in human.

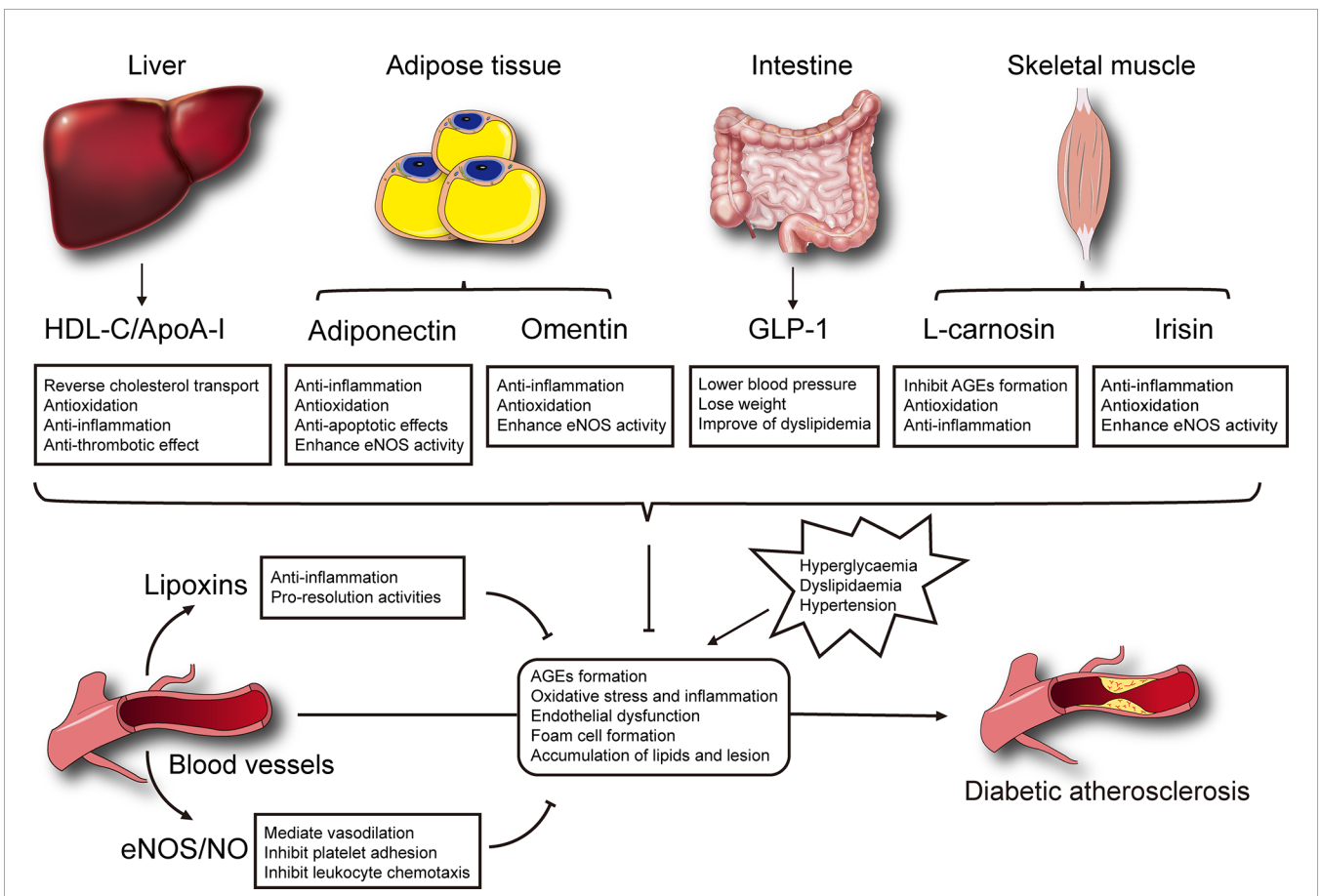

FIGURE 1 | Selected mechanisms of endogenous protective factors on the development of diabetic atherosclerosis.

In contrast, not many, but consistent results show that decreased plasma levels of irisin are independently associated with endothelial dysfunction (137), flow-mediated arterial dilation (141) and presence and severity of coronary artery disease (CAD) (148), implying irisin may ameliorate vascular endothelial dysfunction and treating atherosclerosis, and this is also an explanation for the effective role of physical exercise in the prevention and management of cardiometabolic risk and in the treatment of metabolic syndrome and its complications. A recent animal study has also suggested that irisin treatment suppressed endothelial injury and reduced the degree of aortic atherosclerotic plaque in apolipoprotein E-knock out diabetic mice (149), suggesting irisin could be therapeutic for atherosclerotic vascular diseases in diabetes. Consistently, a case–control study from Egypt showed irisin was a reliable diagnostic or prognostic biomarker for atherosclerosis in type 2 diabetic female patients.

Experiments *in vivo* and *in vitro* indicated that the pathophysiological mechanism of endothelium-protective action of irisin may involve activation of the AMPK–PI3K–Akt–eNOS signaling pathway (149), inhibiting AGEs-induced oxidative stress and NLRP3 inflammasome signaling (150), promoting endothelial cell proliferation (151). Taken together, it has been revealed that irisin level played a beneficial role on metabolic diseases and related vascular complications, but more studies are still needed to prove it to be a therapeutic for atherosclerotic vascular diseases in diabetes mellitus.

CONCLUSION

The imbalance between injury and endogenous protective factors was thought of as an initiating pathogenesis contributing to diabetic vascular complications. In most cases, the serum levels of protective factors were significantly reduced under diabetic condition and diabetic macrovascular complication as shown in **Table 1**, representing a potential to serve as diagnostic or prognostic biomarkers of cardiovascular complications in diabetic patients.

Currently, few effective therapeutic methods are available for the management of diabetic macrovascular complications. The presence of endogenous protective factors secreted by endothelium, liver and other tissues could alleviate development and progression of diabetic atherosclerosis through multiple mechanisms (**Figure 1**). Further clinical therapeutics targeting to enhancing protective factors showed a new promising opportunity in preventing or delaying the vascular complications of diabetes. Incretin mimetics (GLP-1RAs) were convinced significantly of reducing the major cardiovascular adverse events, and recommended as the first-line medicine in type 2 diabetes mellitus patients with cardiovascular risk factors. In contrast, several large-scale clinical trials aiming to raise HDL cholesterol in cohorts fail to show benefits in cardiovascular events. It seems to be a solution to develop novel analogues or mimetic peptides based on function rather quantity. Moreover, adipokines such as adiponectin and omentin, and myokines such as irisin are also providing a new perspective for understanding the development of diabetic complications and representing promising therapeutic prospects. A note of caution is that the therapeutic effects of these factors were obtained in preclinical evidence, thus, human studies with large quantity and high quality are required to validate the results to the clinical situation.

AUTHOR CONTRIBUTIONS

Both CW and JC equally contributed to writing the manuscript and sourcing references for the review. PW and SQ contributed to discussions and editing of the manuscript. WL and JL conceived the outline of this paper and participated in critical review and further revision of the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Trends of Hypercholesterolemia Change in Shenzhen, China During 1997–2018

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To demonstrate the trends of hypercholesterolemia change in Shenzhen, China from 1997 to 2018. Participants were residents aged 18 to 69 years in Shenzhen, China, and were recruited using multi-stage cluster sampling. All participants were surveyed about their socio-demographics, lifestyle, occupation, mental health, and social support. Physical measurements and blood samples for subsequent measurements were collected according to a standardized protocol. A total of 26,621 individuals participated in the three surveys with 8,266 in 1997, 8,599 in 2009, and 9,756 in 2018. In both women and men, there was a significant downward linear trend in age-adjusted mean high-density lipoprotein-cholesterol (HDL-C) from 1997 to 2018 (women: 0.17 ± 0.06, $p = 0.008$ vs. men: 0.21 ± 0.04, $p < 0.001$). In contrast, the age-adjusted total triglycerides and total cholesterol in both sexes have demonstrated an increasing trend in the past two decades. However, no significant changes in age-adjusted low-density lipoprotein-cholesterol (LDL-C) in both men and women between 2009 and 2018 were found (women: 0.00 ± 0.02, $p = 0.85$ vs. men 0.02 ± 0.03, $p = 0.34$). The age-adjusted prevalence of hypercholesterolemia observed a rapid rise from 1997 to 2009 and appeared to be stabilized in 2018, which was similar to the trend of the prevalence of high total triglycerides in women. Changes in trends were varied by different types of lipids traits. Over the observed decades, there was a clear increasing trend of prevalence of low HDL-C (<1.04 mmol/L) in both sexes (women: 8.8% in 1997 and doubled to reach 17.5% in 2018 vs. men was 22.1% in 1997 and increased to 39.1% in 2018), particularly among younger age groups. Hence, a bespoke public health strategy aligned with the characteristics of lipids epidemic considered by sex and age groups needs to be developed and implemented.

Keywords: lipids management, hypercholesterolemia, China, cholesterol, epidemiology

INTRODUCTION

Cardiovascular diseases (CVD) are of significant public health concern globally (1). Lipids control is one of the most critical strategies for CVD risk management, as an increased serum level of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs), as well as decreased serum levels of high-density lipoprotein cholesterol (HDL-C) are the major risk factors of CVD (2).

China has witnessed rapid economic growth and development in industry, technology, and urbanization that have significantly altered people's living environments and lifestyles, such as dietary habits, physical activity, and awareness of health and disease (3). Similar to many Western and economically established countries, the general development of the healthcare system in China improved the overall health status and life expectancy, which resulted in rapid population aging. The increased aging population represents a greater number of people at risk of various non-communicable diseases, such as CVDs (4). Moreover, the incidence of stroke and CVD-related risk factors, such as hypertension and dyslipidemia, has increased among the younger population. It has been reported that about 50% of strokes were in patients aged younger than 65 years in 2012 (5). In addition, national-wide surveys revealed that young and middle-aged people lacked the awareness, treatment, and control of hypertension and dyslipidemia (6, 7). As such, China is now confronted with the greatest public health challenge of chronic non-communicable diseases, particularly CVDs (8). According to the data in 2017, stroke and ischemic heart disease have become the leading causes of death in China, resulting in 124–149 deaths per 100,000 people (9). Therefore, it is crucial to monitor CVD-related risk factors and provide appropriate guidance to the at-risk population, policymakers, and health sectors.

Shenzhen is the first Special Economic Zone in China that has become an iconic model of China's rapid development since the 1970s. Shenzhen has approximately 12 million population, 70% being migrant population (10). A cross-sectional study reported that the prevalence of dyslipidemia was 35.7% in the Shenzhen population in 2015 (11). Moreover, the prevalence of CVD risk factors in the population clustering in Shenzhen has been reported to be higher than in other cities in China and also beyond the Chinese national average level (12). A study of a 6-year trend in the serum lipids in Shenzhen has reported a downward trend in LDL-C and an increased trend in low HDL-C (13). However, this study was based on a single local district. There is a lack of CVD risk factors data that encompass a longer time period and include all Shenzhen residents. Therefore, this study aimed to investigate the trends of blood lipids and the prevalence of dyslipidemia among Shenzhen residents, including three population-based cross-sectional studies in 1997, 2009, and 2018.

MATERIALS AND METHODS

Study Design and Participants

Three population-based cross-sectional studies designed to determine the prevalence of non-communicable diseases and risk factors were conducted in Shenzhen in 1997, 2009, and 2018, respectively. A multi-stage stratified cluster random sampling method was used in each of the survey years to select target communities, streets, towns, households, and individuals.

In 1997, one or two street blocks/towns were randomly selected from five administrative districts, including three urban and two rural areas. Subsequently, from each selected street block/town, one or two communities/villages were chosen randomly, for a total of 16 communities/villages. Lastly, residents aged 18–69 years who have lived in Shenzhen for at least half of the past 1 year from each selected household.

In 2009, a probability proportional to size cluster sampling was applied to choose randomly 34 sub-districts from seven administrative districts. Then, a total of 72 communities were randomly chosen from the selected streets, and 120 households were randomly chosen from each of the selected communities. Lastly, a Kish grid was used to select residents aged between 15 and 69 years who have lived in Shenzhen for at least half of the past 1 year from each selected household.

In the study conducted in 2018, 10 communities were first randomly selected from 10 administrative districts, respectively. Subsequently, 100 households were randomly chosen in proportion to their population from each of the selected communities. Lastly, a Kish grid was applied to select one eligible participant who was aged $\geq$ 18 years and lived in Shenzhen for at least half of the past 1 year from each selected household.

Data Collection

Face-to-face interviews were conducted to collect basic information about participants, such as sex, age, educational level, marital status, smoking behavior, alcohol use, and physical activity participation, according to a structured questionnaire. Participants aged 18–69 years were included in the analysis. Ethics approval was obtained from the Shenzhen Center for Chronic Disease Control and all participants consented in writing.

The height and weight of the participants were measured based on the standard protocol. Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). Overweight was defined as $24.0 \leq$ BMI < 28.0 kg/m^2 and obesity as a BMI of 28.0 kg/m^2 or above (14–16). Current smokers were defined as participants who have smoked at least one cigarette per day in the past 6 months and currently smoking cigarettes, former smokers were participants who have smoked at least one cigarette each day in the past 6 months and quit smoking for at least 1 month, and never smokers were participants who have never smoked or smoked <1 cigarette in a month. Similarly, current drinkers were defined as participants who have drunk at least one time in a week in the past 6 months and currently consume alcohol, former drinkers as participants who had drank regularly in the past 6 months but quit for at least 1 month, and never drinkers as participants who have never drank or drank <1 time in a month. Participants' involvement in physical activity was measured and categorized into regular physical activity or sedentary, according to whether their participation in the physical activity is at least three times per week and at least 10 min each time.

The participants self-sampled no < 30 ml of morning mid urine and sealed and handed it to the study investigators. Overnight fasting blood samples were drawn by venipuncture to measure blood glucose, serum total cholesterol, total triglycerides (TGs), LDL-C, and HDL-C. Blood and urine specimens were collected to measure urine acid, kept at 2–8°C, and sent within 2 h to the Shenzhen laboratory of Guangzhou KingMed Diagnostics Center Co., Ltd, where the specimens were processed and stored at −80°C until laboratory assays could be performed.

Total TGs (≥2.3 mmol/L), total serum cholesterol (≥6.2 mmol/L), LDL-C (≥4.1 mmol/L), and HDL-C (<1.04 mmol/L) cholesterol were classified to be hypercholesterolemia according to the Guidelines for the Prevention and Treatment of Dyslipidemia in Adults in China (2016 Revised Version) (17). Participants were considered to be high uric acid if their uric acid was >420 μmol/L (18) and diabetes mellitus if fasting plasma glucose was ≥ 7.0 mmol/L (19).

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the participants by sex and age for each study period. Continuous and categorical variables were expressed as mean (standard deviation, SD) and frequency (percentage), and between-group differences were tested using the *t*-test or one-way ANOVA and χ^2 test, respectively. Changes in the levels of total TGs, serum total, and HDL cholesterol were determined in comparison with the data in 1997, and changes in LDL-C were determined based on the data in 2009. Restricted maximum-likelihood regressions were used to characterize temporal linear trends. The weights were calculated on the basis of the Chinese Census 2010. SAS analytic software (SAS Institute, Inc) was used for statistical analyses, and a two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

A total of 26,621 individuals were included in the three surveys with 8,266 in 1997, 8,599 in 2009, and 9,756 in 2018. The proportion of men was 38, 43, and 43%, in 1997, 2009, and 2018, respectively. The characteristics of study populations are presented in **Table 1**.

Serum LDL-Cholesterol

The concentrations of serum LDL-C in men and women from 1997 to 2009 are presented in **Table 2**. The age-adjusted mean LDL-C was 3.15 (SD = 0.78) mmol/L and 3.04 (SD = 0.80) mmol/L for men and women, respectively, in 2009. There were no significant changes of age-adjusted LDL-C in both men and women between 2009 and 2018. For men, LDL-C was the highest among the 50–59-year-olds in both 2009 and 2018. For women, the 60–69-year-olds constantly showed the highest LDL-C among all age groups across time. The concentrations of LDL-C increased with age in both sexes. The age group 40–49 years achieved the largest decrease (−0.11 ± 0.03 mmol/L) in LDL-C among men, and the 60–69 years achieved the largest drop (−0.15 ± 0.05 mmol/L) among women.

Serum HDL-Cholesterol

The age-adjusted mean serum HDL-C concentration in 1997 was 1.29 (SD = 0.33) mmol/L in men and 1.47 (SD = 0.35) mmol/L in women (**Table 2**). In both sexes, there was a significant downward linear trend in age-adjusted mean HDL-C from 1997 to 2018. Women had a higher age-adjusted mean HDL-C in 1997 than men. However, a larger drop in magnitude (−0.21 vs. −0.17 mmol/L) was also observed among women in 2018. From 1997 to 2018, significant decreasing trends of HDL-C were observed for all age groups in both sexes. For men, those aged 60–69 years showed the highest HDL-C in 1997, however, they also demonstrated the largest decrease over the years. By 2018, HDL-C was the highest in 18–29-year-oldmen. Women aged 18–29 years had the highest HDL-C in 1997 but had the largest decrease over the years. The 60–69-year-old women with the lowest HDL-C in 1997 showed the smallest reduction in 2018.

Serum Total Cholesterol

The age-adjusted total cholesterol concentration was 4.70 (SD = 1.05) mmol/L in men and 4.74 (SD = 1.03) mmol/L in women in 1997 (**Table 2**). There was an increasing trend of age-adjusted mean total cholesterol in both sexes across years. The younger groups of men and women aged 18–39 with lower total cholesterol levels in 1997 showed larger increases than other age groups over the years. For 40–49-year-olds in men in 2009, the total cholesterol had a sharp increase by 0.33 (SD = 0.09) mmol/L compared with 1997, reaching the borderline increase of total cholesterol defined by the guideline (2016 version). The older age groups (50–69 years) had a higher concentration of total cholesterol in 1997 and it remained stable over the years among both men and women. The 50–69 years groups in women showed total cholesterols above 5.2 mmol/L, exceeding the cut-off of borderline increase in 1997 and continuing to rise by small magnitudes in 2009 and 2018.

Serum Total Triglycerides

In 1997, the age-adjusted total TGs concentration was higher in men (1.37 mmol/L, SD = 1.52) than in women (1.13 mmol/L, SD = 1.06) (**Table 2**). The age-adjusted total TGs in both sexes demonstrated an increasing trend in the past two decades. The younger groups aged below 40 years, for both men and women, showed a larger and more rapid rise in total TGs. For men, total TGs were the highest in the 40–59 age groups with large increases in 2009 and smaller increases in 2018. The women aged 40–69 years experienced a larger rise in total TGs than other age groups in 2009 and the concentrations remained stable from 2009 to 2018.

Prevalence of Hypercholesterolemia

The age-adjusted prevalence of hypercholesterolemia in both men and women showed a rapid rise from 1997 to 2009 and stabilized in 2018 (**Figure 1A**). The age-adjusted prevalence was similar in both sexes in 1997 (about 25%) and rose to 34.8% among men in 2018. Whereas, in 2018, the prevalence among women decreased to 28.9%. The prevalence of hypercholesterolemia among men aged below 50 years was consistently higher than that of women of the same age. At older

TABLE 1 | Characteristics of the study population.

	Man			Woman		
	1997	**2009**	**2018**	**1997**	**2009**	**2018**
N	3,161	3,736	4,208	5,105	4,863	5,548
Age, mean ± SD	37.58 ± 13.05	39.31 ± 11.26	41.90 ± 11.15	37.74 ± 12.55	40.20 ± 12.03	42.79 ± 11.75
N by age groups (%)						
18–29	1,011 (31.98)	693 (18.55)	488 (11.60)	1,565 (30.66)	956 (19.66)	626 (11.28)
30–39	933 (29.52)	1,442 (38.60)	1,540 (36.60)	1,534 (30.05)	1,767 (36.34)	1,900 (34.25)
40–49	598 (18.92)	943 (25.24)	1,178 (27.99)	1,068 (20.92)	1,059 (21.78)	1,450 (26.14)
50–59	320 (10.12)	395 (10.57)	597 (14.21)	525 (10.28)	630 (12.95)	891 (16.06)
60–69	299 (9.46)	263 (7.04)	404 (9.60)	413 (8.09)	451 (9.27)	681 (12.27)
Education, N (%)						
Illiteracy	109 (3.45)	10 (0.27)	26 (0.62)	499 (9.77)	128 (2.63)	172 (3.10)
Primary school	511 (16.17)	235 (6.29)	260 (6.18)	959 (18.79)	616 (12.67)	764 (13.77)
Middle school	818 (25.89)	1,013 (27.11)	1,102 (26.19)	1,417 (27.76)	1,369 (28.15)	1,535 (27.67)
High school	908 (28.73)	1,230 (32.92)	1,354 (32.18)	1,534 (30.05)	1,614 (33.19)	1,490 (26.86)
College and above	814 (25.76)	1,248 (33.40)	1,466 (34.84)	696 (13.63)	1,136 (23.36)	1,587 (28.60)
Marital status, N (%)						
Never married	628 (19.90)	417 (11.16)	373 (8.86)	705 (3.83)	342 (7.03)	305 (5.50)
Married	2,494 (79.05)	3,242 (86.78)	3,742 (88.93)	4,233 (83.03)	4,310 (88.63)	4,960 (89.40)
Divorced	8 (0.25)	37 (0.99)	20 (0.48)	24 (0.47)	101 (2.08)	113 (2.04)
Widowed	18 (0.57)	14 (0.37)	54 (1.28)	131 (2.57)	94 (1.93)	131 (2.36)
Other	7 (0.22)	26 (0.70)	19 (0.45)	5 (0.10)	16 (0.33)	39 (0.70)
BMI, kg/ m^2	22.75 ± 3.31	23.98 ± 3.61	24.22 ± 3.32	22.33 ± 3.41	22.71 ± 3.68	22.93 ± 3.26
Obesity, N (%)	207 (6.56)	439 (11.75)	492 (11.69)	316 (6.20)	351 (7.22)	397 (7.16)
Diabetes, N (%)	655 (20.72)	213 (5.70)	341 (8.11)	1366 (26.76)	230 (4.73)	352 (6.36)
High Urine Acid, N (%)	219 (6.93)	614 (16.43)	867 (20.60)	44 (0.86)	106 (2.18)	234 (4.22)
Smoking, N (%)						
Never	1,656 (52.41)	1,761 (47.14)	2,087 (49.60)	5,063 (99.29)	4,771 (98.11)	5,467 (98.54)
Former	200 (6.33)	358 (9.58)	431 (10.24)	12 (0.24)	39 (0.80)	31 (0.56)
Current	1,304 (41.27)	1,617 (43.28)	1,690 (40.16)	24 (0.47)	53 (1.09)	50 (0.90)
Drinking, N (%)						
Never	2,485 (78.64) 49	1,897 (50.78)	1,582 (37.75) 302	5,019 (98.33)	4,383 (90.13) 66	4,240 (76.52)
Former	(1.55) 626 (19.81)	194 (5.19)	(7.21) 2,307	17 (0.33)	(1.36) 414 (8.51)	322 (5.81)
Current		1,645 (44.03)	(55.05)	68 (1.33)		979 (17.67)
Physical Inactivity, N (%)						
No	1,085 (34.36)	2,212 (59.27)	1,935 (45.98)	1,241 (24.32)	2,395 (49.27)	1,980 (35.69)
Yes	2,073 (65.64)	1,520 (40.73)	2,273 (54.02)	3,862 (75.68)	2,466 (50.73)	3,568 (64.31)
Regular physical activity, N (%)						
No	2,384 (75.49)	2,797 (74.95)	3,052 (72.53)	4,172 (81.76)	3,635 (74.78)	4,129 (74.42)
Yes	774 (24.51)	935 (25.05)	1,156 (27.47)	931 (18.24)	1,226 (25.22)	1,419 (25.58)

ages (50–69 years), hypercholesterolemia was more prevalent in women than in men. Among women, the prevalence of hypercholesterolemia increased with age. This pattern was not observed in men aged over 40 years among which the prevalence was similar across older ages.

Prevalence of High Total Cholesterol

The age-adjusted prevalence of increased total cholesterol (≥6.2 mmol/L) was 5.9% in 1997, increased to 9.96% in 2009, and then slightly decreased to 9.3% in 2018 among men (**Figure 1B**). The age-adjusted prevalence among women was 7.0% and remained stable over the years. The prevalence was similar between the two youngest groups of women and increased with age. This pattern was also observed among men except for the 60–69 years among which the prevalence was lower than the 40–49 years and 50–59 years, and comparable with the age-adjusted mean prevalence.

Prevalence of High Total TGs

The prevalence of high total triglycerides among women increased with age and was consistently lower than that of men (**Figure 1C**). For some age groups of women, the prevalence of high total TGs rose in 2009 and either stabilized or decreased in 2018. For men, the prevalence of high total triglycerides was the highest among those aged 40–49 years. The prevalence among the

TABLE 2 | Age-adjusted lipid profiles from 1997 to 2018.

	Man				Woman			
	1997	**2009**	**2018**	***P* for difference†**	**1997**	**2009**	**2018**	***P* for difference**
LDL-C, mean (mmol/L) ± SD								
18–29	NA	2.82 ± 0.76	0.13 ± 0.06	0.004	NA	2.59 ± 0.67	0.07 ± 0.04	0.038
30–39	NA	3.08 ± 0.74	0.01 ± 0.03	0.669	NA	2.77 ± 0.66	0.01 ± 0.01	0.594
40–49	NA	3.26 ± 0.78	−0.11 ± 0.03	0.002	NA	3.04 ± 0.71	−0.04 ± 0.03	0.192
50–59	NA	3.28 ± 0.72	0.01 ± 0.05	0.852	NA	3.40 ± 0.81	−0.07 ± 0.04	0.103
60–69	NA	3.18 ± 0.75	−0.03 ± 0.03	0.637	NA	3.51 ± 0.85	−0.15 ± 0.05	0.003
Age-adjusted mean		3.15 ± 0.78	0.00 ± 0.02	0.850		3.04 ± 0.80	−0.02 ± 0.03	0.335
HDL-C, mean (mmol/L) ± SD		P for LT*				P for LT		
18–29	1.32 ± 0.32	−0.14 ± 0.05	−0.20 ± 0.10	<0.001	1.53 ± 0.34	−0.21 ± 0.07	−0.26 ± 0.06	<0.001
30–39	1.27 ± 0.32	−0.15 ± 0.05	−0.17 ± 0.05	<0.001	1.49 ± 0.35	−0.17 ± 0.05	−0.23 ± 0.04	<0.001
40–49	1.25 ± 0.31	−0.13 ± 0.10	−0.15 ± 0.05	<0.001	1.45 ± 0.35	−0.15 ± 0.06	−0.19 ± 0.05	<0.001
50–59	1.29 ± 0.33	−0.17 ± 0.10	−0.19 ± 0.10	<0.001	1.44 ± 0.36	−0.14 ± 0.10	−0.17 ± 0.08	<0.001
60–69	1.33 ± 0.36	−0.21 ± 0.08	−0.18 ± 0.07	<0.001	1.40 ± 0.35	−0.09 ± 0.06	−0.15 ± 0.10	<0.001
Age-adjusted mean	1.29 ± 0.33	−0.16 ± 0.07	−0.17 ± 0.06	0.008	1.47 ± 0.35	−0.16 ± 0.05	−0.21 ± 0.04	<0.001
Total cholesterol, mean (mmol/L) ± SD								
18–29	4.34 ± 0.89	0.25 ± 0.07	0.34 ± 0.11	<0.001	4.28 ± 0.86	0.11 ± 0.02	0.13 ± 0.02	0.001
30–39	4.62 ± 1.07	0.29 ± 0.08	0.25 ± 0.09	<0.001	4.43 ± 0.86	0.18 ± 0.03	0.09 ± 0.02	0.007
40–49	4.81 ± 1.11	0.33 ± 0.09	0.16 ± 0.08	0.054	4.79 ± 1.01	0.18 ± 0.08	0.04 ± 0.04	0.502
50–59	4.93 ± 1.10	0.19 ± 0.08	0.17 ± 0.07	0.038	5.23 ± 1.04	0.18 ± 0.03	0.05 ± 0.05	0.684
60–69	4.88 ± 0.96	0.11 ± 0.07	0.03 ± 0.01	0.786	5.30 ± 1.07	0.28 ± 0.05	0.01 ± 0.03	0.444
Age-adjusted mean	4.70 ± 1.05	0.28 ± 0.08	0.24 ± 0.07	0.005	4.74 ± 1.03	0.22 ± 0.06	0.06 ± 0.03	<0.001
Total triglycerides, mean (mmol/L) ± SD								
18–29	1.04 ± 0.82	0.41 ± 0.12	0.48 ± 0.10	<0.001	0.78 ± 0.54	0.24 ± 0.08	0.19 ± 0.09	<0.001
30–39	1.41 ± 1.50	0.57 ± 0.16	0.35 ± 0.08	<0.001	0.95 ± 0.84	0.18 ± 0.07	0.10 ± 0.06	0.001
40–49	1.57 ± 1.67	0.58 ± 0.11	0.37 ± 0.09	0.004	1.17 ± 1.12	0.29 ± 0.07	0.05 ± 0.05	0.594
50–59	1.53 ± 2.29	0.40 ± 0.14	0.25 ± 0.12	0.090	1.44 ± 1.09	0.35 ± 0.09	0.09 ± 0.06	0.594
60–69	1.26 ± 0.84	0.45 ± 0.17	0.14 ± 0.04	0.187	1.58 ± 1.50	0.31 ± 0.07	−0.10 ± 0.09	0.085
Age-adjusted mean	1.37 ± 1.52	0.56 ± 0.15	0.42 ± 0.10	<0.001	1.13 ± 1.06	0.30 ± 0.08	0.14 ± 0.07	<0.001

Data for low-density lipoprotein cholesterol (LDL-C) were not available in 1997.

† The value of p for difference between 2009 and 2018.

**The value of p-value for linear trend across years.*

30–39 and 50–59 years was similar. The 60 to 69 years age group showed the second-lowest prevalence to high total triglycerides, only higher than the youngest age group.

Prevalence of low HDL-Cholesterol

The prevalence of low HDL-C among women was lower than that of men, and there were no large disparities between age groups (**Figure 1D**). There was a clear increasing trend in both sexes across years. The age-adjusted prevalence in women was 8.8% in 1997 and doubled to reach 17.5% in 2018. The age-adjusted prevalence in men was 22.1% in 1997 and increased to 39.1% in 2018. The prevalence among men was similar across the age groups.

DISCUSSION

In this large population-based cohort in Shenzhen over the past two decades, the serum LDL-C has significantly increased from 2007 to 2018 in those of younger age, especially in men (increased 0.13 ± 0.06, $p = 0.004$ in age group of 18–29 years). In contrast, there was a significant decrease in HDL-C in both sexes but more prone in women of younger age (men: -0.20 ± 0.10 vs. women: -0.26 ± 0.06 in age group 18–29 years). The total cholesterol increased in both sexes from 1997 to 2018, but men had a higher increase than women (men: 0.24 ± 0.07 vs. women: 0.06 ± 0.03 from 2007 to 2018). A similar trend was observed in total triglycerides. The prevalence of hypercholesterol increased from 1997 to 2009 but decreased slightly from 2009 to 2018, while the prevalence of low HDL-C increased in both women and men over the decades. In this study, we found the increases in LDL-C and total cholesterol in lipidemia profile were significant at a younger age compared with the older population. A previous study observed the highest estimate of dyslipidemia prevalence (49.3%) in people over 30 years of age in the eastern region of China (20). A large population-based study reported that work-related stress was associated with high LDL-C, low HDL-C, total cholesterol, and hypercholesterolemia diagnosis (21). Shenzhen is a highly developed and urbanized city, with a stressful lifestyle contributing to increasing work pressure, decreased physical activity, and unhealthy diet, particularly among the young

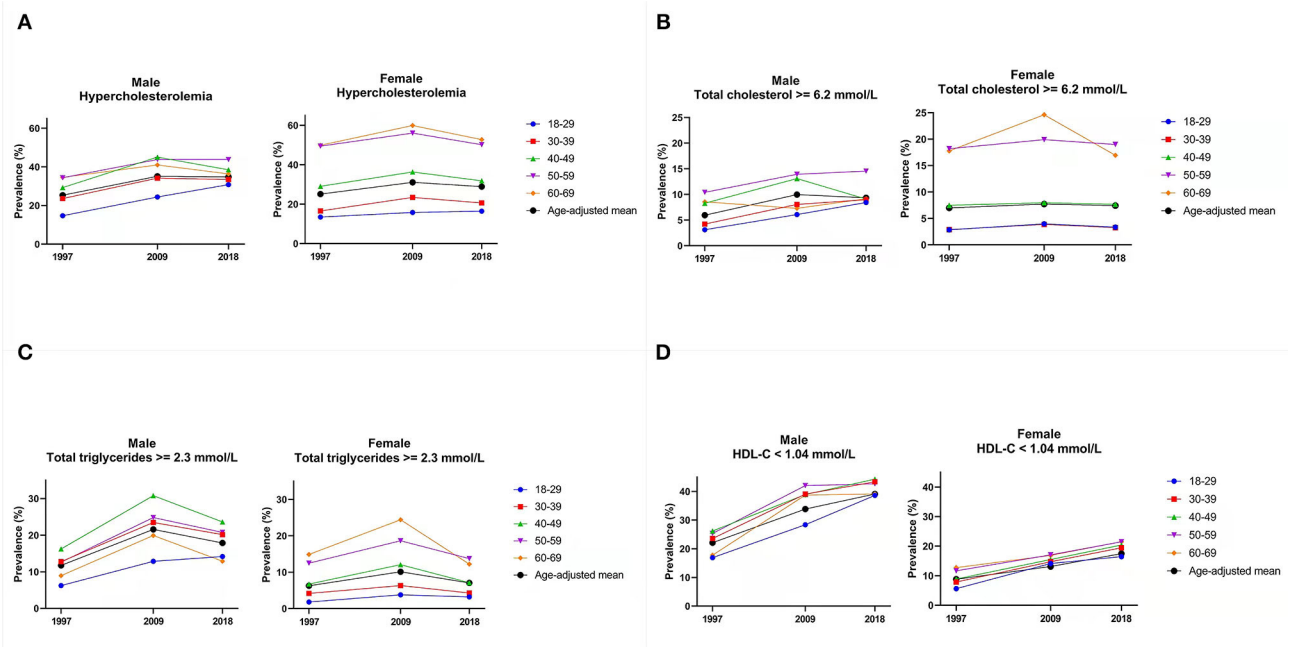

FIGURE 1 | Age-adjusted prevalence of lipid profiles trends from 1997 to 2018. Footnote: Hypercholesterolemia is defined as total triglycerides (≥2.3 mmol/L), total serum cholesterol (≥6.2 mmol/L), low-density lipoprotein cholesterol (LDL-C) (≥4.1 mmol/L), and high-density lipoprotein cholesterol (HDL-C) (<1.04 mmol/L). **(A)** Prevalence of hypercholesterolemia. **(B)** Prevalence of high total cholesterol. **(C)** Prevalence of high total triglycerides. **(D)** Prevalence of low HDL-cholesterol.

to middle-aged population, with men being more likely than women to have increased total cholesterol. This is consistent with the findings from a review on dyslipidemia epidemiology in the Chinese population (20). A possible explanation for this sex disparity in dyslipidemia could be that there was a higher proportion of obesity, cigarette smoking, and alcohol consumption in men compared with women. This may also be relevant to sex differences in awareness, treatment, and self-management. A previous study found that women were more aware of dyslipidemia, more likely to receive treatments for it, and more likely to have their condition controlled compared with men (22). However, the higher prevalence of hypercholesterolemia and low HDL-C in women than in men in the age group of 40–59 years should be noted. This may be related to sex hormones changes that affect the lipidemia parameters due to menopause in women (23).

The prevalence of low HDL-C (42.5%) in 2018 in this study was higher than in the previous studies [30.4% (6) and 41.9% (21)] among Chinese adults. The greater burden of dietary-related chronic conditions, such as dyslipidemia, has been reported in economically developed and highly urbanized areas, predominantly in the east coast of China (24). This may be related to the fact that highly economically developed areas are more likely to have better healthcare services and accessibility to healthcare facilities, where more people can access prompt diagnosis and, therefore, contributed to the higher reported prevalence of dyslipidemia among populations in Shenzhen.

We found that the prevalence of hypercholesterol was decreased in older age people during the most recent decade (2008–2018), which might be related to the implementation of health policy and advocacy in public health strategies for lipid control in the older people in recent years (25). Though age has been reported as the most devastating contributor of dyslipidemia, implementation of policies, such as increase the accessibility of diagnostic technologies, improving awareness of risk factors, changing healthy lifestyles to prevent CVDs, and developing effective hypolipidemic medications, is beneficial for long-term outcomes in the older population (26). In 2004, the China cholesterol education program was initiated for improving and standardizing the interventions for hyperlipidemia management (27). Moreover, since 2007, a joint committee of multidisciplinary experts formulated the "Chinese guidelines for the management of dyslipidemia in adults," which has provided guidance and strategies to effectively control dyslipidemia from a clinical perspective (28). Although a downward trend in the prevalence of dyslipidemia was observed in the study population, other factors associated with the risk of cardiovascular disease, such as hypertension, diabetes mellitus, and lifestyle factors, must be considered when developing prevention strategies. Additionally, total and LDL-C levels tend to increase with age in young or middle-aged adults when evaluated cross-sectionally or prospectively.

Strengths and Weaknesses

The major strength of the current study was the use of a purposeful sampling strategy in a large and representative population, which reduced the risk of selection bias with good generalizability. However, there are several limitations: this

is a cross-sectional study rather than a prospective cohort, therefore, no causal relationships can be determined and the data collected, such as former smokers/drinkers might not be long enough to show a difference in the blood lipid level. Another limitation is the potential selection bias that is induced by emigration and immigration in Shenzhen City. Because of how fast residents change during these two decades, the random selected households might not be representative compared with the others living in the same community. The prevalence of dyslipidemia differences is also relevant to differences in awareness, treatment, and self-management between sexes and age groups. However, this information was not collected, which may influence the interpretation of the findings. Moreover, even though blood sample tests were standardized in all the surveys, measurement errors could not be avoided.

CONCLUSION

In conclusion, the current study investigated the trends of different types of lipid abnormalities in Shenzhen city, China-based on large-scale population samples. The age-adjusted prevalence of hypercholesterolemia observed a rapid rise from 1997 to 2009 and appeared to be stabilized in 2018. There was a clear increasing trend in the prevalence of low HDL-C (<1.04 mmol/L) in both sexes over the observed decades. To improve lipids management in Shenzhen city, it is crucial to explore the underlying reasons for the change in trends, to allow for appropriate public health strategies to be developed and implemented in Shenzhen.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shenzhen Center for Chronic Disease Control. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KP, LL, and JP conceptualized the study. KP, XL, YX, and MO contributed to methodology. WC and YL contributed to formal analysis, software, and analysis. YL, MO, and XL validated the study. LL contributed to resources. MO, XL, YL, WC, YS, and KP wrote the original draft. LS, JG, HZ, and KP contributed to writing, reviewing, and editing the manuscript. YL visualized the study. LL, JP, and KP contributed to project administration. All authors have read and agreed to the published version of the manuscript.

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Effects of Family Doctor Contract Services on the Health-Related Quality of Life Among Individuals With Diabetes in China: Evidence From the CHARLS

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Background: Family doctor contract services (FDCS) has played a key role in diabetes management in China since 2016. The influence of FDCS on the physiological indexes of individuals with diabetes has been examined. However, little attention has been paid to its effect on the Health-Related Quality of Life (HRQoL). This study aims to fill this knowledge gap by evaluating the effect of FDCS on the HRQoL of individuals with diabetes.

Methods: We identified 382 individuals with diabetes receiving all follow-up surveys in 2013, 2015, and 2018 from the China Health and Retirement Longitudinal Study (CHARLS). The HRQoL of the included individuals was estimated using results from the Short Form 36 (SF-36) questionnaire. The propensity score matching with the difference-in-differences (PSM-DID) approach was applied to quantify the effect of FDCS on the HRQoL among individuals with diabetes. A robust test was performed by setting the 2015 data as the treatment group for the placebo test.

Results: The mean score of role-emotional (RE) increased from 54.25 to 61.63 among those who signed up to receive FDCS, while the corresponding score decreased from 57.77 to 51.04 among those who did not receive FDCS. Results from the regression analysis indicated that the use of FDCS was associated with significant improvement in RE (+14.10, $p = 0.04$) among individuals with diabetes. We did not find a statistically meaningful association between the FDCS and any of the other HRQoL domains: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), and mental health (MH), respectively. The robustness analysis of the model indicated that the results were robust.

Conclusion: The FDCS for diabetes in China was associated with a significant improvement in RE. Due to a limited time since the launch of FDCS (i.e., 2016), the recipient's physical health did not show marked improvement. In the future, FDCS should pay more attention to the physiological health of individuals with diabetes. Moreover,

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psychological services also need to be maintained and not slackened. At the same time, it is strongly recommended to pay more attention to the HRQoL of individuals with diabetes and more comprehensive health.

Keywords: family doctor contract services, diabetes, health-related quality of life, China Health and Retirement Longitudinal Study, difference-in-differences

INTRODUCTION

As a chronic and common age-related disease, diabetes has become a great challenge of worldwide public health, considering its high incidence, disability, and mortality (1). The International Diabetes Federation reported that China suffers from a great number of chronic patients, including 28% of the world's diabetics (2). Diabetes and its complications have an increasingly adverse effect on the health and quality of life of patients and increase the concern of patients regarding diet, employment, and leisure (3–5). Additionally, the nature of diabetes for patients means that these adverse effects of diabetes and its complications may be experienced for a long time (6). In this way, the quality of life of individuals with diabetes needs more attention, and more chronic disease management through primary health care is the need for those patients with long-term diabetic complications.

Primary health care is provided by family doctor contract services (FDCS), which plays a key role in the management of chronic diseases (7). In Britain, the National Health Service, founded in 1948, advocates a national management model that enables every citizen to enjoy contracted family doctor services (8). In the United States, the family doctor system originated in the 1960s and incorporated health management into community general practitioner services to provide active health management for patients with chronic diseases (9, 10). China's health care system reform starting from 2009 had given more attention and resources to primary health, which enabled it to lay a good foundation for the implementation of FDCS. In 2011, China began to take measures to establish FDCS in some pilot cities, such as Shanghai (6), and FDCS was fully launched in 2016 by the Chinese government (11). Patients with chronic diseases were listed as the focus group of the contract services considering the high incidence of chronic diseases and their adverse effects on the quality of life (12). By 2020, the goal of universal coverage of FDCS was basically achieved. With the continuous promotion and improvement of the FDCS, it was expected to have a profound influence on the quality of life of patients with chronic diseases.

Health-related quality of life (HRQoL) is the physical and mental health perceived by individuals or groups over time (13). In previous studies, it had been proved that FDCS could improve the quality and continuity of primary health care services as well as have a huge influence on the HRQoL of patients with chronic diseases (14–16). A randomized controlled trial in Norway found that the intervention of a family doctor team could effectively improve the healthy quality of life of elderly patients undergoing multi-drug therapy (17). Another study in Iran indicated that maternal and child health could be effectively improved by family doctor services (18). In addition, a study from Turkey showed that family doctor services could effectively improve the clinical outcome of diabetic patients (19). The research on family doctor services in China mainly focused on the effects for self-management, patient satisfaction, and treatment compliance (20, 21). The research on the effects of FDCS on health paid more attention to whether it could improve the health outcomes of patients. For instance, according to previous studies, FDCS could positively affect hypertension control in hypertensive patients (6). However, recently, few studies have investigated the impact of FDCS on the quality of life of diabetic patients. Therefore, this study aims to evaluate the net effect of FDCS on HRQoL in the diabetic population.

MATERIALS AND METHODS

Data Source

The data used in this study was obtained from the follow-up survey of the China Health and Retirement Longitudinal Study (CHARLS). The CHARLS was a longitudinal survey of people over 45 years old in China, which collected high quality data representing families and individuals. The first baseline survey of the CHARLS was fielded in 2011 and the recent follow-up survey was in 2018. The 2011 baseline survey involved 17,705 practitioners, who were chosen randomly, and covered 450 villages/resident committees, 150 counties/districts, and 28 provinces. All data were collected by using face-to-face interviews and made public 1 year after the end of data collection. In general, the CHARLS is a meaningful and nice representation of the elderly in China. (A complete introduction to CHARLS is shown in **Supplementary Material 1**).

This study used the follow-up data from 2013 to 2018. To investigate the association between FDCS and the HRQoL of individuals with diabetes, we limited the samples to practitioners who had diabetes in 2013 and were included in the 2015 and 2018 tracking surveys. Finally, a total of 382 samples were included.

Measure

We constructed a new scale based on the Short Form 36 (SF-36) and the CHARLS variables to measure the HRQoL of individuals with diabetes. The construction of the new scale originated from eight dimensions of SF-36, and we selected appropriate variables of CHARLS to evaluate these dimensions, including physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH) (shown in **Supplementary Material 2**). The construction of this scale referred to the construction methods of relevant articles which used Cronbach's α coefficient to measure the reliability between SF-36 and the CHARLS variables, and it had good reliability with

all dimensions having alpha values higher than 0.6, except vitality ($\alpha = 0.34$) (22). The content validity index (CVI) was evaluated at the item level (I-CVI) and scale level (S-CVI). I-CVI was higher than 0.83 and S-CVI was 0.94 (22). These indicated that the scale had good reliability and validity.

Statistical Analysis

Propensity Score Matching

Propensity score matching (PSM) is applicable to non-random design and used in estimating the effect of policy interventions. The PSM method can match individuals in the control group who have similar characteristics in the treatment group with the closest propensity score. In this way, the PSM can reduce selection bias.

To evaluate the effect of FDCS on the HRQoL of individuals with diabetes in China, outcome variables between treatment and control groups were compared. But some characteristics of samples in the control group cannot consist with the treatment group. Moreover, in this study, there were more practitioners in the control group than in the treatment group. In order to solve these limitations, we used the kernel matching method, which is one of the PSM methods, to construct the control group. We also used some control covariates that were measured before the treatment, including age, gender, education, marriage, smoking, drinking, and economic situation.

The shortcoming of the kernel matching method is that the matched individuals may be bad matches. Hence, we used a visual analysis of the common support assumption of the propensity score in the treatment and control groups, which checked the overlap and the region of common support between both the groups. We then examined whether the matching procedure could balance the covariates in the treatment and control groups using a two-sample *t*-test.

Difference-in-Difference Model

Difference-in-difference (DID) model is widely used in policy evaluations. DID models compare changes, both in the treatment group and the control group, which attribute the effect of the policy. The FDCS can be viewed as a policy test, and DID models are adopted to analyze the net effect of this policy.

In this study, we used samples for waves 2013 and 2018 which was matched by the propensity score matching (PSM). The basic framework of DID model is given by

$$Y_{it} = \alpha_0 + \alpha_1 treated^{*}_{it} T_{it} + \alpha_2 treated_{it} + \alpha_3 T_{it} + \alpha_4 X_{it} + \varepsilon_{it}$$

where Y_{it} represents the HRQoL of individuals i with diabetes at time t; $treated_{it}$ is a dummy variable which is equal to 1 if individual i received FDCS, and 0 if individual i did not receive FDCS; T_{it} is a time dummy variable which takes a value of 0 before implementation of FDCS, and it takes a value of 1 after implementation of FDCS; X_{it}refers to other observable covariates, including gender, education, marriage, smoking, drinking, and economic situation; and ε_{it} is the error term.

Testing the Robustness of PSM-DID Estimation

The results of the robustness test are directly related to the correctness and credibility of data analysis. When we draw a conclusion, we need a series of methods to verify whether the conclusion is reliable. To ensure the robustness of the PSM-DID results, we chose the placebo test which selected samples from different periods for analysis. The FDCS was fully launched in 2016, and the 2015 data was before the implementation of FDCS. Therefore, we used the 2015 data as the treatment group for the placebo test, and we tested the robustness of DID estimation by comparing the differences between DID estimation and placebo test.

TABLE 1 | Characteristics of the sample ($N = 382$).

Characteristic	*n*	Percentage (%)
Gender		
Female	223	58.4
Male	159	41.6
Age (years old)		
75–85	34	8.9
55–74	251	65.7
45–54	97	25.4
Marital status		
Married	278	72.8
Other	104	27.2
Residential area		
Rural	244	63.9
Urban	138	36.1
Education level		
High school and above	157	41.1
Junior middle school	75	19.6
Primary school	68	17.8
Informal education	82	21.5
Medical insurance type		
Urban employee medical insurance	88	23.0
Urban and rural resident medical insurance	29	7.6
Urban resident medical insurance	223	58.4
New rural cooperative medical insurance	11	2.9
Other medical insurance	15	3.9
No insurance	16	4.2

Research Hypothesis

Based on previous studies, this study assumes that FDCS could effectively improve the HRQoL of diabetic patients.

RESULTS

Characteristics of the Sample

Table 1 shows the personal characteristics of 382 practitioners. The practitioners included 58.4% ($n = 223$) women, and 91.1% ($n = 348$) were under 75 years old. A total of 72.8% ($n = 278$) of the practitioners were married and lived with their spouses, and 63.9% lived in rural areas. In addition, among the practitioners, about 41.1% ($n = 157$) had a high school degree or above, and

TABLE 2 | Covariate balance test before and after matching.

Variable	Unmatched/matched	Treated	Control	*P*-value	Bias%	Reduce bias%
Age	U	64.30	61.62	0.102	30.6	
	M	64.44	63.92	0.818	5.9	80.8
Gender (%)	U	45.45	41.49	0.623	8.9	
	M	46.88	43.45	0.992	−0.2	97.2
Education (%)	U	69.69	58.20	0.197	24.1	
	M	68.80	66.61	0.824	5.5	77.0
Marriage (%)	U	90.91	76.72	0.324	13.4	
	M	90.63	74.41	0.784	7.3	45.7
Smoking (%)	U	48.49	26.57	0.007	46.2	
	M	50.00	46.02	0.761	8.1	82.4
Drinking (%)	U	36.36	34.93	0.880	2.7	
	M	37.50	35.38	0.960	−1.3	53.2
Economic	U	91,058	27,455	0.004	25.3	
	M	33,248	42,098	0.734	−3.5	86.1

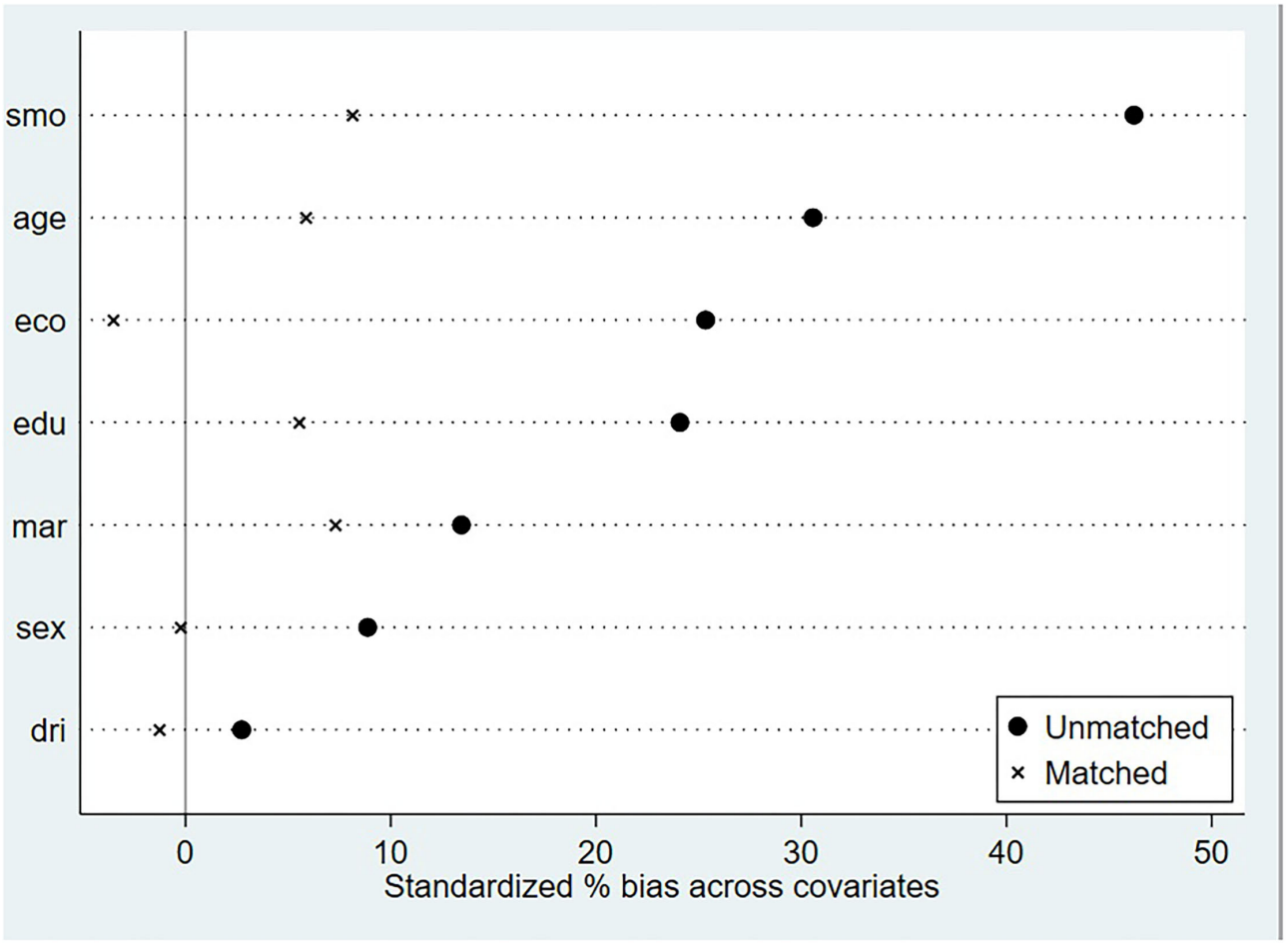

FIGURE 1 | Standard deviation of covariates.

58.4% ($n = 223$) of whose medical insurance was the urban resident medical insurance.

Balancing Proper Test for PSM Result

The result of balancing proper test shows that all observable covariates were balanced by the kernel matching between the treatment and control groups. The covariate difference in the two groups decreased significantly and became statistically insignificant at 5%.

As shown in **Table 2**, the balancing property could be verified by comparing the significance of all matching variables in the models before and after matching. Before matching, there was a significant difference in the "smoking" and "economic situation" covariates between the treatment and control groups ($p < 0.05$). After matching, all covariates became insignificant ($p > 0.05$). The standardized bias was <10% and had reduced substantially by kernel matching (shown in **Figure 1**). It could also be seen intuitively in **Figure 1** that the standardized bias of each covariate after matching was significantly reduced.

Figure 2 dedicates a visual analysis of the covariate of the common support assumption in the treatment and control groups. In the figure, the treatment group is shown above the midline, while the control group is shown under the midline. The distribution of the propensity score between the treatment and control groups was similar, which confirmed the common support assumption of the covariate.

Effects of Family Doctor Contract Services on HRQoL of Individuals With Diabetes

Table 3 shows the estimated result of PSM-DID. The "PSM-DID Estimator" in the table is the net policy effect reflecting FDCS on HRQoL of individuals with diabetes, including physical functioning (PF), role physical (RP), body pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH).

Before the implementation of FDCS, there was no significant difference in the scores of all dimensions between the treatment and control groups. After the implementation, there was a significant difference in RE. The mean score of RE increased from 54.25 to 61.63 in the treatment group, while the corresponding score decreased from 57.77 to 51.04 in the control group, and

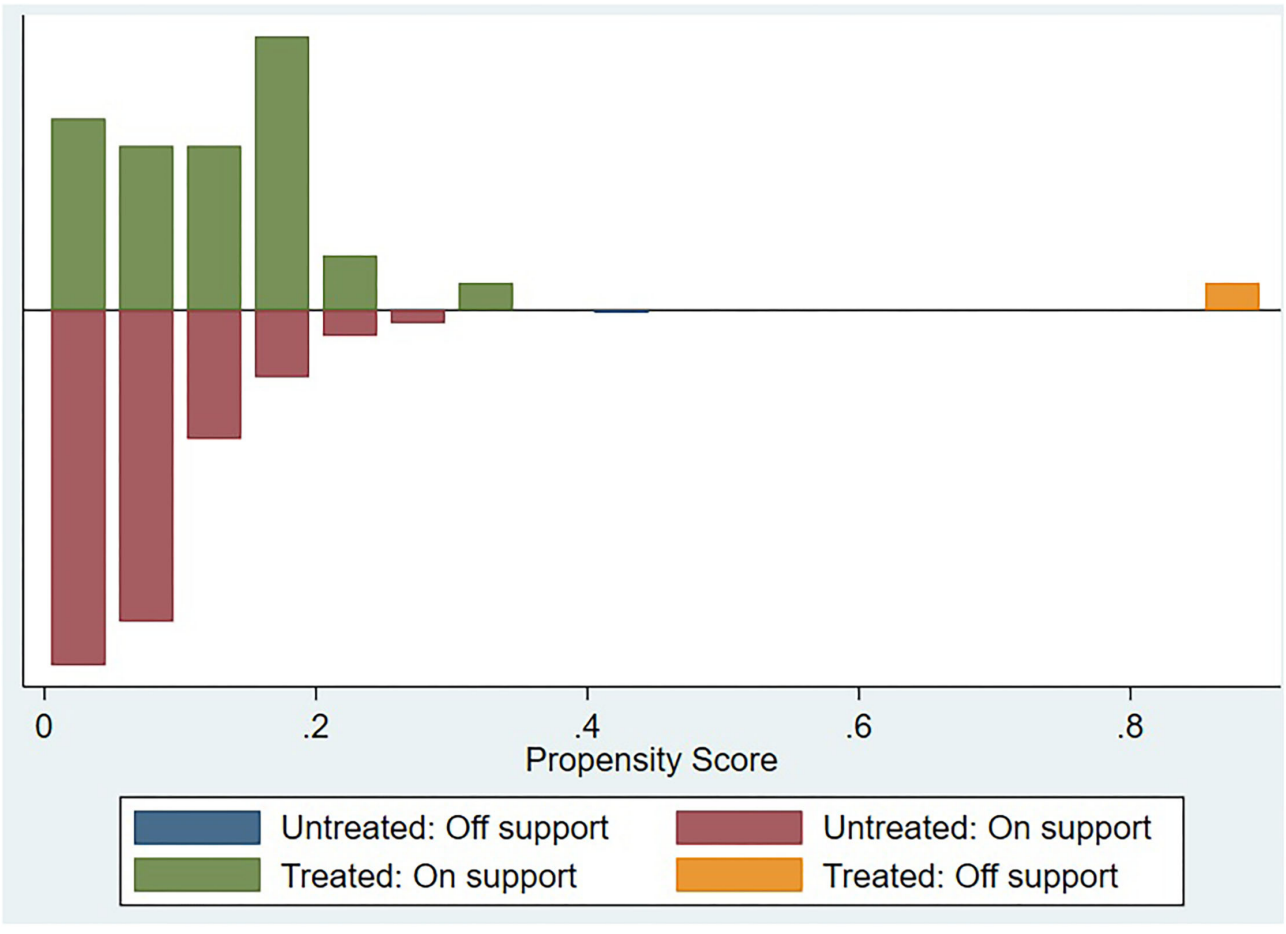

FIGURE 2 | Visual analysis of the validity of the common support assumption.

TABLE 3 | Propensity score matching with difference-in-differences (PSM-DID) estimate result.

Independent variable	Intervention	Treated mean	Control mean	Difference	PSM-DID estimator
PF	Before	93.59	92.18	1.41 (0.75)	
	After	87.58	90.92	−3.34 (1.07)	−4.75 (1.32)
RP	Before	96.09	93.95	2.14 (0.65)	
	After	85.67	88.86	−0.19 (0.06)	−2.33 (0.50)
BP	Before	80.96	84.63	−3.68 (−0.99)	
	After	68.51	64.99	−3.53 (−0.02)	0.15 (0.02)
GH	Before	47.69	45.37	2.32 (0.54)	
	After	42.87	43.71	−0.85 (0.17)	−3.17 (0.50)
VT	Before	56.80	60.76	−3.96 (−0.82)	
	After	51.37	57.34	−5.97 (0.95)	−2.02 (0.25)
SF	Before	19.32	20.81	−1.50 (−0.66)	
	After	17.18	20.00	−2.82 (1.60)	−1.33 (0.44)
RE	Before	54.25	57.77	−3.52 (−0.70)	
	After	61.63	51.04	10.59** (2.10)	14.10** (2.02)
MH	Before	47.33	52.13	−4.80 (−1.21)	
	After	50.76	50.96	−0.19 (0.05)	4.60 (0.85)

** $P < 0.05$.

TABLE 4 | Robustness test results of PSM-DID model.

Independent variable	Intervention	Treated mean	Control mean	Difference	PSM-DID estimator
PF	Before	86.30	84.90	1.40 (0.72)	
	After	89.16	85.81	3.47 (1.18)	1.94 (0.55)
RP	Before	96.09	93.95	2.14 (0.65)	
	After	91.52	91.06	0.47 (0.15)	−1.68 (0.39)
BP	Before	84.47	87.60	−3.13 (−0.82)	
	After	71.26	81.22	−9.96 (1.64)	−6.83 (0.96)
GH	Before	53.70	50.51	3.19 (0.74)	
	After	80.70	70.20	10.50 (1.97)	9.31 (1.06)
VT	Before	58.06	62.44	−4.38 (−0.91)	
	After	53.42	55.42	−2.00 (0.39)	2.38 (0.36)
SF	Before	15.65	17.93	−2.28 (−1.00)	
	After	17.37	17.79	−0.42 (0.13)	1.86 (0.46)
RE	Before	75.34	76.91	−1.57 (−0.32)	
	After	74.01	77.84	−3.83 (0.26)	−2.26 (0.26)
MH	Before	51.35	55.60	−4.25 (−1.05)	
	After	55.73	55.55	0.18 (0.04)	4.44 (0.73)

the DID value was 14.10 ($p = 0.044$). However, other dimensions had no significant difference before and after the implementation of FDCS.

Testing the Robustness of PSM-DID Estimation

The robustness analysis of the model found that the research results were robust and reliable. The placebo test results shown in **Table 4** were obtained by PSM-DID analysis of 2013 data and 2015 data. Focusing on the PSM-DID results of the RE dimension, the results showed that the difference between the treatment and control groups was insignificant. Based on the placebo test, it could be considered that the research results are robust and reliable.

DISCUSSION

To the best of our knowledge, most studies paid more attention to the influence of FDCS on physiological indexes of individuals with diabetes, while few studies paid attention to its effect on HRQoL, especially the specific dimension of HRQoL. In this way, this study assessed changes in each dimension of HRQoL of individuals with diabetes to evaluate the net effect of FDCS. The results demonstrated that FDCS effectively improved the scores

of RE in individuals with diabetes, but not that of MH, VT, SF, PF, RP, BP, and GH.

According to the results, FDCS for individuals with diabetes significantly improved the scale scores of RE. This result is similar to the finding by Moffatt (23), who reported that care for chronic diseases effectively raised the population's RE score. Moreover, FDCS could provide high-quality home care services for patients with chronic diseases and bring convenience to patients with inconvenient actions. According to a previous study, RE reflects role impairment due to emotional distress in aspects of work or task performance as well as the degree of satisfaction with achievements (24). Since the sample population in this study was mostly the elderly who had retired, RE more reflects the emotional distress and satisfaction when completing certain tasks or behaviors in life. According to Sabbah's research (25), FDCS could reduce the occupancy rate of nursing homes and hospitals and maintain the independent living ability of the elderly. Therefore, the elderly who signed up to receive FDCS had higher satisfaction when completing certain tasks or behaviors in their life, and the RE value was higher.

Although FDCS significantly improved the RE of individuals with diabetes, it did not improve the MH, VT, and SF. A similar situation was also revealed in a previous study, which showed that psychological well-being was more related to the quality of life, compared to physical health and socioeconomic status (26). According to the WHO report, mental health is the fifth leading cause of disability-adjusted life years among the elderly in China (27). However, FDCS did not pay enough attention to mental health, and there was no routine mental health examination for individuals with diabetes (28). Additionally, despite being both mental and physical health very important for the quality of life of individuals with diabetes, FDCS providing primary health care services usually paid more attention to the physical health of residents than mental health (29). In terms of the mental health, although role-emotional has improved significantly, the other three dimensions are still not improved. Therefore, FDCS need continue to pay attention to the other three dimensions of diabetic patients.

This study showed that the contract service did not improve PF, RP, BP, and GH. For individuals with diabetes, the progression of diabetes is a slow process. In this way, the result may be explained by the finding of Behma's study (30), which indicated that a postponed progression of morbidity and symptom may not directly affect the self-rated health of elderly patients, and there are differences between elderly patients' perception of health and satisfaction with health. Thus, due to this cognitive bias toward health, patients with chronic diseases may also have certain errors in their own health evaluation. Moreover, since FDCS was implemented after 2016, the progression and physical health of individuals with diabetes could also not be significantly improved in the short period of 2 years. Additionally, another explanation could be connected to a stereotypic view that "be old is to be ill". This view shows that although the physical condition is deteriorating, the elderly patients are satisfied with their overall health status (31). Although FDCS has paid much attention to the physiological health of individuals with diabetes, the four dimensions of physiological health of the population have not been significantly improved. In the future, FDCS should pay more attention to the physical health of individuals with diabetes. At the same time, service on physical health needs further adjustment and optimization. Above all, FDCS had no significant effect on the health of diabetic patients at present, but the effect could be expected over a longer period.

In comparison with previous studies, this study is strengthened by two features (14–19). First, the data for this study were obtained from CHARLS, which is a national database with good representation. Second, this study uses PSM-DID to evaluate the causal relationship between FDCS and HRQoL, which could effectively eliminate the influence of external confounding factors on evaluation. Moreover, some limitations of this study should be recognized. On the one hand, since the latest CHARLS data of 2021 has not yet been published, this study selected the CHARLS data of 2013 and 2018 to evaluate the net effect of FDCS on HRQoL of individuals with diabetes. On the other hand, only those individuals with diabetes receiving all follow-up surveys in 2013, 2015, and 2018 were included in this study, which made the sample size of this study relatively small, but these samples are from the whole national data of CHARLS without additional elimination.

CONCLUSION

In this study, we evaluated the net effect of FDCS on eight dimensions of the HRQoL of individuals with diabetes. The findings showed that the FDCS probably has an influence on the HRQoL by significantly improving the RE. However, the improvement of the other seven dimensions of HRQoL was not significant. In the future, more attention should be paid to FDCS to the physiological health of patients with diabetes, and the frequency of regular follow-up visits by family doctors should be increased. Additionally, since the other three dimensions of mental health did not improve significantly, psychological services need to be maintained and not slackened. It is also recommended to pay more attention to the HRQoL of individuals with diabetes and more comprehensive health.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: http://charls.pku.edu.cn/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committees of Peking University (IRB00010529611015). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WL and LW contributed to the conception and design of the study. LW conducted the data reduction and analyses and also wrote the manuscript. WL guided the whole process and reviewed the manuscript. All authors read and approved the manuscript before submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.865653/full#supplementary-material

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ORIGINAL RESEARCH
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Economic Burdens for Treatment of Patients With Type 2 Diabetes in North Thailand: A Hospital-Based Observational Study

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Purpose: Diabetes and its complications pose an economic burden to healthcare systems, family, and society. Therefore, this study aimed to estimate the real-world financial burden of type 2 diabetes (T2D) treatment, complications, and cardiovascular death.

Materials and Methods: An electronic database of the largest university-affiliated hospital in the North of Thailand was retrieved for a 10-year period (2009-2019). We used the International Classification of Disease 10th Revision codes of diabetes and complications to obtain relevant patient records. All included records based on the inclusion and exclusion criteria were analyzed. Expenditures for diabetes treatment, complications, and cardiovascular death for two years were reported as mean, standard deviation, median, and interquartile range.

Results: Of a total of 9,161 patient records, the average age of patients was 57.8 ± 12.7 years. The average total outpatient cost was THB 22,874 ± 38,066 (US$ 759 ± 1,264) for the first year and THB 23,462 ± 34,441 (US$ 779 ± 1,143) for the second year. The average inpatient expenditure was THB 160,790 ± 411,607 (US$ 5,338 ± 13,666) for the first year and THB 181,804 ± 190,257 (US$ 6,036 ± 6,317) for the second year. Drug was the main component for outpatient expenditure while surgery was the main component for inpatient expenditure. Diabetes patients with complications incurred a greater cost of treatment than those without complications. Cardiovascular death led to about seven times higher cost of treatment than the average total cost of diabetes treatment. Heart failure complications (THB 846,345 ± 752,884 or US$ 28,099 ± 24,996) had the highest inpatient costs compared with other complications in the first year. Stroke complications

(THB 71,927 ± 143,414 or US$ 2,388 ± 4,761) had the highest outpatient costs compared with other complications. In general, the first-year expenditure was higher than the second year for all complications.

Conclusions: Diabetes incurs a substantial financial burden resulting from its complications. Effective management of diabetes with a multi-sectoral effort from government, providers, patients, and private is required.

Keywords: economic, cost, complication, cardiovascular complication, Thailand, type 2 diabetes

INTRODUCTION

Thailand is an upper-middle-income country in Southeast Asia with gross national income per capita growing from $4,580 USD in 2010 to $7,050 USD in 2020. Life expectancy in 2010 was 74 and increased to 77 in 2019 (1). The extension in life expectancy has contributed to a change in the age distribution of the Thai population. With the increasing age of the elderly population, disease patterns and causes of death have shifted toward non-communicable diseases, which are estimated to account for 71% of all deaths (2). Of those deaths, 27% were cardiovascular, 12% were cancers, and 6% were diabetes (3).

Previous Thai National Health Examination Surveys have shown that diabetes prevalence has been increasing dramatically over time. For diabetes patients aged 20 years and over, the prevalence increased from 7.1% in 2004 to 7.5% in 2009, and to 9.7% in 2014. The proportion of diabetes unawareness declined from 66% in 2004 to 33% in 2009, whereas the proportions of treatment and control for all diabetes increased from 15% in 2004 to 31% in 2009 (4). The increased prevalence of type 2 diabetes (T2D) is likely to be related to multiple factors including environmental factors that affect the lifestyle, especially unhealthy dietary patterns and decreased physical activity levels (4).

Diabetes can lead to many serious health problems, usually after a number of years and particularly if diabetes is not detected early or well treated. The most common diabetic complication is nephropathy at 43.8%, followed by diabetic retinopathy at 30.7%, ischemic heart disease at 8.1% and cerebrovascular disease at 4.4% (5). In addition, T2D presented in about 40% of patients with atherosclerotic cardiovascular disease (6). As the number of people with diabetes and its complications arises, the disease takes a large proportion of national healthcare expenditure. Complications are the main cost driver for diabetes because they require more intensive care such as hospitalization and multiple surgeries. Patients with diabetic complications incurred higher cost of treatment compared to those without complications. However, the magnitude of the difference is varied site by site. Pongcharoensuk P, et al. reported that diabetic complications in patients with diabetes would lead to almost six times higher average cost of treatment compared to those without complications ($1,611 USD vs $281 USD) (7). Another study reported the median cost of diabetic patients with complications in comparison to those without complications was $480 USD vs $115 USD, respectively (8). Preventing complications and related disability by improving diabetes control is therefore of paramount importance to reduce the health and economic burden of diabetes. Although advances in diabetic treatment have improved cardiovascular and renal outcomes (9–11), the access to new treatments is limited in low- and middle-income countries (6, 12). For new diabetic treatment to be listed in the national list of essential medicine, robust cost data and proven cost-effectiveness need to be evaluated for local application.Hence, this study aimed to estimate the real-world economic burden of T2D treatment and its complications in local Thai context.

METHODS

This study is a retrospective database analysis to estimate healthcare resources and financial burden incurred in patients with T2D. Electronic database from Maharaj Nakorn Chiang Mai Hospital, which is the largest university-affiliated tertiary care hospital in the North of Thailand, was retrieved for 10 years.We used the International Classification of Disease 10th Revision (ICD-10) as a primary diagnosis coding E10-E14 to retrieve patient records from the years of 2009 to 2019. The index date was the first visit to a hospital (either in an inpatient or outpatient setting) as aforementioned ICD-10.

Patient records that met the following criteria would be included into the analysis. Firstly, patients were ≥18 years of age and diagnosed with T2D. Secondly, patients should have one year of recorded data without a visit of related T2D in that period. We used a one-year period as a washout period to obtain the incident diabetes cases. Next, patients must have the data of at least a two-year follow-up period after the index date. This was the objective of this study to estimate financial consequences for two consecutive years. Finally, patients must have another visit after the index date within the next six months. This was to confirm consistent visits to this hospital. Other patient records that did not meet the above inclusion criteria were excluded from data analysis.

Once the T2D patient records had been selected, we retrieved the database of diabetes-related complications and cardiovascular death that occurred after the index date using the following ICD-10 codes. Both primary and secondary diagnoses of patient visit with the following diabetes-related complications were included into the analysis. Those complications and ICD-10 codes were myocardial infarction

(I21, I22), angina (I20), congestive heart failure (I50), stroke (I64), peripheral vascular disease (I73), neuropathy (G56-64, (E10-E14).4), diabetic retinopathy (E10.3, E11.3, E12.3, E13.3, E14.3, H360), transient ischemic attack (G45, G45.8, G45.9), renal failure (N17, N19), chronic renal failure (N18), hypoglycemia (E16.0-E16.2)), lactic acidosis (E87.2), ketoacidosis ((E10-E14).1), gangrene (R02), and ulcer (L97). In addition, amputation complications were also included using the International Classification of Disease 9th Revision-Clinical Modification (ICD-9-CM) as 8400-8419.

Data Analysis

We analyzed the healthcare resources in terms of the number of outpatient visits and the number of hospital admissions. Total cost of diabetes treatment, diabetes-related complications, and diabetes-related cardiovascular death was analyzed and reported as mean (standard deviation) and median (interquartile range, IQR). Costs of diabetes treatment were disaggregated into individual cost items such as drugs, laboratory, services, operations, food, and room and reported for two consecutive years. In addition, attributable costs related to T2D with and without complications were estimated for two consecutive years. We started counting the date of complications when thoe T2D patient record reported either primary or secondary diagnosis of ICD-10 of aforementioned complications. Then, costs of outpatients and inpatients were analyzed dividing into those T2D with or without complications. For admitted T2D patients with cardiovascular complications which had a discharge status as dead, all inpatient costs incurred at such admission were analyzed and defined as a cost of cardiovascular death. All costs were inflated by the consumer price index with the medical care section (13), and presented in the year of 2019. Costs in this study were the expenditure or economic burden incurred to the patients or charge. All costs were converted to US$ at the rate of 1 US$ = 30.12 THB (14).

RESULTS

Figure 1 shows the flow diagram of included patient records for analysis. A total of 21,561 patient records from 2009 to 2019 were retrieved from the electronic database of the Maharaj Nakorn Chiang Mai Hospital. Of the total patient records, 8,175 records were excluded due to having less than one year wash-out period from the index date or having less than a two-year follow-up period. Next, 4,206 patient records were excluded due to not having a second visit within six months after the index date. The remaining 9,180 patient records were initially included into the data analyses. However, 19 patient records were incomplete; therefore, they were excluded from the data analyses. The final of 9,161 T2D patient records were used for data analyses.

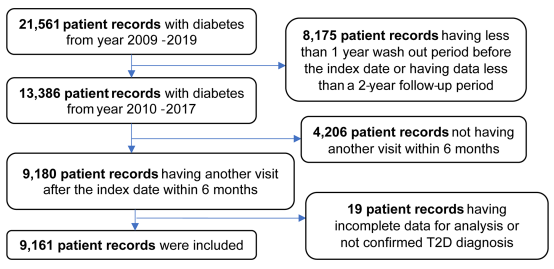


FIGURE 1 | Selection of patient records based on inclusion criteria.

From a total of 9,161 patient records, patient's mean age was 57.8 ± 12.7 years and 53.2% were female. The majority of them (49.6%) had the health insurance of the Civil Servant Medical Benefit Scheme (CSMBS) (**Table 1**).

Of all included patient records, 9,161 T2D patients visited the outpatient department in the first year and 5,330 T2D patients revisited in the second year. Costs of the outpatient visits for T2D patients were shown as mean (standard deviation, SD) and median (interquartile range, IQR). The average number of outpatient visit was 5.87 (3.93) for the first year and 5.19 (3.98) for the second year. The mean (SD) of total outpatient costs was THB 22,874 (38,066) or US$ 759 (1,264) and THB 23,462 (34,441) or US$ 779 (1,143) for the first and second year, respectively. The median (IQR) of total outpatient costs was THB 10,210 (3,699;26,872) or US$ 339 (123;892) for the first year and THB 10,827 (3,935;29,731) or US$ 359 (131;987) for the second year. Of the overall total cost, drug cost was the major component, followed by operation and laboratory costs.

Of all included patient records, 445 unique T2D patients were admitted in the first year and 136 patients were admitted in the second year. However, the 136 unique patients in the second year could be the same or different patients as those admitted in the first year. The average number of admissions was 2.70 (3.14) and 3.63 (3.02) per patient during the first and second year, respectively. The mean (SD) total cost per admission was THB 160,790 (411,607) or US$ 5,338 (13,666) for the first year and THB 181,804 (190,257) or US$ 6,036 (6,317) for the second year. The median (IQR) of total cost per admission was THB 85,818 (54,527;151,452) or US$ 2,849 (1,810;5,028) for the first year and THB 112,486 (65,071;225,377) or US$ 3,735 (2,160;7,483) for the second year. Surgery was the main cost contribution, followed by drug and operation. The detail of outpatient and inpatient costs is shown in **Table 2**.

Of all 880 patient visits with cardiovascular cause (ICD code: Ixx.xx), 27 admitted patients were discharged with dead status. Therefore, inpatient costs incurred from this patient group were estimated as the cost of cardiovascular death. We found that the mean cost (SD) was THB 193,596 (270,929) or US$ 6,427 (8,995). The median with IQR was THB 90,108 (35,836;227,515) or US$ 2,992 (1,190;7,554).

Of all 9,161 T2D patients who visited the outpatient department in the first year, diabetic retinopathy was the highest number of complications found, followed by renal failure, neuropathy, and heart failure (850, 312, 263, 181 patients, respectively). T2D patients with complications usually incurred greater cost of outpatient treatment than those without complications, except for diabetic retinopathy (**Figure 2**). Among T2D patients with complications, those with stroke

TABLE 1 | Baseline characteristics.

Demographics	N (%)
Number of included patient records	9,161
Age (mean, standard deviation)	57.8 ± 12.7
Gender	
Male	4,290 (46.8)
Female	4,871 (53.2)
Health insurance scheme	
Civil servant medical benefit scheme	4,540 (49.6)
Universal coverage scheme	2,467 (26.9)
Social security scheme	1,637 (17.9)
Others	517 (5.6)

incurred the highest average cost of treatment (THB 71,927 or US$ 2,388), followed by angina (THB 62,596 or US$ 2,078), and peripheral vascular disease (THB 60,042 or US$ 1,993). The average outpatient treatment cost of T2D without complication was about THB 22,000-23,000 (US$ 730-764) in the first year. The attributable treatment cost with complication was highest in stroke (THB 49,188 or US$ 1,633), followed by angina (THB 39,870 or US$ 1,324), and peripheral vascular disease (THB 37,233 or US$ 1,236) compared with those without such complications.

Of all 5,330 T2D patients who visited the outpatient department in the second year, the top four complications were similar to those found in the first year. Costs of treatment

TABLE 2 | Economic burden of type 2 diabetes treatment.

Variables	First year of treatment (THB/US$)		Second year of treatment (THB/US$)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Outpatient treatment (all included patients (N = 9,161 for first year and N = 5,330 for second year)				
Number of visits per year	5.87 (3.93)	5 (3-7)	5.19 (3.98)	4 (3-7)
Total cost (THB)	22,874 (38,066)	10,210 (3,699-26,872)	23,462 (34,441)	10,827 (3,935-29,731)
(US$)	759 (1,264)	339 (123-892)	779 (1,143)	359 (131-987)
Drug (THB)	17,843 (37,259)	3,552 (174-19,872)	19,967 (33,229)	6,845 (1,443-25,502)
(US$)	592 (1,237)	118 (6-660)	663 (1,103)	227 (48-847)
Laboratory (THB)	1,605 (2,413)	654 (0-2,514)	1,306 (2,073)	504 (0-1,963)
(US$)	53 (80)	22 (0-83)	43(69)	17 (0-65)
Service (THB)	548 (961)	272 (161-492)	495 (709)	267 (160-508)
(US$)	18 (32)	9 (5-16)	16 (24)	9 (5-17)
X-ray (THB)	214 (1,700)	0 (0-0)	115 (1,296)	0 (0-0)
(US$)	7 (56)		4 (43)	
Operation (THB)	2,235 (7,215)	0 (0-377)	1,237 (6,516)	0 (0-144)
(US$)	74 (240)	0 (0-13)	41 (216)	0 (0-5)
Food (THB)	19 (572)	0 (0-0)	27 (836)	0 (0-0)
(US$)	0.63 (19)		1 (28)	
Other (THB)	409 (1,415)	0 (0-0)	315 (1,410)	0 (0-0)
(US$)	14 (47)		10 (47)	
Inpatient treatment (only admitted patients; N = 445 for first year and N = 136 for second year)				
Number of admissions per year	2.70 (3.14)	2 (1-3)	3.63 (3.02)	3 (2-5)
Total cost (THB)	160,790 (411,607)	85,818 (54,527-151,452)	181,804 (190,257)	112,486 (65,071-225,377)
(US$)	5,338 (13,666)	2,849 (1,810-5,028)	6,036 (6,317)	3,735 (2,160-7,483)
Drug (THB)	26,129 (149,179)	5,236 (2,307-11,476)	35,495 (79,047)	6,194 (2,614-28,941)
(US$)	868 (4,953)	174 (77-381)	1,178 (2,624)	206 (87-961)
Laboratory (THB)	9,750 (63,635)	206 (0-1,717)	12,657 (25,434)	739 (51-13,145)
(US$)	324 (2,113)	7 (0-57)	420 (844)	25 (2-436)
Service THB)	16,656 (68,406)	5,650 (2,825-12,364)	18,213 (25,938)	8,827 (5,340-21,617)
(US$)	553 (2,271)	188 (94-410)	605 (861)	293 (177-718)
X-ray (THB)	3,062 (11,090)	0 (0-283)	5,115 (12,150)	274 (0-2,546)
(US$)	102 (368)	0 (0-9.40)	170 (403)	9 (0-85)
Operation (THB)	23,389 (79,165)	9,361 (5,289-18,231)	24,759 (33,927)	11,893 (6,099-25,801)
(US$)	777 (2,628)	310.79 (175.60-605.28)	822 (1,126)	395 (202-857)
Food (THB)	107 (887)	0 (0-0)	123 (758)	0 (0-0)
(US$)	4 (29)		4 (25)	
Room (THB)	9,928 (36,910)	2,476 (1,273-5,657)	12,776 (30,681)	3,981 (1,650-12,368)
(US$)	330 (1,225)	82.20 (42.26-187.82)	424 (1,019)	132 (22-411)
Surgery (THB)	68,149 (73,970)	54,669 (33,483-86,321)	68,005 (50,940)	60,271 (35,374-91,130)
(US$)	2,263 (2,456)	1,815.04 (1,111.65-2,865.90)	2,258 (1,691)	2,001 (1,174-3,026)
Other (THB)	3,619 (17,011)	772 (377-1,780)	4,660 (13,290)	1,130 (553-2,701)
(US$)	120 (565)	25.63 (12.52-59.10)	155 (441)	38 (18-90)

IQR, interquartile range; SD, standard deviation.

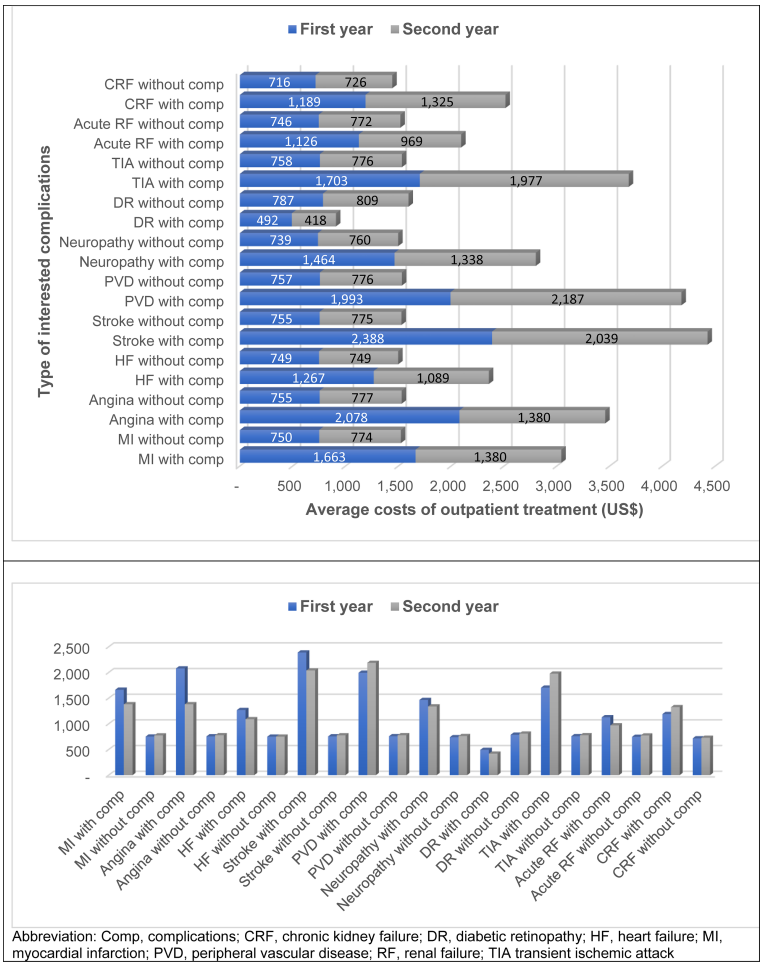


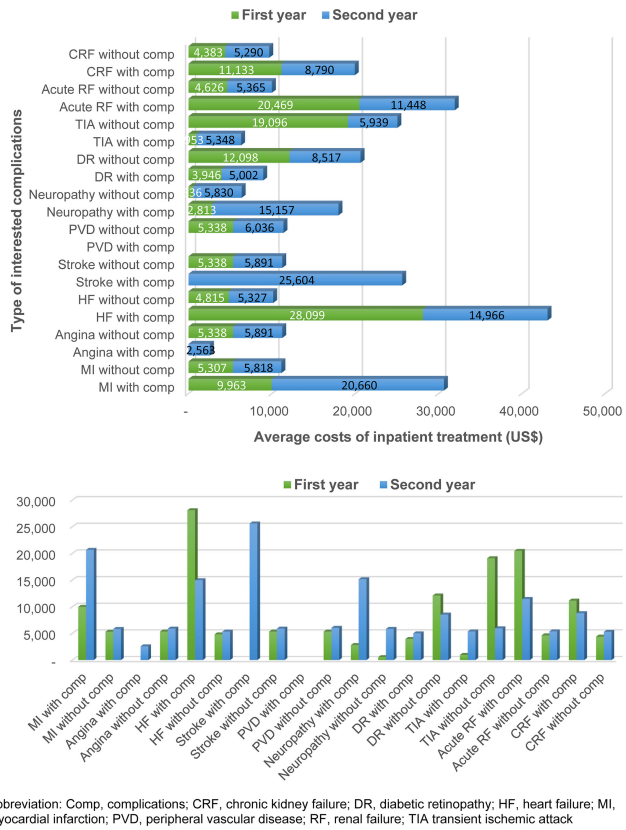
FIGURE 2 | Outpatient treatment costs for type 2 diabetes with and without interested complications.

for T2D patients without complications in the second year were slightly higher than those in the first year. Costs of complication treatment in the second year were lower than those in the first year. There might be several explanations. First, we selected incident cases of T2D, thus, first event of the complications is likely to be more severe than the following events. Therefore, cost of the first year of complication is higher than that of the second year. Second, the number of patients with complications in the first year is higher than that of the second year. Some patients were lost which could be the patient with high treatment cost.The attributable treatment cost with complication was highest in peripheral vascular disease (THB 42,496 or US$ 1,411), stroke (THB 38,078 or US$ 1,264), and transient ischemic attack (THB 36,172 or US$ 1,201). Again, T2D without diabetic retinopathy had greater treatment cost than those with diabetic retinopathy (**Figure 2**).

Of all 445 admitted T2D patients in the first year, diabetic retinopathy was the highest number of complications found, followed by renal failure, and heart failure (369, 20, 10 patients, respectively). There were no T2D patients admitted with stroke, angina, or peripheral vascular disease during the first year; hence, cost of inpatient treatment was not available. Of all 136 admitted T2D patients in the second year, diabetic retinopathy, renal failure, and heart failure were still the top three admission from T2D patients (**Figure 3**).

In general, patients with complications had higher cost of inpatient treatment than those without complications. The difference in treatment cost was substantial, especially in T2D with heart failure compared to those without heart failure (THB 846,345 vs THB 145,031 or US$ 28,099 vs US$ 4,815). T2D patients admitted with heart failure and renal failure incurred the highest cost of treatment (THB 846,345 (US$ 28,099) and THB 616,532 (US$ 20,469), respectively). In the second year, T2D with stroke, angina, or myocardial infarction had greater cost burdens than those without such complications (**Figure 3**).

Figure 4 shows the total cost of treatment for T2D patients with or without complications. For the first year, T2D patients with complications had incurred higher treatment costs than



Abbreviation: Comp, complications; CRF, chronic kidney failure; DR, diabetic retinopathy; HF, heart failure; MI, myocardial infarction; PVD, peripheral vascular disease; RF, renal failure; TIA transient ischemic attack

FIGURE 3 | Inpatient treatment costs for type 2 diabetes with and without interested complications.

those without complications. The difference in average total treatment costs ranged from THB 14,472 to 55,344 (US$480 to 1,837). In general, the mean total cost of treatment for T2D patients without complication were about 30,000 THB (US$ 996) per patient per year. Once T2D patients had complications, treatment costs would increase to THB 44,000-84,000 (US$ 1,461-2,789), depending on the type of complication. It was found that heart failure (THB 84,935 or US$ 2,820), renal failure (THB 73,449 or US$ 2,439), and stroke (THB 71,927 or US$ 2,388) were the top three complications that incurred highest treatment costs.

Cost of diabetes treatment in T2D patients without complications was slightly decreased in the second year compared to the first year. Transient ischemic attack (THB 103,787 or US$ 3,446), peripheral vascular disease (THB 65,871 or US$ 2,187), and heart failure (THB 64,875 or US$ 2,154) incurred highest treatment costs for T2D with complications in the second year (**Figure 4**).

We estimated some diabetes complication costs as their event-based costs. Those complications were amputation, hypoglycemia, lactic acidosis, ketoacidosis, and ulcer. Ketoacidosis had the highest number of outpatient visit and highest cost of outpatient treatment (THB 4,230 or US$ 140). Hypoglycemia event incurred the second highest cost of outpatient treatment even though the number of outpatient visits was much lower than those with ketoacidosis. In case of inpatient costs, T2D patients with ulcer complication incurred the highest treatment cost (THB 107,067 or US$ 3,555), followed by hypoglycemia (THB 74,532 or US$ 2,475), and ketoacidosis (THB 70,391 or US$ 2,337) as shown in **Figure 5**.

DISCUSSION

This study aimed to capture real-world evidence of expenditures incurred from diabetes treatment. We used the electronic database from the largest university-affiliated hospital in the North of Thailand. The medical records from the period of 2009 to 2019 were retrieved using the specified ICD-10 codes and were analyzed in terms of financial burden from treatment of diabetes and its complications. We found that the average outpatient treatment cost was THB 22,874 (38,066) or US$ 759 (1,264) and THB 23,462 (34,441) or US$ 779 (1,143) for the first and second year, respectively, in T2D patients with or without complications. Drug costs were the main contribution and accounted for 78% of all outpatient costs. Financial burden was

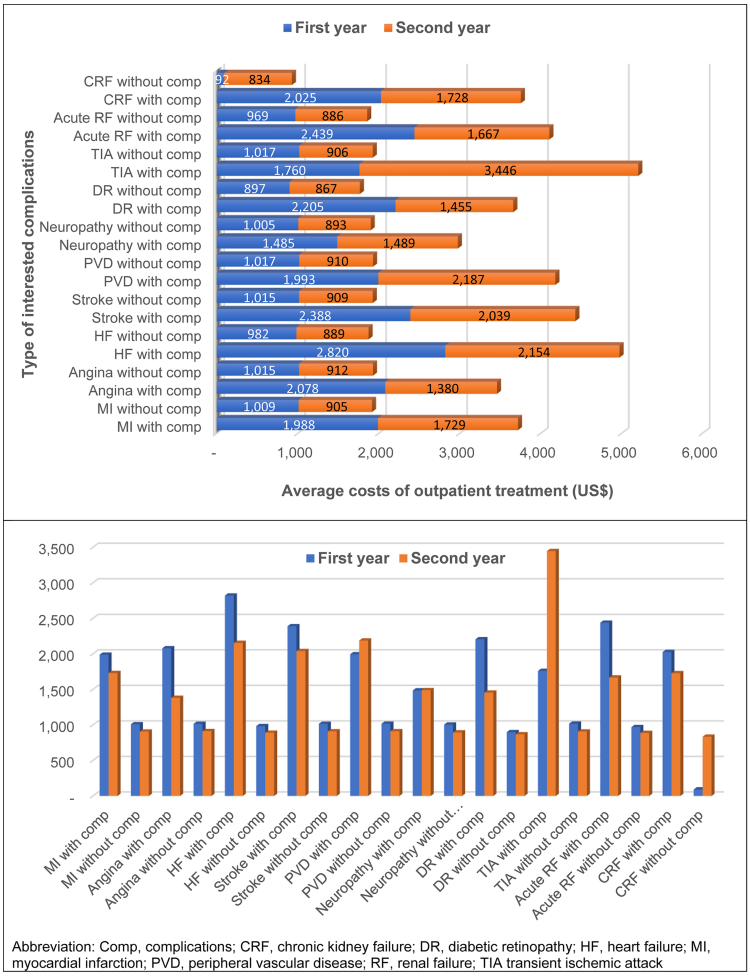


FIGURE 4 | Total treatment costs for type 2 diabetes with and without interested complications.

about seven times higher in inpatient treatment than outpatient treatment.The average inpatient cost was THB 160,790 (411,607) or US$ 5,338 (13,666) in year 1 and THB 181,804 (190,257 or US $ 6,036 (6,317) in year 2. Approximately 40% of inpatient expenditure was from surgery. Diabetes patients with complications incurred greater financial burden than those without complications. Heart failure, renal failure, and stroke were of important complications that led to financial burden for T2D patients. Cardiovascular death from T2D patients had the average cost of THB 193,596 (US$ 6,427).

Cost of diabetes care has been estimated in several studies in Thailand. A small study conducted in 475 diabetic patients found that the median cost for patients without complications was lower than those with complications (US$ 115 vs US$ 479, respectively) (15). A larger study of 24,501 diabetic patients reported US$ 551 for diabetes cost of care (16). The average spending per admission in a tertiary care hospital in Bangkok, the capital, was estimated at US$ 1,682 (17). Therefore, the estimation of diabetes care costs was varied depending on the hospital care levels, presence of complications, among other factors.

The findings of this study were somewhat different from the findings from another study (18) that obtained the economic burden from the database of the largest tertiary hospital, Buddhachinaraj hospital, located in the lower North of Thailand. This might be due to different healthcare contexts in each setting such as physicians and patients. Maharaj Nakorn Chiang Mai hospital is the university tertiary hospital serving both referred patients around the upper northern Thailand and walk-in patients, while Buddhachinaraj hospital is a tertiary regional hospital serving patients around the lower northern Thailand. The complexity of T2D patients visiting those hospitals might be different leading to different costs of T2D treatment.

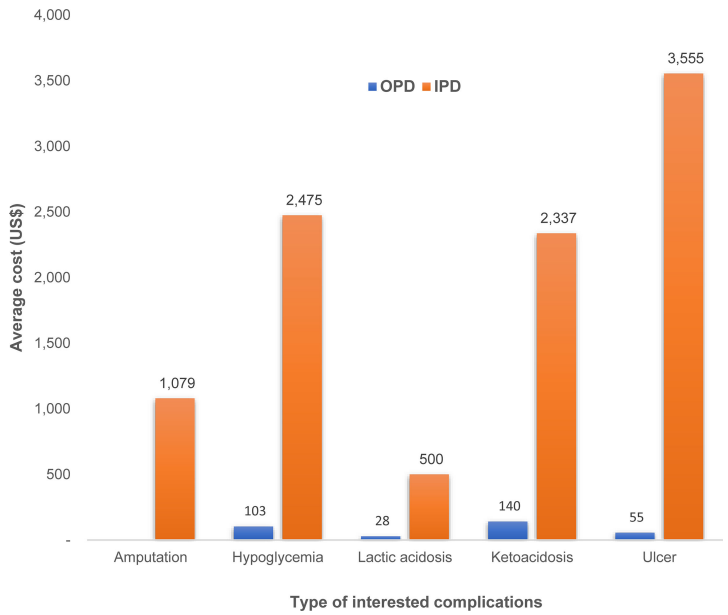


FIGURE 5 | Event-based treatment costs for type 2 diabetes related complications.

Our findings were in line with other studies that have indicated the rising costs of diabetes from complications. A study was conducted in Thailand to estimate the cost of diabetes and its complications using a micro-costing approach. The average cost per diabetic patient was US$ 882 in 2008 (1 US$ = 32 THB) (8). Existence of complications increased the cost substantially (3, 8). The median cost of illness of patients with complications was significantly higher than for people without complications (US$ 479.93 vs US$ 115.12 in 2008) and increased with increasing numbers of complications (19). A study predicted the cost of diabetes to increase up to 232% depending on the type of complications (20).

With the study design of retrospective database analyses, several limitations were taken into consideration. Firstly, patients must not visit a hospital with the diagnosis of diabetes for a year to confirm as an incident case. It is possible that patients are not really an incident case due to loss to follow-up over a year or referral from other hospitals. In such instances, some expenditures might be neglected. Secondly, we cannot definitely conclude that the complications were the result of diabetes although complication data were obtained later than the diabetes data. It is possible that such complications had been found and treated before diabetes was diagnosed. Then, those complications were relapsed or reoccurred after diabetes occurrence. Third, since we are looking at patients identified over a 10-year period, there may have been changes in the treatment guidelines,e.g., greater use of DPP4i in the latter years.

Although this study has aforementioned limitations, it creates some value and has become the source of information for cost-effectiveness study and budget impact analysis. This is because the findings of the study reflect the real-world treatment costs for diabetes as opposed to the protocol driven costs based on restrictive patient inclusion/exclusion criteria, which are used very often in randomized controlled trials. In addition, we obtained almost all cost data from patients who met the inclusion criteria except for 19 incomplete patient records. These findings could be an important input for further cost-effectiveness analysis of new health technology for T2D treatment in Thailand. For example, the cost-effectiveness of sodium-glucose cotransporter 2 (SGLT2) inhibitors for T2D patients with high risk of cardiovascular disease or the cost-effectiveness of SGLT2 inhibitors for T2D patients with chronic kidney disease.

CONCLUSION

Diabetes and its complications have posed an economic burden to healthcare system. Average annual expenditure for diabetes treatment was about THB 25,000 (US$ 830). Once complicationsoccurr, they lead to substantial financial burden. Cost of cardiovascular death from T2D patients was about seven times higher than the average annual cost of T2D treatment. Cardiovascular complications, such as stroke, angina, and heart failure were the main drivers of substantial cost of complication treatment. Effective management of diabetes with a multi-sectoral effort from government, providers, patients, and private is required.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

This study was reviewed and approved by the Institutional Research Board of the Faculty of Medicine, Chiang Mai University, Study code: MED-2562-06811.

AUTHOR CONTRIBUTIONS

Conceptualization: AP, PD, UP. Data retrieval: AP. Data analysis and interpretation: PD, UP, AP. Project administration: UP. Writing-original draft: UP. Writing-review and editing: PD, AP, UP. All authors read and approved the final manuscript.

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A Bibliometric Analysis of the Hotspots Concerning Stem Cell Extracellular Vesicles for Diabetes in the Last 5 Years

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Background: Diabetes mellitus (DM) is a metabolic disease that endangers human health, and its prevalence is exploding and younger. Stem cell-derived extracellular vesicles (SC-EVs) have a repair function similar to SCs and no risk of tumor formation, which have been widely used in the repair of DM and its complications. We aim to map the hot trends of SC-EVs for the treatment of DM and providing directions for future research.

Methods: We screened all relevant publications on SC-EVs for DM from the Web of Science (Wos) during 2017–2021, and research trends in this field were analyzed by VOSviewer and CiteSpace.

Results: A total of 255 articles related to SC-EVs for DM were screened out according to the search strategy. China (122 publications and 2,759 citations) was the most productive country, followed by the USA (50 publications and 1,167 citations) and Italy (16 publications and 366 citations). The top five institutions with the most publications were located in Italy and China, with Turin University being the most productive. The journals Stem Cell Research and Therapy and International Journal of Molecular Sciences published most of the studies on SC-EVs for DM. ASHOK KUMAR published the majority of articles in this field, while QING LI was the most cited. Cluster analysis indicated that the current research trend is more focused on the repair mechanism and clinical translation of exosomes and their related preparations in promoting DM and its complications.

Conclusion: In this study, a comprehensive summary and analysis of the global research trends of SC-EVs used in DM and its complications was performed. In the past 5 years, relevant high-quality publications in this field have increased significantly, and SC-EVs have a good prospect for development in the treatment of DM and its complications.

Keywords: diabetes mellitus, stem cells, extracellular vesicles, bibliometric analysis, hotspot

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease whose main manifestation is chronic hyperglycemia, combined with defective insulin secretion or action, and is one of the major diseases endangering human health, and its prevalence is exploding and younger (1). According to a recent report by the International Diabetes Federation (http://www.diabetesatlas.org/), in 2021, ∼537 million adults (20–79 years old) are living with DM worldwide, and this number is predicted to rise to 643 million in 2030 and 783 million in 2045. Notably, DM causes 6.7 million deaths in 2021 and is responsible for at least USD 966 billion in health expenditure. Patients with diabetes in a continuous state of elevated glucose can lead to the development of various complications, such as diabetic wound, nephropathy, and retinopathy (2). Unfortunately, DM cannot be cured at present, and the primary way to strictly control hyperglycemia is to improve the patient's lifestyle habits, such as diet and exercise, combined with medication to prevent and delay the development of related complications and improve the quality of life. However, this requires a high degree of patient compliance, which is difficult to achieve for many patients. At the same time, existing treatments are slightly inadequate for patients who have developed diabetic complications. Therefore, there is an urgent need for new approaches to treat DM and its related complications.

Stem cells (SCs) are a class of pluripotent progenitor cells with multidirectional differentiation potential, which have been widely used in tissue regeneration engineering due to their abundant source, easy extraction and expansion, and remarkable tissue repair effects confirmed by numerous studies (3). SCs have the role of delaying the progression of DM and promoting the repair of diabetic complications through immunomodulation, vascularization, and modulation of graft-vs.-host response to recover the insulin sensitivity of peripheral tissues, improve the peri-islet microenvironment, and upgrade islet β-cell regeneration (4–6). However, the challenges of SC storage and transport and the risk of pro-tumor formation have not yet been overcome, which greatly limit the clinical translation of SC therapies (7–9).

Extracellular vesicles (EVs) are lipid bilayer vesicles secreted by most cells and are classified into exosomes (30–150 nm), microsomes (100–1,000 nm), and apoptotic vesicles (1–5 μm) based on their diameters. The secreted EVs, which contain various substances, such as lipids, proteins, and noncoding RNAs, act on adjacent target cells *via* autocrine or paracrine secretion, or act on specific and distant target cells through humoral transport, and then act directly on target cells through membrane fusion or endocytosis to participate in complex and delicate intercellular communication. Previous studies have found that SC-derived EVs (SC-EVs) have a repair function similar to SCs and no risk of tumor formation (10, 11). Notably, numerous studies have shown that SC-EVs (especially exosomes) exert anti-inflammatory, anti-apoptotic, and pro-vascularization mechanisms through their abundant growth factors and therapeutic noncoding RNAs to promote the repair of organs damaged by DM and diabetic complications (2, 12).

Literature is a carrier that can record scientific progress. Bibliometrics uses quantitative methods such as mathematics and statistics to study the internal connections and distribution patterns among the literature to discover the current state of research, research hotspots, and future trends in a certain field (13). As research on the repair potential of SC-EVs in DM and its related complications has made tremendous progress, the number of related publications has increased dramatically, but relevant bibliometric studies have not been reported. In this study, we analyzed the publications on SC-EVs for DM and its related complications in the Web of Science (WoS) database during 2017–2021, in which the number of publications, institutions, and keywords were statistically analyzed with the aim of mapping hot trends in SC-EVs for the treatment of DM and providing directions for future research.

MATERIALS AND METHODS

Data Collection Strategy

Web of Science is an authoritative academic database that has been widely used by researchers worldwide. In this study, the WoS core collection was selected as the retrieval data source of SC-EVs for DM from 2017 to 2021. The search strategy and screening process were as follows (**Figure 1**; **Supplementary Figure 1**): TS = (stem cell* OR SC) AND TS = (diabet* OR diabetes mellitus OR DM) AND TS = (extracellular vesicle* OR EV OR exo*) AND Language = (English) AND Publication Date = (2017-01-01 to 2021-12-31). All documents that included the above search strategy were reviewed, but letters, case reports, withdrawals, bibliography, etc. were excluded. Publicly available data sets were analyzed in this study, and ethics statement was not required. All searches were conducted on 14 January 2022 to avoid bias related to database updates.

Data Collection

Two authors (HQ and RG) independently retrieved data and excluded studies irrelevant to the collection strategy. All data, including title, keywords, authors, institutions, etc., were extracted from the WoS and were eventually included in this study. A bibliometric analysis was performed using Microsoft Excel 2021, CiteSpace V, and VOSviewer.

The Bibliometric Analysis Method

Based on the data extracted from the WoS, we first analyzed the publication and citation trends of SC-EVs for diabetes and visualized them using Excel. Then, bibliometric analyses, including country and institution bibliographic coupling analysis, reference co-citation analysis, and keyword co-occurrence, were performed and visualized using CiteSpace V and VOSviewer. The newest edition of the Journal Citation Report (JCR) was used to obtain the latest impact factors (IF). The scimago journal and country rank (https://www.scimagojr.com/) and eigenfactor (http://www.eigenfactor.org/index.php) websites were used to obtain the H-index and eigen factor score, respectively.

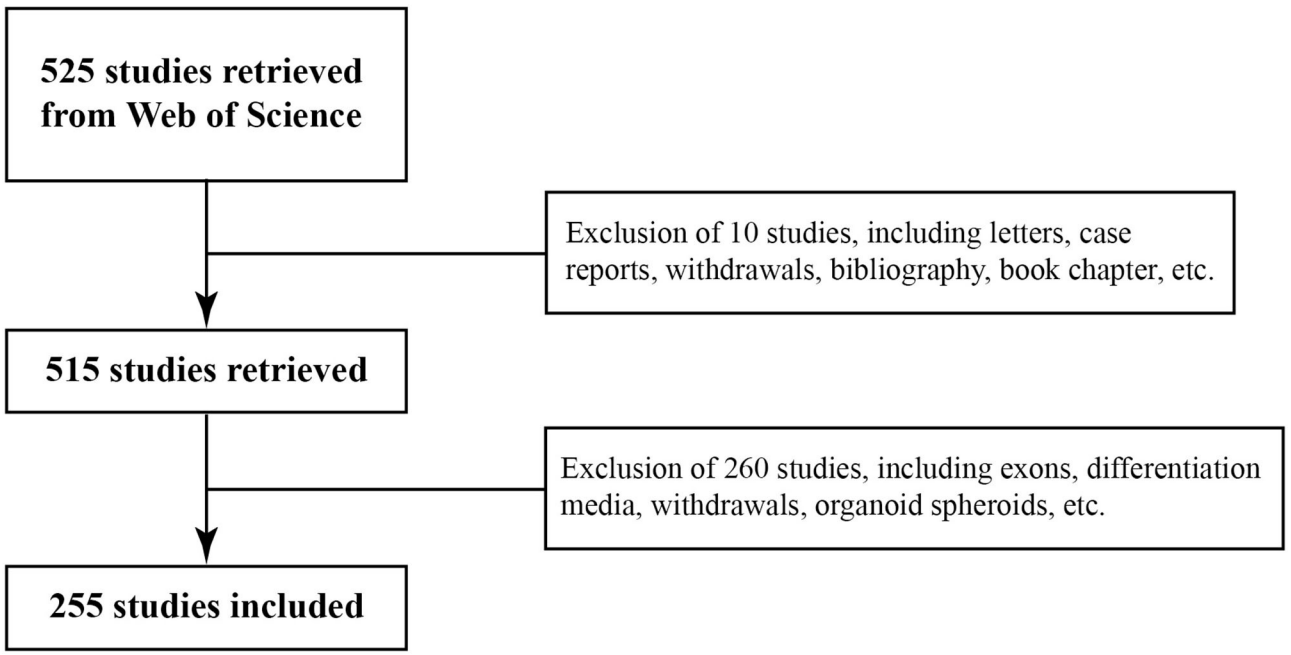

FIGURE 1 | Flow chart of the screening process for research on stem cell-derived extracellular vesicles (SC-EVs) for diabetes.

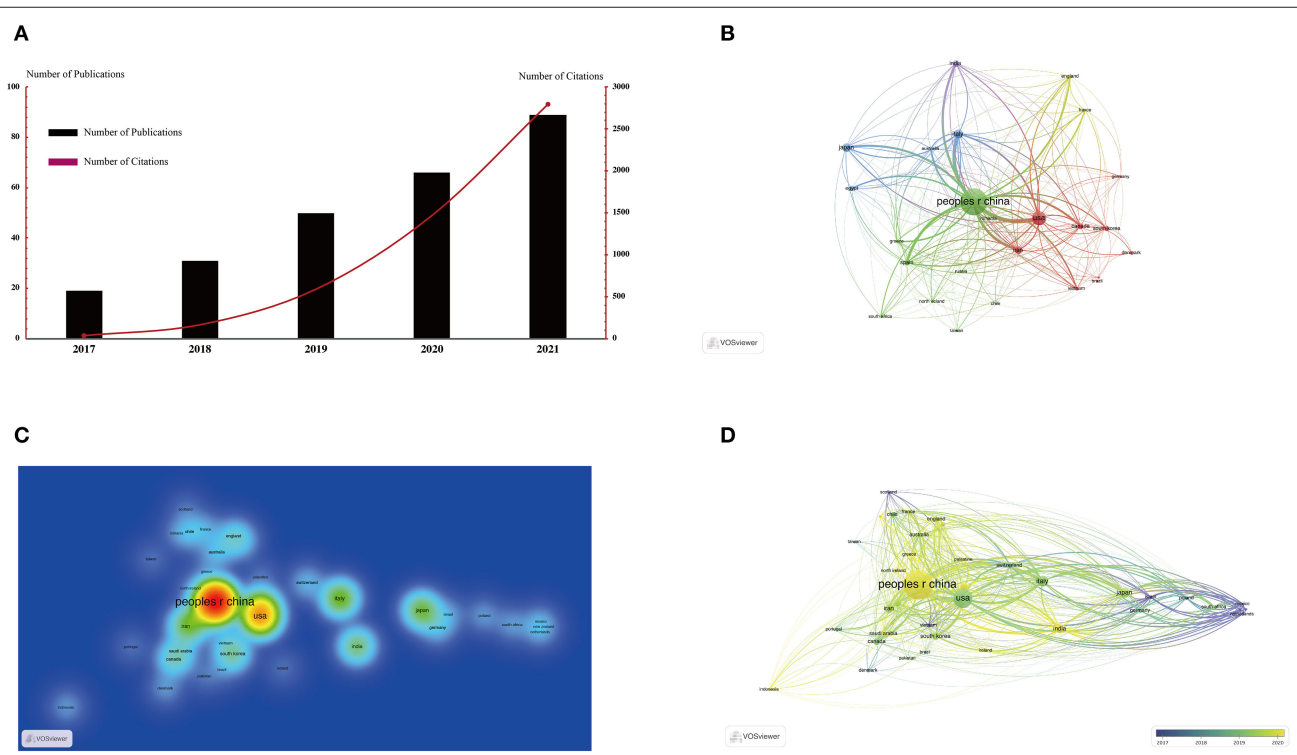

FIGURE 2 | Articles related to SC-EVs for diabetes published worldwide. **(A)** Annual publications and citations worldwide of SC-EVs for diabetes. **(B)** Network visualization of the country distribution of articles based on VOSviewer. The size of the circles signifies the number of publications, and the width of the connecting line between the two circles signifies the intensity of collaboration. **(C)** Density map of the country distribution of articles based on VOSviewer. **(D)** Chronological order of countries based on VOSviewer.

RESULTS

Publishing Trends and Global Contributions

A total of 255 articles were related to SC-EVs for DM according to the search strategy and were included in the final bibliometric analysis. Based on the number of annual publications (**Figure 2A**), the overall trend of publication research has significantly increased year by year, especially 2018–2019 (31–50 publications per year) and 2020–2021 (66–89 publications per year) as hot study periods. Notably, the citation trends show a more significant growth in 2018–2019 (169–593 citations per year) and 2020–2021 (1,472–2,798 citations per year), suggesting that the application of SC-EVs in the field of DM is receiving numerous attentions in general.

The global country distribution network of publications was visualized with VOSviewer, and the association strength method was used for normalization. The threshold for the minimum number of documents from a country was set at two, and a total of 23 countries met the threshold (**Figure 2B**). China (122 publications) was the most productive country, followed by the USA (50 publications) and Italy (16 publications). Subsequently, the density map was used to display all publishing centers more visually (**Figure 2C**). In terms of total citations, the top three countries were China (2,759 citations), the USA (1,167 citations), and Italy (366 citations). The countries with the highest total link strength were as follows: China (7,908), the USA (5,939), and Italy (3, 11), indicating that China and the USA have the predominant influence in this field. The top 10 countries with the most contributions are listed in **Table 1**. In addition, according to the year of concentration of country publications (**Figure 2D**), Mexico, the Netherlands, and New Zealand had publications mainly concentrated in 2017; The USA, Italy, and Japan had publications mainly concentrated in 2019; articles from China, Egypt, and India were mainly published after 2020.

Institutional Distribution Analysis

The top five institutions with the most publications are located in Italy and China. Turin University (eight publications) was the most productive institution, followed by the Central South University (seven publications), Shanghai Jiaotong University (seven publications), Tianjin Medical University (seven publications), and Sun Yat Sen University (seven publications). According to citations, Shanghai Jiaotong University (306 citations) has the highest citations, followed by Central South University (242 citations) and Shangdong University (239 citations). The top 20 institutions with the most publications are listed in **Table 2**.

Then, the close and complex collaborative relationships between the different institutions were analyzed with VOSviewer. The threshold for the minimum number of documents of an organization was set at four, and the top 20 institutions met the threshold and were presented in a network map by the year of concentration of institutional publications (**Figure 3A**). The result indicated that Turin University, Shanghai Jiaotong University, and Cent S University had publications mainly concentrated in 2019; articles from Sun Yat Sen University and Tianjin Medical University were mainly published after 2020.

Journal Distribution Analysis

Journal distribution analysis helps to understand the hot journals in the field of SC-EVs for DM. The journal Stem Cell Research and Therapy (IF = 6.832, 2020) with 15 publications, and the journal International Journal of Molecular Sciences (IF = 5.924, 2020) with 15 publications, published the most studies. The journals Frontiers in Endocrinology (IF = 5.555, 2020),

TABLE 1 | The top 10 countries that contributed publications on stem cell-derived extracellular vesicles (SC-EVs) for diabetes.

Country	Publications	Citations	Average citation rate
Peoples R China	122	2,759	22.61
Usa	50	1,167	23.34
Italy	16	366	22.88
Japan	14	219	15.64
India	11	167	15.18
Iran	10	299	29.90
South Korea	8	166	20.75
Egypt	8	127	15.88
Spain	7	159	22.71
Canada	6	42	7.00

TABLE 2 | The top 20 institutions with the most publications in the field of SC-EVs for diabetes.

Institutions	Publications	Citations	Average citation rate
Turin University	8	181	22.63
Central South University	7	41	5.86
Shanghai Jiaotong University	7	306	43.71
Sun Yat Sen University	7	117	16.71
Tianjin Medical University	7	114	16.29
Cairo University	6	126	21.00
Tongji University	5	173	34.60
Zhejiang University	5	205	41.00
Southern Medical University	5	74	14.80
Indian Inst Technol Kanpur	5	71	14.20
Harbin Medical University	5	69	13.80
Nantong University	5	48	9.60
Jinan University	5	43	8.60
Maryland University	4	70	17.50
Harvard Medical School	4	63	15.75
Peking University	4	36	9.00
Fourth Military Medical University	4	28	7.00
Huazhong University of Science and Technology	4	14	3.50
Cent S University	4	242	60.50
Shangdong University	4	239	59.75

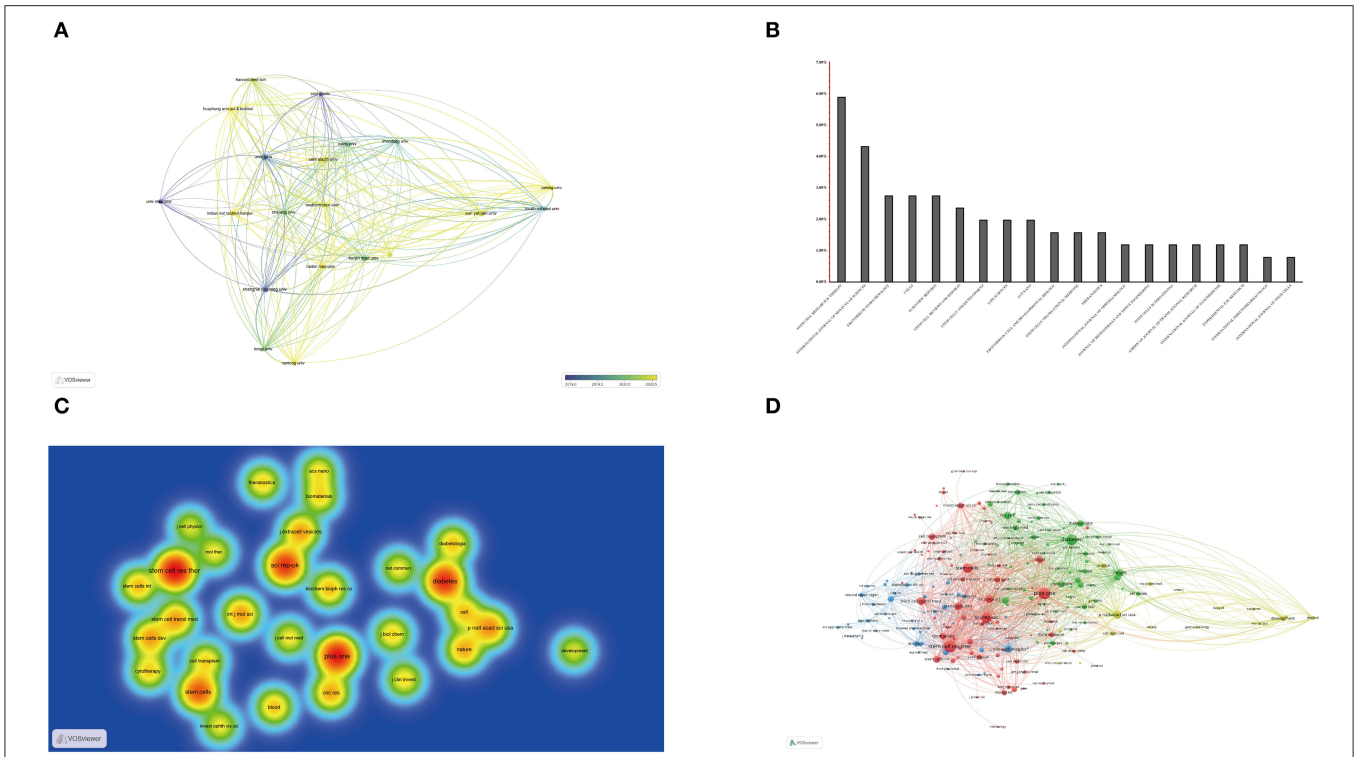

FIGURE 3 | Articles on SC-EVs for diabetes published in different institutions and journals. **(A)** Collaboration between institutions based on VOSviewer. **(B)** The top 20 journals produced the largest number of articles. **(C)** Density map of article reference distribution based on VOSviewer. **(D)** Network visualization of article reference distribution based on VOSviewer.

TABLE 3 | Impact index of the top 10 journals with the largest number of articles.

Journals	Impact factor	Eigen factor Score	H-index
Stem Cell Research & Therapy	6.832	76	76
International Journal of Molecular Sciences	4.556	98	162
Frontiers In Endocrinology	5.555	No records	68
Cells	6.6	No records	22
Scientific Reports	3.998	100	213
Stem Cell Reviews and Reports	5.739	73	73
Stem Cells and Development	3.272	91	114
Life Sciences	5.037	89	164
Acs Nano	15.881	100	382
Frontiers in Cell and Developmental Biology	6.684	No records	53

Cells (IF = 6.6, 2020), and Scientific Reports (IF = 4.35, 2020) had seven publications each. The top 20 journals with the most publications and the impact index of the top 10 journals with the largest number of articles are presented in **Figure 3B**; **Table 3**, respectively.

Then, reference co-citation analysis was performed to understand the close association between the referenced journals. The threshold for the minimum number of citations from a source was set at 20, and 210 journals met the threshold. The top 30 referenced journals were visualized in a density map, and all referenced journals were presented in a network visualization (**Figures 3C,D**). Stem Cell Research and Therapy, Scientific Reports, Diabetes (IF = 9.461, 2020), Plos One (IF = 3.24, 2020), and SCs (IF = 6.277, 2020) were the most thermal publication center, and they were most closely associated with other journals.

Author Distribution Analysis

The most productive authors with the highest number of publications and citations from 2017 to 2021 are listed in **Table 4**. ASHOK KUMAR, from the Indian Institute of Technology Kanpur, India ranked first (five publications), and other authors from Italy, China, and Egypt followed with four publications each. The number of article citations is an important indicator of an author's influence. The top 10 authors with the most citations were all from China. QING LI, from the Chinese Academy of Sciences, published only two articles, the number of citations reached 307 in total, suggesting that he has drawn tremendous achievements and attention in the field of SC-EVs for DM research. Then, we used CiteSpace to analyze and visualize the co-citation network of the top 10 references of the shortlisted publications (**Figure 4A**). The article published by Sun et al.

TABLE 4 | The top authors in the field of SC-EVs for diabetes ranked by publication and citation numbers.

	Author	Country	Affiliation	Publications	Citations
Top publications (n ≥ 4)	Ashok Kumar	India	Indian Institute of Technology Kanpur	5	71
	Giovanni Camussi	Italy	University of Turin	4	99
	Fang Liu	China	Shanghai Jiao Tong University Affiliated Sixth People's Hospital	4	92
	Dina Sabry	Egypt	Cairo University	4	86
	Anamika Singh	India	Indian Institute of Technology Kanpur	4	70
	Chiara Gai	Italy	University of Turin	4	63
	Wei Wang	China	Central South University	4	43
	Xiao Lin	China	Central South University	4	25
	Yi Wang	China	Central South University	4	25
Top Citations (n ≥ 300)	Qing Li	China	Chinese Academy of Sciences	2	307
	Weiyang Gao	China	Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University	2	303
	Bo lei	China	Xi'an Jiaotong University	2	303
	Cai lin	China	First Affiliated Hospital of Wenzhou Medical University	2	303
	Cong Mao	China	Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University	2	303
	Chenggui Wang	China	Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University	2	303
	Min Wang	China	Xi'an Jiaotong University	2	303
	Tianzhen Xu	China	Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University	2	303
	Xingxing Zhang	China	First Affiliated Hospital of Wenzhou Medical University	2	303
	Ying Wang	China	Chinese Academy of Sciences	3	301

in ACS NANO in 2018 (doi: 10.1021/acsnano.7b07643) was a hub node in the co-citation network, followed by the article published by Li et al. in Experimental and Molecular Medicine in 2018 (doi: 10.1038/s12276-018-0058-5). To better understand the scientific frontiers of the field on SC-EVs for DM, we analyzed the references using the burst detection function (the minimum duration threshold was set as one) in CiteSpace. The top 25 references with the strongest citation bursts are presented in **Figure 4B**, and none of the articles had sudden changes in the number of citations in the last 3 years.

A title cluster analysis was implemented to generalize the references in the co-citation network to understand the frontier directions. The references in the co-citation network were divided into nine different clusters, including diabetic wound, human umbilical cord, kidney diseases, hypothesis evidence, cell–cell communication, cell-derived EV, engineered exosome, key miRNA, and tissue repair (**Figure 4C**). Based on the clustering display of the timeline, it can be found that the early publications focus on tissue repair and intercellular communication, and the publications in the last 5 years were mainly based on diabetic wound, kidney diseases, and engineered exosome. The top 10 references with the most total citations in the field of SC-EVs for diabetes are listed in **Table 5**.

Keyword Co-occurrence Cluster Analysis

Keywords represent the central topic of a publication, and keyword co-occurrence analysis helps to systematically understand the hot topics and current progress of SC-EVs for diabetes and their intrinsic connections. VOSviewer was used to analyze keywords, and the threshold was set at a minimum of five occurrence of a keyword in the titles and abstracts of the included publications. A total of 112 keywords were identified and were mainly divided into seven different clusters: EVs, exosomes, angiogenesis, SCs, mesenchymal SCs, diabetes, and oxidative stress (**Figures 5A,B**). In the overlay visualization, keywords were shown in different colors with their annual distribution according to the average year of publication (**Figure 5C**). For example, "microvesicles," "conditioned medium," and "microRNAs" appeared mainly in early 2019, while the keywords "inflammation," "exosome," and "angiogenesis" have emerged in recent years. The keywords that have emerged in recent years bode well for the growing

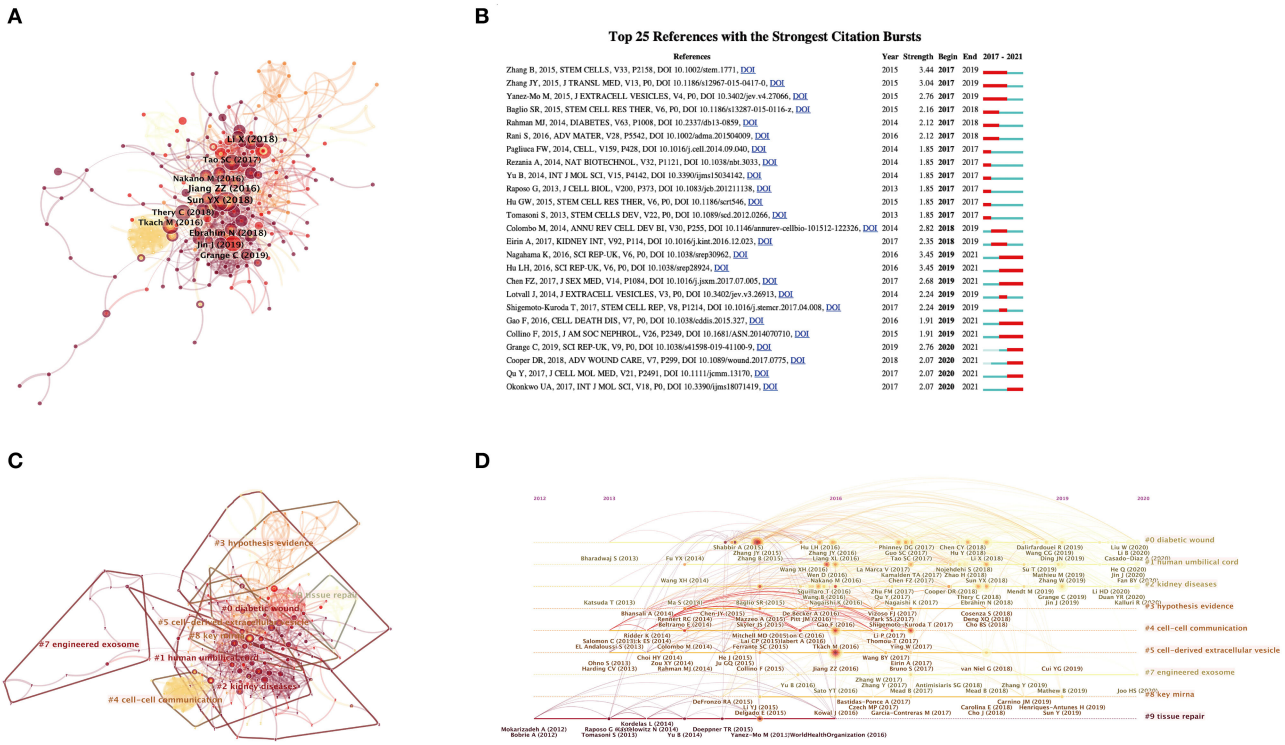

FIGURE 4 | Mapping of references in studies on SC-EVs for diabetes. **(A)** A simplified co-citation network of references on SC-EVs for diabetes based on CiteSpace, and burst references are represented by red nodes. **(B)** The top 25 references with the strongest citation bursts based on CiteSpace. **(C)** Title clustering analysis of the co-citation network based on CiteSpace. **(D)** Timeline visualization of references from 2012 to 2020.

popularity of these areas, which may become hot in the future. At the same time, co-occurrence cluster analysis was also performed in CiteSpace. The top 25 keywords with the strongest citation bursts (the minimum duration threshold was set as one) are presented in **Figure 5D**, and none of the keywords had sudden changes in the number of citations in the last 3 years. Based on the timeline clustering display, it can be found that angiogenesis, diabetic nephropathy, diabetic wound healing, embryonic SCs, miRNA, cell therapy, and mitochondrial transfer have been the hot topics of research in recent years and show the direction of future research.

DISCUSSION

Diabetes mellitus is a metabolic disease caused by islet dysfunction or insulin action disorder, and its incidence has increased steeply in the last decade (14). Long-term hyperglycemia causes complications in various organs such as kidneys, nerves, and blood vessels. It has the characteristics of slow onset, long duration, and prolonged disease progression, which eventually leads to the loss of self-care ability and even death of patients. At present, clinical control of diabetes is mainly through medication, diet control, and insulin injection therapy, and a combination with symptomatic treatment to control diabetic complications, but the effect is still unsatisfactory (2). Therefore, there is an urgent need for new therapeutic interventions for DM and its complications.

Published research in the field of diabetes continues to increase year by year, and the intervention and management of diabetes have attracted widespread attention (15). In recent years, SCs are hotspots of regenerative medicine research and have broad application prospects in the treatment of various complex diseases. The continuous breakthrough of SC technology is expected to change the existing clinical treatment model and become a new biological therapy following traditional treatments, such as drugs and surgery (16). However, the potential tumorigenic risk and the difficulties of storage and transport of SCs have led to slow advancement in the clinical translation of cell therapy. EVs are nanosized particles secreted by cells, which contain a variety of biologically active substances, such as lipids, proteins, and RNAs, and play an important role in intercellular communication, cell survival and apoptosis, and the regulation of disease progression. Interestingly, numerous previous studies have shown that SC-EVs, especially exosomes, have repairing effects similar to SCs without the risk of tumor formation and can be stably preserved for transport, which has attracted a great deal of attention from researchers (2, 17). To explore the process and trend of SC-EVs for DM, this study conducted a bibliometric analysis of the publication on SC-EVs for DM from 2017 to 2021.

TABLE 5 | The top 10 references with the most citations in the field of SC-EVs for diabetes.

Title	Corresponding author	Journal	IF	Publication year	Total citations	Level of evidence
Immunoregulatory Mechanisms of Mesenchymal Stem and Stromal Cells in Inflammatory Diseases	Ying Wang	NATURE REVIEWS NEPHROLOGY	28.314	2018	281	Review
Exosomes From Adipose-Derived Stem Cells (SCs) Attenuate Adipose Inflammation and Obesity Through Polarizing M2 Macrophages and Beiging in White Adipose Tissue	Qun Wang	DIABETES	9.461	2018	213	*In vitro*, animal
Engineering Bioactive Self-Healing Antibacterial Exosomes Hydrogel for Promoting Chronic Diabetic Wound Healing and Complete Skin Regeneration	Cong Mao	THERANOSTICS	11.556	2019	198	*In vitro*, animal
Chitosan Wound Dressings Incorporating Exosomes Derived from MicroRNA-126-Overexpressing Synovium Mesenchymal SCs Provide Sustained Release of Exosomes and Heal Full-Thickness Skin Defects in a Diabetic Rat Model	ChangQing Zhang	STEM CELLS TRANSLATIONAL MEDICINE	6.94	2017	147	*In vitro*, animal
Exosomal DMBT1 from human urine-derived SCs facilitates diabetic wound repair by promoting angiogenesis	Hui Xie	THERANOSTICS	11.556	2018	135	*In vitro*, animal
MSC-derived Extracellular Vesicles Attenuate Immune Responses in Two Autoimmune Murine Models: Type 1 Diabetes and Uveoretinitis	Ryang Hwa Lee	STEM CELL REPORTS	7.765	2017	131	*In vitro*, animal
Human Mesenchymal SC-Derived Exosomes Alleviate Type 2 Diabetes Mellitus by Reversing Peripheral Insulin Resistance and Relieving beta-Cell Destruction	Hui Qian	ACS NANO	15.881	2018	127	*In vitro*, animal
Exosomes from adipose-derived SCs overexpressing Nrf2 accelerate cutaneous wound healing by promoting vascularization in a diabetic foot ulcer rat model	Maoquan Li	EXPERIMENTAL AND MOLECULAR MEDICINE	8.718	2018	124	*In vitro*, animal, human
Efficient Angiogenesis-Based Diabetic Wound Healing/Skin Reconstruction through Bioactive Antibacterial Adhesive Ultraviolet Shielding Nanodressing with Exosome Release	Bo Lei	ACS NANO	15.881	2019	105	*In vitro*, animal
GMSC-Derived Exosomes Combined with a Chitosan/Silk Hydrogel Sponge Accelerates Wound Healing in a Diabetic Rat Skin Defect Model	Ximin Guo	FRONTIERS IN PHYSIOLOGY	4.566	2017	92	*In vitro*, animal

Bibliometrics is now widely used in various fields of global research, helping researchers to gain an intuitive and systematic understanding of a field and to identify significant scientific achievements and future research hotspots. Statistics on the number and citation frequency of SC-EVs used in DM publications show that the number of publications and the frequency of citations have increased significantly over the past 5 years, indicating that this field is a current research hotspot (**Figure 2A**). Notably, more than half of the top 20 journals in this field have an IF above five, which means that the topic of SC-EVs for DM has attracted a lot of attention (**Figure 3B**). Therefore, more in-depth studies will be conducted to explore the feasibility and mechanism of action of SC-EVs for the treatment of DM.

To better understand the national and regional contributions in this field, a national distribution analysis of publications was performed. China ranks first in the world in terms of total number of publications and citations, but the average citation rate in China (22.61) is lower than that of the USA (23.34), Iran (29.9), and Italy (23.34), which means that China still needs to improve the quality of publications (**Table 1**). A recent bibliometric study on diabetes showed that India, the USA, China, South Korea, and Brazil were the most productive

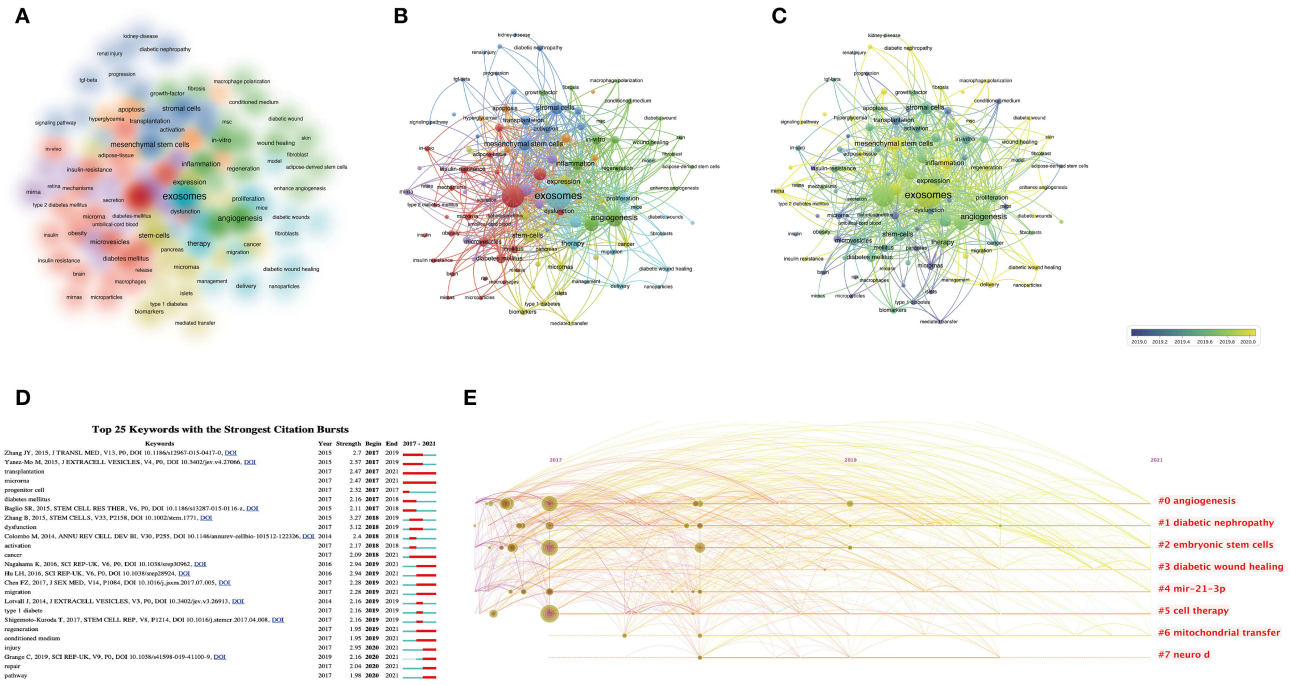

FIGURE 5 | Keyword mapping in studies on SC-EVs for diabetes. **(A)** Clustering analysis of key words based on VOSviewer. **(B)** Network visualization of keywords based on VOSviewer. **(C)** Chronological order of keywords based on VOSviewer. **(D)** The top 20 keywords with the strongest citation bursts based on CiteSpace. **(E)** Keyword timeline visualization from 2017 to 2021.

countries (18). Among them, the average citation rate of the USA remains at the top, but China's development trend is strong and is expected to overtake the USA. The contribution of research institutions is an important part of the country's contribution in this field. For the total publication volume, 75% of the top 20 institutions are located in China, with Shanghai Jiaotong University having the highest number of citations (**Table 2**). In terms of temporal distribution (**Figure 2D**), China mainly focuses on the use of SC-EVs for the treatment of diabetes after 2020, which shows that China has attached great importance to the application of SC-EVs as a biological therapy for the treatment of DM and its complications in recent years.

In terms of author distribution (**Table 4**), ASHOK KUMAR (Indian Institute of Technology Kanpur) from India is the most productive and has a certain number of citations. GIOVANNI CAMUSSI (University of Turin) from Italy published the second highest number of papers, but has the highest number of citations in the top publishing authors. Notably, QING LI (Chinese Academy of Sciences) from China has published only two studies in this field, but the number of citations is as high as 307 citations, which is the highest average citation rate among all researchers. The article by Shi (doi: 10.1038/s41581-018-0023-5) had the largest number of citations in the co-citation network, and Ying Wang was the corresponding author (**Table 5**). However, Ying Wang and his team mainly reviewed the immunomodulatory mechanism of mesenchymal SCs and their therapeutic applications, and did not provide a detailed overview of the application of SC-EVs in the field of DM (19). The articles by Sun (doi: 10.1021/acsnano.7b07643) and Li (doi: 10.1038/s12276-018-0058-5) are hub nodes in the co-citation network (**Figure 4A**). Sun et al. (20) found that human umbilical cord mesenchymal SC-derived exosomes reversed peripheral insulin resistance and attenuated islet β-cell destruction in type 2 diabetes by improving glucose utilization in peripheral tissues, increasing glycogen storage in the liver, and reducing islet β-cell apoptosis. Li et al. (21) applied adipose SC-derived exosomes to diabetic foot ulcers and found that adipose SC-derived exosomes accelerate chronic wound healing by promoting wound vascularization, epithelialization, and reducing inflammation and oxidative stress. It is evident that SC-EVs, especially exosomes, have broad application prospects in the treatment of DM and its complications.

A title cluster analysis of the references and a keyword co-occurrence cluster analysis of the publications were performed to summarize the latest hot trend of SC-EVs for DM. For the cluster analysis of references and distribution in a timeline (**Figure 4D**), researchers were particularly interested in EVs for intercellular communication and organizational repair research in 2016, and then researchers seemed to focus more on the microRNA repair mechanism of EVs and the clinical transformation of engineered exosomes. For instance, Yan et al. (22) used milk-derived exosomes as a delivery medium for miR-31-5p, which could effectively promote the healing of diabetic wounds. In terms of the cluster analysis of publications and their distribution in a

timeline (**Figures 5B,E**), it is not difficult to find that SC-derived exosomes can improve DM and its complications (especially diabetic wounds and diabetic nephropathy) through various mechanisms such as improving insulin resistance, promoting vascularization, and regulating inflammation, which is a current research hotspot.

This study extracted the relevant publications on SC-EVs for DM and its complications in the WoS database and fully analyzed the current hotspot trend, but there is still a certain limit. For example, we only analyze English language publications, resulting in possibly ignoring non-English quality documents. Therefore, subsequent collaboration with researchers from other countries should be initiated to achieve more in-depth and comprehensive analysis results.

CONCLUSION

In summary, this study provides a comprehensive summary and analysis of the global research trends of SC-EVs used in DM and its complications. In the past 5 years, relevant high-quality publications in this field have increased significantly, and SC-EVs s have a good prospect for development in the treatment of DM and its complications.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JX and YY were responsible for the study design and administrative support. HQ and RG were responsible for data collection. JY were responsible for analyzing the data. JX and HQ were responsible for manuscript drafting. YZ revised this manuscript. All authors critically reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.868440/full#supplementary-material

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The Association Between FGF21 and Diabetic Erectile Dysfunction: Evidence from Clinical and Animal Studies

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Erectile dysfunction (ED), a complication of diabetes mellitus (DM), affects 50–75% of men with diabetes. Fibroblast growth factor 21 (FGF21) is a liver-derived metabolic regulator which plays a role in insulin-independent glucose uptake in adipocytes. We designed a clinical study and an animal experiment to investigate the relationship between FGF21 and DM-induced ED. The clinical study enrolled 93 participants aged > 18 years (61 patients with type 2 DM and 32 healthy controls) from Taian City Central Hospital (TCCH) in Shandong Province, China, amongst whom the association between serum FGF21 and diabetic ED was analyzed. To further validate this association, we developed animal model of diabetic ED using Sprague-Dawley (SD) rats. Serum FGF21 concentration and FGF21 mRNA expression in penile samples of the rats were determined with Western blotting and quantitative real-time PCR. Among the 93 participants, the level of serum FGF21 was negatively correlated with the IIEF-5 score (r = -0.74, $P < 0.001$). The analysis on the performance of FGF21 for ED diagnosis showed that the area under the receiver operating characteristic (ROC) curve was 0.875 (95% confidence interval [CI]: 0.803 to 0.946). In the animal experiment, the levels of serum FGF21, $2^{-\Delta\Delta Ct}$ values of FGF21 mRNA expression, and relative levels of FGF21 in penile samples were higher in the ED group compared to the DM and control groups. Our findings demonstrated an association between the FGF21 level and diabetic ED, indicating the potential of this cytokine in predicting diabetic ED.

Keywords: fibroblast growth factor 21, erectile dysfunction, diabetes mellitus, diagnosis, clinical study, rat

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INTRODUCTION

The prevalence of diabetes mellitus (DM) has been growing at an alarming speed, affecting 8.4% of adults in 2017, accounting for 9.9% of global all-cause death (1). As a metabolic disorder resulting from defective insulin secretion and insulin action, DM is characterized by a state of hyperglycemia (2). The complications of DM, including vascular disease, neuropathy, nephropathy, eye disease, and erectile dysfunction (ED), are the major sources of DM-related mortality and morbidity (3, 4). DM-induced erectile dysfunction (DMED) impacts roughly 50–75% of men with DM (5, 6). The prevalence of ED is three times higher in diabetic men versus the general male population, among whom the onset of ED is up to 10 years earlier than those without diabetes (7). The development of ED is a multifactorial process involving changes in vascular dilatation capacity, peripheral sympathetic activity, and endothelial function (5). Hyperglycemia is one of the contributors of endothelial lesions and vasculogenic dysfunction, which are the main causes of DMED (2).

The fibroblast growth factor (FGF) family consists of 22 members that display multiple biological functions, such as improving insulin sensitivity, glucose and lipid metabolism (8, 9). FGF21, mainly expressed in the liver and adipocytes, plays a role in ameliorating glucose tolerance and insulin sensitivity *via* regulating glucose uptake in adipocytes and restraining glucose production in hepatocytes (10, 11). Research has demonstrated that FGF21 protects a variety of cells (*e.g.*, islet β-cells, endothelial cells, cardiomyocytes, and dopaminergic neurons) from acute injuries (12). In addition, studies have reported the preventive effect of FGF21 on atherosclerosis and coronary artery disease (CAD) through protecting endothelial function and antioxidation (13, 14). Since endothelial dysfunction is one of the pathophysiological pathways of ED, it is hypothesized that FGF21 is associated with ED in men with diabetes. Here we conducted a clinical study and an animal experiment to investigate the association between FGF21 and diabetic ED.

METHODS

Study Participants

We randomly recruited 31 adult men with type 2 diabetes mellitus (T2DM), 30 patients with DMED and 32 healthy controls from Taian City Central Hospital (TCCH) in Shandong Province between January 2017 and June 2018.

Inclusion criteria of T2DM patients were as follows: (1) diagnosed in accordance with American Diabetes Association criteria (15); (2) age > 18 years; (3) not enrolled in other clinical studies; (4) the International Index of Erectile Function (IIEF-5) score > 21. Inclusion criteria of DMED patients were as follows: (1) diagnosed in accordance with American Diabetes Association criteria; (2) age > 18 years; (3) not enrolled in other clinical studies; (4) IIEF-5 score≤21. Exclusion criteria were as follows: (1) patients with severe diseases, such as cardiovascular disease (CVD), stroke, cancers, hypothyroidism, tuberculosis, or communicable diseases; and (2) patients with psychiatric conditions. The Ethical Committee of TCCH approved this study (No. 2017-06-27). Informed consent was obtained from each study participant.

Physical and Biochemical Examinations

Participants' demographics, disease history, and anthropometric data were collected through face-to-face interviews. Trained clinicians examined participants' external genitalia (i.e., penis shape, size, nerve reflexes, and skin sensations). IIEF-5 was developed to identify the presence or absence of ED on the basis of the National Institute of Health (NIH) definition of ED. The five items reflected erectile function and intercourse satisfaction of respondents (16). The degree of ED was defined based on the IIEF-5 score: severe ED (0–7), moderate ED (8–11), mild ED (12–21), and normal function (22–25) (17, 18).

All participants were asked to fast overnight for ≥ 10 h before blood samples were taken. Serum FGF-21 levels were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Kanglang Biotechnology, Shanghai, China). Fasting blood glucose (FBG) was measured with an automatic analyzer (Hitachi, Tokyo, Japan). Glycated hemoglobin A1c (HbA1c) was detected *via* high-performance liquid chromatography (Bio-Rad Laboratories, CA, USA). Total cholesterol (TC), triglycerides (TG), mean platelet volume (MPV), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were determined with an automatic analyzer (Hitachi, Tokyo, Japan). Fasting insulin (FINS) and testosterone were measured *via* electrochemiluminescence assay (Roche Diagnostics, Basel, Switzerland). Homeostasis model assessment of insulin resistance (HOMA-IR) was conducted based on the following formula:

$$\mathrm{HOMA-IR} = \mathrm{FINS(mU/L)} \times \text{fasting glucose (mmol/L)}/22.5$$

Animals

The association between FGF21 and diabetic ED was validated in specific pathogen-free (SPF) Sprague-Dawley (SD) rats. Forty male rats aged 8 weeks were provided by Hunan Slac Jingda Laboratory Animal Co., Ltd (Changsha, China). The 10 rats in the control group were treated with an injection of 0.9% normal saline (NS). To develop T2DM models, 30 rats were randomly selected and treated with streptozotocin at 60 mg/kg body weight *via* intraperitoneal injection. The rats that had a fasting blood glucose level ≥ 16.7 mmol/L on the 3th and 7th day after the injection were defined diabetic. Twelve weeks later, 25 of the 30 rats injected with streptozotocin had survived. Five rats that died during streptozotocin administration were excluded from this study. Then apomorphine (APO) test was conducted to assess erectile function in rats. After weighing, erectile responses were assessed by injection of APO (80 mg/kg, subcutaneously) in the loose skin of the back of the neck. Then the rats were placed in a dark and quiet room for 30 min, and the number of erections was recorded. A penile erection was regarded to occur complete emergence of an engorged glans penis and distal penile shaft. Twelve rats without penile erection were diagnosed as DMED rats (19).

Penile tissues were obtained from the rat post-executed by dislocation, and stored in 10% paraformaldehyde solution at -80 °C for further examinations. The FGF21 levels in serum in the DM, DMED, and control groups were detected with an ELISA kit (Cusabio Biotech CO. LTD, Wuhan, China) according to the manufacturer's instructions.

Western Blotting

The target protein in the rat penile samples was analyzed using Western blotting assay. Briefly, triturated frozen penile samples were lysed on ice for 30 min in lysis buffer (150 mM NaCl, 20 mM Tris-HCl, pH 7.4, 0.1% SDS, 1.0% NP-40, 0.5% Na-deoxycholate, 0.2 mM PMSF, and protease inhibitor cocktails). The lysates were centrifuged at 12,000 r for 20 min and separated in 10% polyacrylamide gel. The samples were next transferred to polyvinylidene fluoride (PVDF) membranes, blocked with 5% skimmed milk for 60 min, and probed with the primary antibodies of FGF21 at 4°C overnight. The blots were then incubated with horseradish peroxidase–conjugated anti-IgG for 1h at room temperature and detected using ECL Western Blotting Detection Reagents (Thermo Scientific Pierce, Rockford, IL, USA).

Quantitative Real-Time PCR

Quantitative real-time PCR (qRT-PCR) was employed to measure relative levels of FGF21 mRNA. Briefly, total RNA was isolated from the penile samples with Trizol reagent (Invitrogen, Grand Island, NY, USA). The amount of RNA in each sample was identified by absorbance at 260 nm. The following primers synthesized by TaKaRa (Dalian, China) were used: forward primer (5'-GGGTCAAGTCGACAGGTAT-3') and reverse primer (5'- ATCAAAGTGGAGGCGATAGA-3'). The cDNAs were synthesized with MuLV Reverse Transcriptase (Applied Biosystems, CA, USA). The qRT-PCR method was used with a Rotor-Gene Q real-time PCR cycler (Qiagen, Germany) and a SYBR-green PCR master mix kit (Applied Biosystems, CA, USA). Relative mRNA levels were quantified using the $2^{-\Delta\Delta Ct}$ method and normalized *via* β-Actin mRNA. Each experiment was repeated five times.

Statistical Analysis

The Kolmogorov-Smirnov test was used to check the normal distribution of variables. Continuous data that were normally distributed were presented as means and standard deviations (SDs). The statistical significance between groups was tested using one-way analysis of variance (ANOVA), followed by the Student–Newman–Keuls (SNK) test and Pearson's correlation. Continuous variables with a non-normal distribution were represented as the median (P25-P75) and were compared with the Wilcoxon rank-sum test. Spearman correlation analysis was used to calculate the correlation coefficient between IIEF-5 scores and relevant parameters for all participants. The multiple linear regression model and Logistics regression analyses were used to analyze the DMED-related factors. The receiver operating characteristic (ROC) curve was modeled to analyze the performance of circulating FGF21 levels for DMED diagnosis. Statistical analyses were carried out in SPSS software (v25.0, SPSS Inc. Chicago, USA). A probability value of less than 0.05 was considered statistically significant for each test.

RESULTS

Characteristics of Study Participants

The clinical characteristics of all participants enrolled in the human study appear in **Table 1**. Among the 61 diabetic men, the

TABLE 1 | Characteristics of study participants in human study.

Variables	DMED(n = 30)	DM(n = 31)	Control(n = 32)	$F/Z/\chi^2$	P
Age (years)	49.83 ± 6.14	48.32 ± 6.69	48.31 ± 4.94	0.658	0.521
Education years	11.57 ± 3.64	11.97 ± 3.75	11.06 ± 3.44	0.499	0.609
Smoking (%)	11 (36.7)	11 (35.5)	12 (37.5)	0.028	0.986
Alcohol drinking (%)	12 (40.0)	11 (35.5)	10 (31.3)	0.518	0.772
BMI (kg/m^2)	25.15 ± 3.01	24.63 ± 3.69	24.34 ± 2.34	0.548	0.580
SBP (mmHg)	134.10 ± 9.07 #	131.06 ± 8.85	128.06 ± 6.79	4.118	0.019
DBP (mmHg)	84.97 ± 7.39 #	80.35 ± 8.50	79.81 ± 5.84	4.586	0.013
HbA1c (%)	8.09 ± 1.02 #	7.96 ± 1.39 #	5.30 ± 0.28	77.753	<0.001
FBG (mmol/l)	8.51 ± 1.15 #	8.02 ± 1.02#	5.13 ± 0.37	126.196	<0.001
TC (mmol/L)	4.97 ± 0.53 #	4.76 ± 0.52 #	4.11 ± 0.30	29.751	<0.001
TG (mmol/L)	2.13 ± 0.39 #	1.96 ± 0.32 #	1.35 ± 0.29	47.346	<0.001
LDL-C (mmol/L)	2.97 ± 0.43 #	2.82 ± 0.31 #	2.24 ± 0.34	35.816	<0.001
HDL-C (mmol/L)	1.13 ± 0.23 #	1.11 ± 0.25 #	1.30 ± 0.25	6.153	0.003
FGF21(pg/mL)	112.46 ± 9.16*#	103.97 ± 6.20 #	91.94 ± 3.89	73.372	<0.001
Testosterone (ng/ml)	5.02 ± 0.62 #	5.25 ± 0.55 #	6.25 ± 0.42	46.833	<0.001
FINS (uIU/ml)	9.06 ± 1.94 #	8.58 ± 1.23 #	7.88 ± 1.05	5.158	0.008
MPV (fL)	9.83 ± 1.51 #	9.28 ± 1.18 #	8.62 ± 0.75	8.200	0.001
HOMA-IR	3.44 ± 0.91 #	3.07 ± 0.63 #	1.8 ± 0.25	54.765	<0.001
IIEF-5 scores	12.00(7.75,16.00)*#	23.00(22.00,23.00)*#	24.00(23.00,24.00)	70.385	<0.001

*BMI, body mass index; DBP, Diastolic blood pressure; FBG, Fasting blood glucose; FGF21, Fibroblast growth factor 21; FINS, Fasting insulin; HbA1c, Hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IIEF-5, international index of erectile function-5; LDL-C, low-density lipoprotein cholesterol; MPV, mean platelet volume; TC, cholesterol; TG, triglycerides; SBP, Systolic blood pressure; *P < 0.05 compared with DM group; #P < 0.05 compared with the controls.*

30 with ED were enrolled in the DMED group; the 31 participants without ED were in the DM group. Among the 30 participants in the DMED group, 7 ED cases (23.3%) were severe, 8 (26.7%) were moderate, and 15 (50%) were mild.

No significant differences were identified in participants' age, alcohol consumption, smoking habits, education level, and body mass index between the DMED, DM, and healthy control groups. Levels of serum FGF21 in the DMED group were significantly higher than in the DM and control groups ($P < 0.05$). Levels of HbA1c, systolic blood pressure (SBP), diastolic blood pressure (DBP), FBG, TC, TG, HDL-C, LDL-C, HOMA-IR, MPV and FINS were higher in the DMED group than in the control group ($P < 0.05$). No differences were identified between the DMED and DM groups. Testosterone and IIEF-5 score were significantly lower in DMED cases compared to controls ($P < 0.05$).

Correlation Between Serum FGF21 Level and IIEF-5 Score

A spearman correlation analysis was conducted to explore the relationships among IIEF-5 scores and relevant parameters for all participants. As depicted in **Figure 1**, a negative correlation was observed between the serum FGF21 level and IIEF-5 score (r_s = -0.738, $P < 0.001$). As listed in **Table 2**, SBP, DBP, HbA1c, FBG, TC, TG, HOMA-IR, FINS, MPV, and LDL-C were negatively correlated with IIEF-5 scores. Moreover, the serum FGF21 level was negatively correlated with HDL (r = -0.414, $P < 0.001$) and testosterone (r = -0.716, $P < 0.001$), respectively. Meanwhile, the serum FGF21 level was positively correlated with SBP (r = 0.386, $P < 0.001$), DBP (r = 0.336, $P = 0.001$), HbA1c (r = 0.656, $P < 0.001$), FBG (r = 0.749, $P < 0.001$), TC (r = 0.676, $P < 0.001$), TG (r = 0.712, $P < 0.001$), LDL-C (r = 0.694, $P < 0.001$), MPV (r = 0.374, $P < 0.001$), HOMA-IR (r = 0.675, $P < 0.001$), and FINS (r = 0.293, $P = 0.004$), respectively.

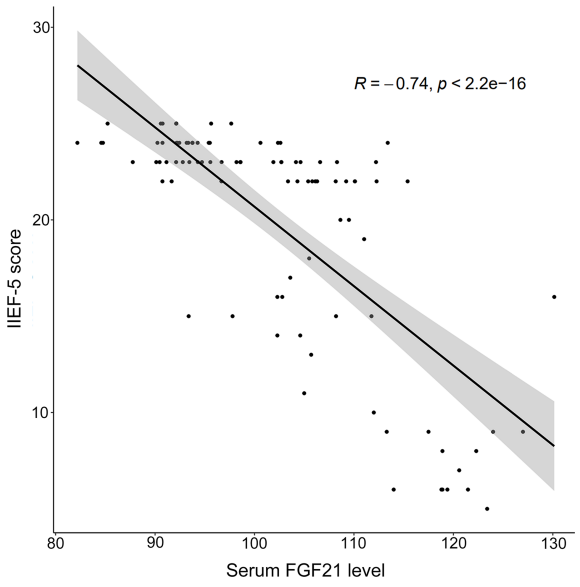

FIGURE 1 | The Spearman correlation between serum FGF21 and IIEF-5 score in human study.

TABLE 2 | Correlation analysis on serum FGF21 level and IIEF-5 score in human study.

Variables	IIEF-5		FGF21	
	r_s	*P*	*r*	*P*
Age (year)	-0.108	0.303	0.062	0.552
Education year	-0.104	0.323	0.052	0.619
Smoking	0.034	0.745	-0.005	0.963
Alcohol drinking	0.070	0.505	0.063	0.550
BMI (kg/m^2)	-0.236	0.023	0.123	0.240
SBP (mmHg)	-0.388	<0.001	0.386	<0.001
DBP (mmHg)	-0.320	<0.001	0.336	0.001
HbA1c (%)	-0.698	<0.001	0.656	<0.001
FBG (mmol/l)	-0.716	<0.001	0.749	<0.001
TC (mmol/L)	-0.641	<0.001	0.676	<0.001
TG (mmol/L)	-0.688	<0.001	0.712	<0.001
LDL-C (mmol/L)	-0.645	<0.001	0.694	<0.001
HDL-C (mmol/L)	0.299	0.004	-0.414	<0.001
Testosterone (ng/ml)	0.706	<0.001	-0.716	<0.001
FINS (uIU/ml)	-0.397	<0.001	0.293	0.004
MPV (fL)	-0.305	0.003	0.374	<0.001
HOMA-IR	-0.665	<0.001	0.675	<0.001

BMI, body mass index; DBP, Diastolic blood pressure; FBG, Fasting blood glucose; FGF21, Fibroblast growth factor 21; FINS, Fasting insulin; HbA1c, Hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IIEF-5, international index of erectile function; LDL-C, low-density lipoprotein cholesterol; MPV, mean platelet volume TC, cholesterol; TG, triglycerides; SBP, Systolic blood pressure.

Multiple Linear Regression and Logistics Regression Analyses on DMED-Related Factors

A multiple linear regression model was established to screen DMED-related factors. As shown in **Table 3**, FGF21 was one of the independent determinants significantly associated with the IIEF-5 score.

In order to evaluate the effects of these factors on DMED, we performed multiple logistic regression analyses. As shown in **Table 4**, the odds ratios (ORs) and 95% confidence intervals (CIs) were 1.193 (1.073 to 1.326) for FGF21, and 10.765 (2.277 to 50.895) for HOMA-IR and 24.373 (1.007to 610.416) for HDL.

Role of FGF21 in DMED Diagnosis

To detect the performance of FGF21 for discrimination of DMED from DM patients and control group, we established a ROC curve. As presented in **Figure 2A**, the area under the curve (AUC) of FGF21 was 0.875 (95% CI: 0.803 to 0.946 P < 0.001). A cut-off value of FGF21 (102.75 pg/ml) was selected with a sensitivity of 0.867 and a specificity of 0.714. The AUC value was 0.799 (95% CI: 0.712 to 0.887, $P < 0.001$) in the model established with HbA1c, while it was 0.807 (95% CI: 0.706 to 0.907, $P < 0.001$) in the model established with HOMA-IR an (**Figures 2B, C**). We also established a model with testosterone, and the AUC was 0.772 (95% CI: 0.675 to 0.870, $P < 0.001$) (**Figure S1**).

Serum FGF21 Level in DMED Rats

Figure 3A indicates that FGF21 levels were significantly higher in the DMED group (241.12 ± 8.5 pg/ml) than in the DM (160.32 ± 7.2 pg/ml) and control (114.91 ± 5.6 pg/ml) groups. This finding was consistent with our human study.

TABLE 3 | Multivariate linear regression analysis on the influencing factors of IIEF-5 score in human study.

Variables	*B*	*SE*	*β*	*t*	*P*
FGF21	-0.229	0.061	-0.410	-1.770	0.000
HOMA-IR	-1.161	0.656	-0.185	-0.466	0.080
Testosterone	1.284	0.896	0.161	-3.735	0.156
TC	-0.545	1.170	-0.053	3.996	0.643
DBP	-0.120	0.077	-0.152	-0.005	0.122
SBP	0.000	0.073	-0.001	1.433	0.996

DBP, Diastolic blood pressure; FGF21, Fibroblast growth factor 21; HOMA-IR, homeostasis model assessment of insulin resistance; IIEF-5, international index of erectile function; TC, cholesterol; SBP, Systolic blood pressure; SE, standard error.

TABLE 4 | Logistic regression analysis on the determinants of erectile function in human study.

Variables	*B*	*SE*	*Walds*	*P*	*OR*	95% CI of OR	
						LCI	UCI
FGF21	0.177	0.0540	10.699	0.001	1.193	1.073	1.326
HOMA-IR	2.376	0.7926	8.988	0.003	10.765	2.277	50.895
HDL	3.211	1.6345	3.858	0.049	24.373	1.007	610.416

B, regression coefficient; CI, confidence interval; FGF21, Fibroblast growth factor 21; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LCI, lower confidence interval; OR, odds ratio; SE, standard error. SE, standard error; UCI, upper confidence interval.

Expression of FGF21 Protein in Rat Penis

Western blotting assays revealed that the mean level of FGF21 in the penis was higher in DMED rats (0.82 ± 0.08) versus rats in the DM (0.51 ± 0.09) and control (0.23 ± 0.09) groups (**Figures 3B, D**).

Level of FGF21 mRNA in Rat Penis

As shown in **Figure 3C**, the relative level of FGF21 mRNA as measured by $2^{-\triangle\triangle CT}$ values in the penis was significantly higher in the DMED group (2.61 ± 0.04) than in DM rats without ED (1.51 ± 0.04) and the controls (0.95 ± 0.02).

DISCUSSION

We investigated the relationship between FGF21 and diabetic ED in populations with T2DM and in diabetic rat models. Results of the human study demonstrated that the serum FGF21 level correlated with the IIEF-5 score. The International Index for Erectile Function (IIEF) is a patient-reported outcome measure, widely used in urology to measure erectile dysfunction (ED), applied both in clinical research and in daily clinical practice (16, 18, 20). Higher levels of FGF21 were observed in both humans and in rats with DMED compared to those with normal erectile function. Moreover, rats with DMED had increased expression of FGF21 protein and FGF21 mRNA compared to rats with normal erectile function, which validated our findings in humans.

ED is a complication that significantly harms the quality of life and psychological well-being of men with diabetes (21). Compared to DM treated with insulin, ED usually worsens in individuals with poor blood glucose control (2). Hyperglycemia is a major contributor to endothelial dysfunction, namely by disrupting vascular endothelial cells' homeostasis and altering eNO-dependent vasodilation processes (22). Under physiologic conditions, insulin promotes relaxation of the precapillary sphincter which induces vasodilation by directly stimulating the expression and activation of NO synthase (23, 24). An aberrant vascular response to insulin and subsequent vasoconstriction have been observed in individuals with insulin resistance; these issues may contribute to ED (23, 25). A mendelian randomization study showed that T2DM has a causal relationship with ED independently from obesity and dyslipidemia (26).

Our study also showed that the serum FGF21 level is correlated with HOMA-IR and fasting glucose. This finding is consistent with prior studies (27–29). The administration of recombinant FGF21 in animal models has been deemed effective in ameliorating insulin sensitivity and reducing serum glucose levels (30, 31). FGF21 exerts direct effects on increased glucose uptake in skeletal muscle and insulin-stimulated glucose transport, which may contribute to glucose homeostasis (32). In

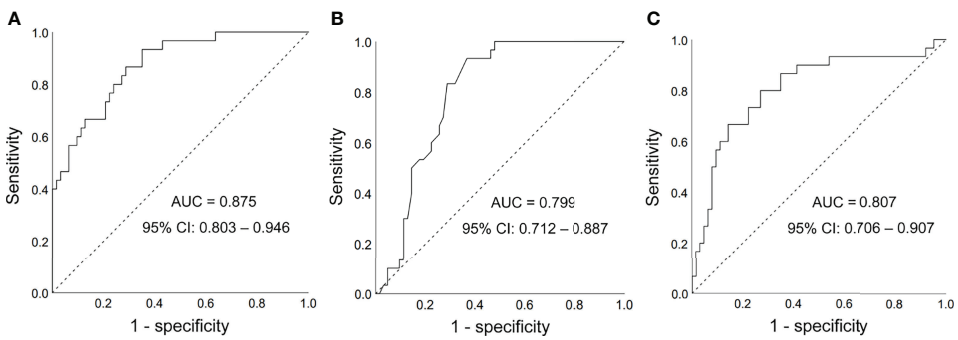

FIGURE 2 | Receiver operating characteristic (ROC) curves. **(A)** FGF21 for diagnosis of DMED; **(B)** HbA1c for diagnosis of DMED; **(C)** HOMA-IR for diagnosis of DMED; AUC, area under the curve; CI, confidence interval.

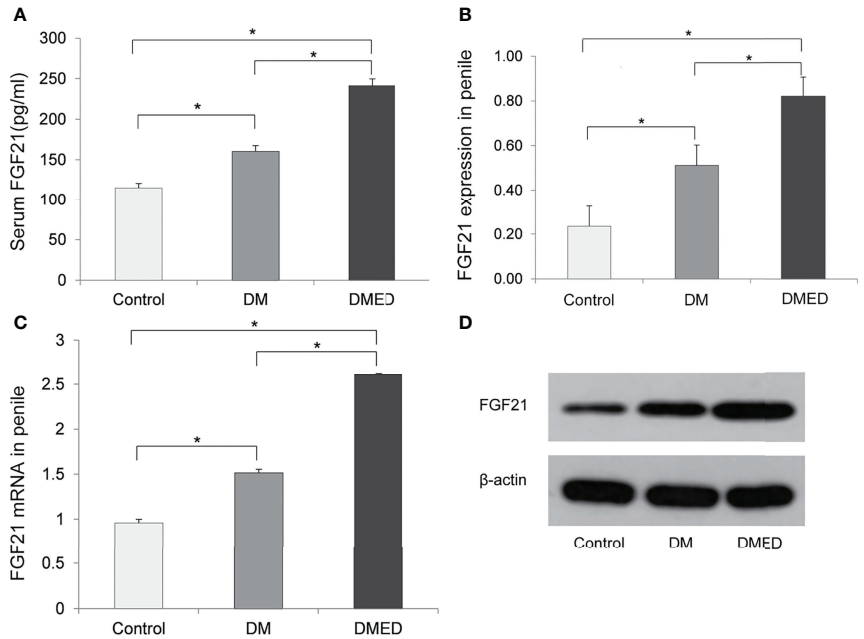

FIGURE 3 | The expression of FGF21 and FGF21 mRNA in rat model. **(A)** The level of serum FGF21; **(B)** The relative level of FGF21 protein in penile samples; **(C)** The relative level of FGF21 mRNA in penile samples; **(D)** The representative result of western blotting assay of FGF21 in penile samples. The data shown in the graphs represent the mean ± SD, $^*P < 0.05$.

addition, FGF21 promotes insulin secretion in islet β cells through the PI3K/Akt signaling pathway (33). The high levels of serum FGF21 observed in diabetic patients may be a compensatory response to decreased insulin sensitivity or potential FGF21 resistance (29, 34). FGF21 levels have been shown to be elevated 2–3 fold in oral glucose tolerance tests for patients with metabolic syndrome but not among healthy subjects (35).

Apart from the function of modulating energy metabolism, FGF21 plays a significance effect on vascular endothelium (36, 37), and is understood as a biomarker for subclinical vascular lesions (38). In addition, FGF21 stimulates the expression of adiponectin which suppresses proliferation and migration of smooth muscle cells and reduces uptake of oxidized LDL (39). Thus, FGF21 alleviates cardiovascular risk factors *via* improved lipid profiles. FGF21-induced activation of the CaMKK2-AMPKα signaling pathway suppresses oxidative stress and enhances endothelium-dependent vasorelaxation of the aorta, thus alleviating endothelial dysfunction (40). FGF21 directly prevents endothelial progenitor cell (EPC) damage induced by high glucose and promotes ischemic angiogenesis by increasing NAD+ content in an AMPK-dependent manner (10). FGF21 can also enhance EPC mobilization and angiogenic function under diabetic conditions (41). Vasculogenic is one type of ED including arteriogenic ED, venogenic ED and mixed vasculogenic ED (42). Studies have investigated the role of mean platelet volume (MPV) in diagnosis of vasculogenic ED, and patients with vasculogenic ED showed higher MPV compared with non-vasculogenic ED patients (43–45). Our findings showed that MPV level is not higher in the DMED group compared to the diabetic men without ED. It should be noted that in the clinical studies investigating the level of MPV among vasculogenic ED, the patients with diabetes were excluded (42, 46). However, in our study the ED patients were with diabetes.

Studies have also documented that FGF21 inhibits endothelial cell apoptosis and promotes DNA synthesis and differentiation of endothelial cells, which has been verified in the development of atherosclerosis (47, 48). Endothelial cells play a crucial role in maintaining erectile function by regulating contractions in the arteries of the corpus cavernosum and smooth muscle (49). The penile endothelium is a specialized extension of the vascular system (50). An impaired vascular endothelium induced by oxidative stress can cause ischemia and hypoxia of the corpus cavernosum. These conditions lead to cavernous smooth muscle damage and fibrosis, which result in DMED (51). Abnormal increase in FGF21 levels has been consider as a signal of endothelial cell injury (52) as reported in the diseases including obesity, dyslipidemia, metabolic syndrome, hypertension, CAD, DM, and nonalcoholic fatty liver (53–55). FGF21 can reduce oxidative damage and protects against high glucose–induced declines in cell viability (e.g., endothelial cell) (41). In addition, FGF21 is found to play a role in protection against eNOS dysfunction in endothelial cells exposed to high glucose (27).

LIMITATIONS

This study did not investigate the specific pathophysiological mechanism between diabetic ED and FGF21. The possible

beneficial effect of FGF21 in DMED treatment was not yet explored. Further studies are needed to clarify the potential metabolism and explore the therapeutic effect of FGF21 on DMED.

CONCLUSIONS

Our study evidenced that FGF21 is closely associated with diabetic ED. Even though the pathophysiological mechanism has not been fully explored, our findings display the potential role of FGF21 in the development of diabetic ED. FGF21 could be employed as an indicator of ED in diabetic men.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Taian Central Hospital. The patients/participants provided their written informed consent to participate in this study. The animal study was reviewed and approved by Taian Central Hospital.

AUTHOR CONTRIBUTIONS

HH and YaZ designed the study. SY, YiZ, YG, XL and GZ performed data collection and conducted experiments. YiZ, PL, YuZ and ZG performed data analysis and interpretation of results. YiZ, XL and SY drafted the manuscript. HH and YaZ revised the manuscript. All authors have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.874796/full#supplementary-material

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Association Between Globulin and Diabetic Nephropathy in Type2 Diabetes Mellitus Patients: A Cross-Sectional Study

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Background: With the development of economy, the living standard of people all over the world has been greatly improved, and the incidence of diabetes is also increasing. Many people with diabetes also develop other complications that reduce their quality of life. Diabetic nephropathy is a common complication of type2 diabetes. Understanding the related factors of diabetic nephropathy is greatly significant to control the occurrence of diabetic nephropathy and improve patient's life quality.

Data and Methods: Data were collected from 2009 to 2018 in NHANES. Curve fitting graph was performed to investigate the association between globulin (GLB) and diabetic nephropathy(DN). Four logistic regression models were conducted to control the potential confounding factors. Subgroup analysis was carried out to assess the stability of results.

Results: GLB was positively correlated with the occurrence of DN after controlling for potential confounders. Higher GLB was associated with an increased risk of diabetic nephropathy [odds ratio(OR), 1.10; 95% confidence interval (CI), 1.07-1.13, $P < 0.001$].

Conclusions: In this cross-sectional study, GLB was significant positively correlated with the occurrence of DN in patients with type2 diabetes mellitus.

Keywords: globulin, logistic regression, curve fitting, type 2 diabetes mellitus, diabetic nephropathy

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INTRODUCTION

Diabetes mellitus, characterized by chronic hyperglycemia, is a global metabolic disease caused by spontaneous metabolic disorders (1, 2). Recently, the diabetes incidence has increased significantly (3). It is estimated that by 2,045, there will be 642 million people worldwide living with diabetes, according to a report released by the International Diabetes Federation (4). Diabetes, is one of the most common chronic diseases, which brings great pressure to patients and medical system (5), especially to those patients with diabetes complications, such as nephropathy (6). The occurrence of diabetic nephropathy can shorten lifespan of diabetics. A cohort study of diabetes by Livingstone SJ

Abbreviations: GLB, globulin; DN, diabetic nephropathy; NHANES, the National Health and Nutrition Examination Survey; GLP, globulin; ACR, urinary microalbumin creatinine ratio; BMI, body mass index; GGT, gamma-glutamyltransferase; BUN, blood urea nitrogen; ALP, alkaline phosphatase; TP, total protein; UA, uric acid; TG, triglyceride; HBP, high blood pressure; HDL, high-density lipoprotein; ALB, albumin.

et al. revealed that the life expectancy of patients with diabetic nephropathy was shorter than that of patients without diabetic nephropathy, which may be one of the main reasons for the decline of diabetic patients' life expectancy (7). In 2016, Miller RG et al. revealed that the occurrence of diabetic nephropathy may lead to an increased risk of cardiovascular disease in diabetic patients albeit in early stages of diabetic nephropathy (8). Simultaneously, some related studies have indicated that people with diabetic nephropathy are at higher risk of death after contracting COVID-19 (9). Therefore, a comprehensive understanding of diabetic nephropathy and its related factors may contribute to the prevention and control of diabetic nephropathy, thus improve the prognosis and quality of life of diabetic patients.

Globulin is a serum protein existing in the human body, which is also known as immunoglobulin because of its immune function. Globulin is mainly composed of α 1, α 2, β and γ (10). In previous studies, globulin was considered as a sensitive indicator of liver function damage (11), especially in cases of severe liver disease. Globulin is also a reliable biomarker that is readily available in the basal metabolome. However, the relationship between globulin and diabetic nephropathy in diabetic patients has not been elucidated yet.

Consequently, we aim to use the real world public database of NHANES screening diabetic participants in its 5 cycles (2009-2018), investigating the relationship between GLB and diabetic nephropathy and assess its clinical value.

METHODS

Participants Selection and Study Grouping

The dataset for five ten-year periods from 2009 to 2018 were downloaded from the NHANES official websiteand weighted. We divided all participants into diabetic participants and non-diabetic participants, according to the commonly used international diagnostic criteria for diabetes. All patients with diabetes were included in this study. Meanwhile, we excluded people without GLP, ACR and other relevant data. This study is a cross-sectional study. Participants with ACR ≥ 30ug/mg were defined as diabetic nephropathy and those with ACR < 30ug/mg as non-diabetic nephropathy.

Data Collection

The basic information of the population was collected by trained professionals, and all experimental measurement data were strictly performed in the whole process by professionals in accordance with the technical standards published on the official website of NHANES. All data and experimental methods can be downloaded from the NHANES website. The experiments were carried out in a laboratory in Minnesota.

Demographics data (sex, age, race/nationality, etc.), anthropometric measurements (height, weight and waistline, etc.), health-related behaviors (smoking and drinking, etc.), biochemical tests (high density lipoprotein, fasting blood glucose, albumin, globulin, total cholesterol, uric acid, etc.) were selected (12). Then all units were quantified in terms of international standard units. Globulin is a group of proteins that transport various substances in the blood, and are involved in various defense mechanisms in the body (13). Serum globulin is the measure of dividing the total protein by the albumin.

Evaluation Criteria

Diagnosis of Diabetes Mellitus

The diagnostic criteria of diabetes were formulated by referring to international and previous research literatures (14). The criteria is: taking diabetes drugs, fasting blood glucose ≥ 7.0mmol/L or glycosylated hemoglobin ≥ 6.5mmol/L. The measured blood glucose values are rounded to three decimal places and converted from mg/dL to mmol/L.

Measurement of BMI

The body mass index (BMI) is the measure of dividing the weight (kg) by the square of the height (m^2) (15). According to World Health Organization standards, BMI of 18.5 kg/m^2 to 24.9 kg/m^2 is normal, BMI of 25.0 to 29.9 $kg/m^2$is overweight, and BMI ≥ 30.0kg/m^2 is obese (16).

Diagnosis of Hypertension

Participants were assessed for high blood pressure using the average of three or two measurementsof all participants' blood pressure, if only once was taken directly into the study, and assessed whether they were taking hypertension drugs. Subjects with systolic blood pressure ≥ 140mmHg and/or diastolic blood pressure ≥ 90mmHg were identified as hypertension (17).

Determination of Alcohol Consumption and Smoking Determination

We defined participants' drinking status based on clinical experience combined with previous relevant studies, and finally divided alcohol consumption into two levels (18, 19). Non-drinker, a person who have no more than 12 drinks a year, more than 12 are considered drinkers. There are also two levels of smoking. According to previous research combined with data analysis, people with no more than 100 cigarettes in their lifetime or those who do not smoke into a group and are defined as non-smokers, because the number of non-smokers in the data was too small. Participants who are current smokers or had smoked more than 100 cigarettes are smokers (20).

Covariable Screening

Here, we filter the covariates according to the following rules.

(1) demographic data;

(2) factors that may affect diabetic nephropathy reported in previous literature;

(3) the introduction of variation leads to the change of regression coefficient of the basic model by more than 10%;

(4) based on our clinical experience.

Demographics include age, sex and race. Biochemical indicators include GGT, BUN, Hba1c, ALT, AST, UA, TP, ALB. Other covariates include height, weight, BMI, blood pressure, etc. Height and weight were measured by rangefinder

and electronic scale (21). BMI and blood pressure were described above.

Statistical Methods

Using R language (version 4.10) and Free Statistics analysis platform for statistical analysis, and bilateral P< 0.05 was considered statistically significant. Continuous variables are represented by detailed sample descriptions with an average confidence interval of 95%. Categorical variables are expressed by counts and weighted percentages. The abnormal distribution is represented by median and Q1-Q3. The normal distribution is described by the median and standard deviation. Participants were divided into diabetic nephropathy group and non-diabetic nephropathy group according to whether ACR was greater than 30. In order to maximize the statistical efficiency and minimize the deviation, the missing data were interpolated for several times, and the sensitivity analysis of the interpolated data was analyzed to assess whether the generated data was significantly different from the original data. After sensitivity analysis, there was no statistically significant changes between the two groups. Therefore, tour interpolated data is consistent with the Robin guidelines research.

The statistical analysis of this study mainly consists of the following three stages to assess the correlation between GLB and diabetic nephropathy in selected subjects.

(1)The weighted single-factor and weighted multi-factor logical regression models were established, We established four different models according to the type of variables: model 1, without adjust any variables, that is, the single-factor logical regression model. Model 2 was adjusted for age, sex, race, BMI, waist. Model 3 was adjusted for variables in model 2 as well as GGT, BUN, Hba1c, ALT, AST, UA, TP, and ALB Model 4 was adjusted for variables in model 3 plus smoking, drinking status, HDL, TG, TBIL, and HBP.

(2)The smooth curve fitting graph was established and adjusted according to the covariables contained in model 4.The linear relationship between GLB and diabetic nephropathy was observed after logical regression.

(3) Subgroup analysis and weighted hierarchical logical regression were conducted on all subgroups to determine the stability of the results. Meanwhile, the GLB was converted into categorical variables based on the quartile for interactive testing. In addition, in the effect correction test, likelihood ratio test is carried out for the interaction terms between subgroups.

RESULT

Basic Information Characteristics When Obtaining Participant Data

A total of 49,694 participants from the NHANES dataset were selected for this study, which lasted for ten years and five cycles. After screening according to the above strict criteria, a total of 4,393 diabetic patients with an average age of 60.4 ± 14.5 years were enrolledin the final analysis (**Figure 1**). 2,315 male patients (52.7%) were slightly higher than 2,078 females (47.3%), and the proportion of males (57.3%) was higher than that of females (42.7%). Diabetic nephropathy patients' age (63.8 ± 13.4), waist circumference(110.1 ± 16.8 cm), glycosylated hemoglobin(7.2 (6.3, 8.6) %), ALP (76.0(61.0, 95.0) g/L), BUN(6.1(4.6, 8.6 U/L) and GLB (31.0 (28.0, 35.0) g/L)were significantly higher than those of non-diabetic nephropathy.The proportion of participants with diabetic nephropathy varies by race. In contrast, HDL (1.2 (1.0, 1.4) mmol/L) and ALB (42.0, (39.0,44.0) g/L) were higher in non-diabetic nephropathy groups than in the diabetic nephropathy patients. There was no significant difference in BMI or alcohol consumption between the two groups (**Table 1**).

Univariate Analysis of Factors Related to Diabetic Nephropathy

Univariate logistic regression analysis (**Table2**) showed that gender, age, race, GGT, waist circumference, BUN, glycosylated hemoglobin, ALP, TP, UA, GLB, TG, smoking, HBP, HDL and ALB were the related factors of diabetic nephropathy. Women have a lower risk of diabetic nephropathy than men. Other Hispanics had a lower risk of diabetic nephropathy compared toMexican-Americans, and there was no statistical difference between other ethnic groups and Mexican-Americans. HDL and ALB were negatively correlated with the occurrence of diabetic nephropathy. On the contrary, some factors were positively correlated with the occurrence of diabetic nephropathy, including age, GGT, waist circumference, BUN, glycosylated hemoglobin, ALP, TP, UA, GLB, TG, smoking, and HBP, etc.

Multivariate Analysis of GLB and Related Factors of Diabetic Nephropathy

Four logical regression models were established to analyze the relationship between GLB and diabetic nephropathy. **Table 3** indicated the relationship between GLB and diabetic nephropathy in detail, and its effect value is expressed as OR and 95%CI. The magnitude of the effect value can be interpreted as a relative increase in the risk of diabetic nephropathy for each additional GLB unit. For example, in unadjusted model 1, the effect value was 1.08 (1.06-1.09) could be interpreted as an 8% increase in the risk of diabetic nephropathy for each additional GLB unit. In slightly adjusted model 2, the effect value was 1.08 (1.07-1.10), with an 8% increase in the risk of diabetic nephropathy for each additional GLB unit. In further adjusted model 3, the effect value was 1.10 (1.07 to 1.13) indicating a 10% increase in the risk of diabetic nephropathy for each additional unit of GLB. In fully adjusted model 4, the effect value was 1.10 (1.07-1.13), that is, each additional GLB unit increased the risk of diabetic nephropathy by 10%, P < 0.05, which was statistically significant. To verify the stability of the results, sensitivity analysis and subgroup analysis were conducted, and smooth fitting curves of GLB and diabetic nephropathy were plotted., The participants were divided into three groups according to GLB level and verified by four models. In all models, the group with the highest GLB content had the highest risk of developing diabetes, followed by the moderate group, with a consistent trend

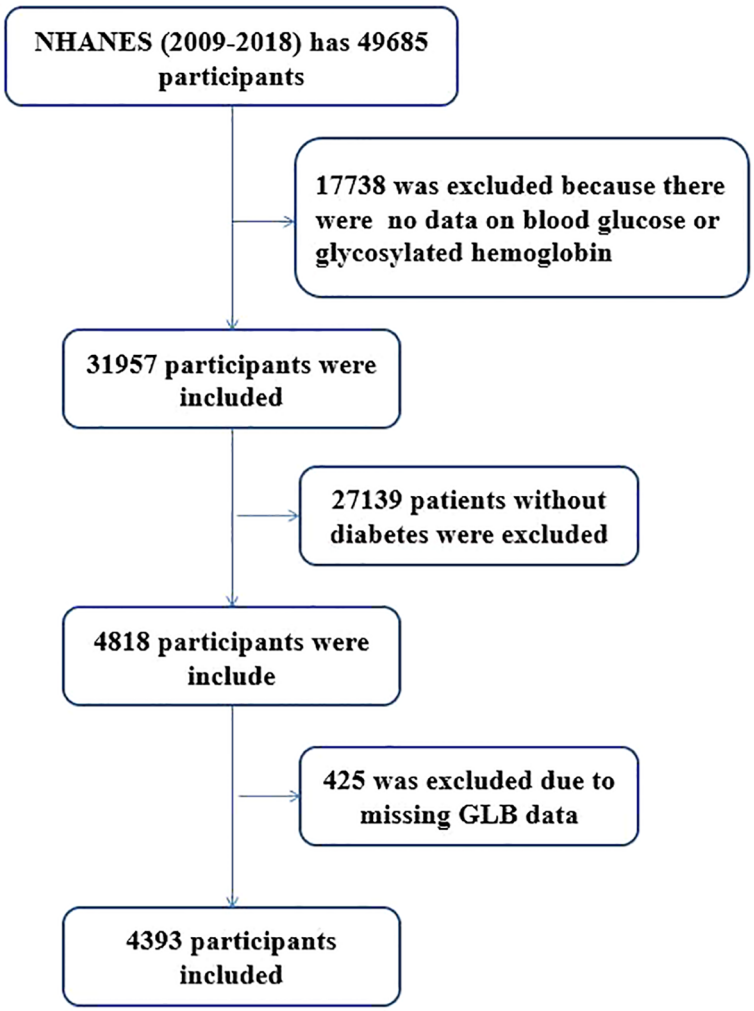

FIGURE 1 | Flowchart of participant selection.

test, P < 0.001(**Table 3**). After fully adjusting its potential confounding factors based on the clinical consensus, GLB can be considered to have a strong positive correlation with the incidence of diabetic nephropathy if the influencing factors changed bymore than 10%.

Subgroup Analysis and Curve Fitting

After adjustment according to model 4, the fitting curve of GLB and diabetic nephropathy were drawn (**Figure 2**), in order to better explain the relationship between GLB and diabetic nephropathy. The results showed that there was a linear relationship between GLB and diabetic nephropathy (P for non-linearity = 0.673). The effects of different GLB levels were equal. In addition, we investigated whether there were differences in age, sex and race between GLB and diabetic nephropathy. The results revealed that the relationship between GLB and diabetic nephropathy was stable in all subgroups (**Figure 3**), there was no interaction ($P > 0.05$).

DISCUSSION

With the development of the world economy, the incidence of diabetes in the world has increased significantly. It is estimated that by 2040, the number of people with diabetes will reach 642 million, accounting for about 10% of the world's total population (22). Diabetes is one of the most common chronic diseases confering about a two-fold excess risk for coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes (23). And patients tend to have pathological changes in other organs during a period of time (24), which will bring a lot of psychological and economic burden to patients and reduce their life experience (25). Therefore, a full understanding of the risk factors for these lesions can reduce the risk of diabetic complications and improve the well-being of patients.

This study investigated diabetic nephropathy, one of the most feared diabetic chronic microvascular complications of diabetes

TABLE 1 | Demographic characteristics describe whether diabetic nephropathy occurs.

Variables	Total (n = 4393)	Is there diabetic nephropathy?		*P*-value
		No (n = 3108)	Yes (n = 1285)	
Sex, n (%)				< 0.001
Male	2315 (52.7)	1579 (50.8)	736 (57.3)	
female	2078 (47.3)	1529 (49.2)	549 (42.7)	
Age, Mean ± SD	60.4 ± 14.5	59.0 ± 14.8	63.8 ± 13.4	< 0.001
Race, n (%)				0.016
Mexican American	776 (17.7)	533 (17.1)	243 (18.9)	
Other Hispanic	478 (10.9)	354 (11.4)	124 (9.6)	
Non-Hispanic White	1514 (34.5)	1093 (35.2)	421 (32.8)	
Non-Hispanic Black	1020 (23.2)	688 (22.1)	332 (25.8)	
Other Race	605 (13.8)	440 (14.2)	165 (12.8)	
BMI(kg/m^2), Mean ± SD	32.1 ± 7.6	32.0 ± 7.6	32.3 ± 7.7	0.349
Waist(cm), Mean ± SD	108.7 ± 16.7	108.2 ± 16.7	110.1 ± 16.8	< 0.001
Alchol use, Mean ± SD	1.5 ± 1.8	1.5 ± 2.0	1.5 ± 1.0	0.724
Smoking, n (%)				0.007
No	2250 (51.2)	1633 (52.5)	617 (48)	
Yes	2143 (48.8)	1475 (47.5)	668 (52)	
Hypertension, n (%)				< 0.001
No	829 (18.9)	691 (22.2)	138 (10.7)	
Yes	3564 (81.1)	2417 (77.8)	1147 (89.3)	
Hba1c(%), Median (IQR)	6.8 (6.0, 7.8)	6.6 (6.0, 7.6)	7.2 (6.3, 8.6)	< 0.001
ALB(g/L), Median (IQR)	41.0 (39.0, 43.0)	42.0 (39.0, 44.0)	40.0 (38.0, 43.0)	< 0.001
ALT(U/L), Median (IQR)	21.0 (16.0, 29.0)	22.0 (16.0, 30.0)	20.0 (15.0, 28.0)	< 0.001
HDL(mmol/L),Median (IQR)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	1.1 (1.0, 1.4)	< 0.001
AST(U/L), Median (IQR)	22.0 (18.0, 28.0)	23.0 (19.0, 28.0)	22.0 (18.0, 28.0)	0.003
GLB(g/L), Median (IQR)	30.0 (27.0, 33.0)	29.0 (27.0, 32.0)	31.0 (28.0, 35.0)	< 0.001
ALP(U/L), Median (IQR)	72.0 (58.0, 90.0)	71.0 (58.0, 87.0)	76.0 (61.0, 95.0)	< 0.001
BUN(mmol/L),Median (IQR)	5.4 (3.9, 6.8)	5.0 (3.9, 6.4)	6.1 (4.6, 8.6)	< 0.001

BMI, Body Mass Index; ALB, Albumin; ALT, alanine aminotransfease; AST, aspartate transaminase; ALP, alkaline phosphatase; BUN, blood urea nitrogen.

(26). The results suggested that high levels of GLB was positively correlated with the occurrence of diabetic nephropathy. To control for potential confounders, we established four logical regression models to analyze the association between GLB and diabetic nephropathy. In fully adjusted model 4, the effect value is 1.10 (1.07-1.13). This means that for each additional unit of GLB, the risk of diabetic nephropathy increases by 10%. According to the clinical consensus, after fully adjusting the potential confounders, the effect value of GLB has changed more than 10% of the influencing factors, which can be considered that there is a strong positive correlation between GLB and the incidence of diabetic nephropathy. Simultaneously, we divided GLB into three groups and conducted sensitivity analysis on the results, which showed that the results were stable and reliable (**Table 2**). Additionally, we validated the results in age, sex and race subgroups and found that they were stable in all subgroups without interaction (**Figure 3**). The fitting curve (**Figure 2**) between GLB and diabetic nephropathy was drawn after adjustment according to model 4, in order to better present this result and observe the linear relationship between GLB and diabetic nephropathy. This is also consistent with our validation of trend lines.

Some studies may partially explain the underlying mechanisms of GLB and diabetic nephropathy. GLB is one of the common inflammatory factors and has been used in liver function analysis. Liu et al. found that GLB elevation may reduce BCL2 expression through TNF regulation (22). Khater et al. found in the animal experiment of diabetic nephropathy, that the expression of BCL2 could effectively reduce renal tissue damage in diabetic nephropathy rats. Animal studies have also indicated that GLB aggravates renal injury by promoting the expression of TNF- α, IL-6 and IL-1 β (27).

Furthermore, Guo et al. proposed that miRNA-29c can regulate the expression of inflammatory cytokines in diabetic nephropathy by targeting tritetraproline (28). GLB can inhibit some miRNA expression by stimulating the secretion of inflammatory cells (29). RS et al. found a positively correlation between GLB and the occurrence and development of diabetes in a cohort study of Indians (30). Nakazawa D et al. found that elevated GLB can stimulate the secretion of neutrophils (31), which is also a risk factor for diabetic complications (32). These studies also indicated the association between GLB and diabetic nephropathy to some extent. Therefore, we speculate that lowering GLB level may be a good way to regulate the health status of diabetics patients. However, more prospective studies are needed to determine whether this study is applicable to a wider population.

Strength of the Study

In this study, compared with previous studies, some other aspects are worth mentioning. The population we selected was more broadly representative, due to the polycentric nature of the NHAENS database (12). Furthermore, in order to more intuitively represented the relationship between GLB and

TABLE 2 | Univariate analysis of association between factors of T2DM and diabetic nephropathy.

Variable	Diabetic nephropathy	
	OR (95%CI)	P-value
Gender		
Male	1	
female	0.77 (0.68~0.88)	<0.001
Age	1.03 (1.02~1.03)	<0.001
GGT	1 (1~1)	<0.001
RACE		
Mexican American	1	
Other Hispanic	0.77 (0.6~0.99)	0.043
Non-Hispanic White	0.84 (0.7~1.02)	0.08
Non-Hispanic Black	1.06 (0.87~1.29)	0.579
Other Race	0.82 (0.65~1.04)	0.103
BMI	1 (1~1.01)	0.349
Waist	1.01 (1~1.01)	<0.001
Alchol use		
No	1	
Yes	0.99 (0.95~1.04)	0.727
BUN	1.21 (1.19~1.24)	<0.001
Hba1c	1.28 (1.24~1.33)	<0.001
ALT	1 (1~1)	0.705
AST	1 (1~1)	0.957
ALP	1.01 (1~1.01)	<0.001
TP	1.03 (1.02~1.04)	<0.001
UA	1 (1~1)	<0.001
GLB	1.08 (1.06~1.09)	<0.001
TG	1.1 (1.05~1.14)	<0.001
Smoking		
no		
yes	1.2 (1.05~1.37)	0.006
HBP		
no		
yes	2.38 (1.95~2.89)	<0.001
HDL	0.74 (0.61~0.88)	0.001
ALB	0.91 (0.89~0.93)	<0.001
TBIL	0.99 (0.98~1)	0.147

BMI, Body Mass Index; ALB, Albumin; ALT, alanine aminotransfease; AST, aspartate transaminase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; TBIL, total bilirubin; GLB, globulin.

diabetic nephropathy, a smooth fitting curve was drawn to illustrate the relationship.

Limitations of the Study

Unfortunately, there are some limitations to this study. Although our results suggest that GLB level was strongly positively correlated with the occurrence of diabetic nephropathy, this study was a cross-sectional study, it is impossible to draw a causal relationship between the two, which require further cohort studies or case-control studies to clarify the relationship between GLB levels and diabetic nephropathy. Secondly, we excluded people younger than the population we included in the study, but considering that we used the population-weighted weight of the official NHANES website, this disadvantages has been well avoided. Moreover, our

TABLE 3 | Multivariate analysis of association between GLB and diabetic nephropathy.

Variable	Model 1		Model 2		Model 3		Model 4	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
GLB	1.08 (1.06~1.09)	<0.001	1.08 (1.07~1.10)	<0.001	1.10 (1.07~1.13)	<0.001	1.10 (1.07~1.13)	<0.001
GLB group								
GLB low	1		1		1		1	
GLB middle	1.32 (1.11~1.57)	0.002	1.39 (1.16~1.66)	<0.001	1.26 (1.04~1.52)	0.016	1.26 (1.05~1.52)	0.015
GLB high	2.3 (1.94~2.72)	<0.001	2.51 (2.1~3)	<0.001	1.86 (1.53~2.26)	<0.001	1.88 (1.54~2.28)	<0.001
Trend test	1.54 (1.41~1.67)	<0.001	1.6 (1.47~1.75)	<0.001	1.37 (1.24~1.51)	<0.001	1.38 (1.25~1.52)	<0.001

Model 1: Non-adjusted.
Model 2: Age, gender, Race, BMI, waist.
Model 3: Model 2 + GGT, BUN, Hba1c, ALT, AST, UA, ALB.
Model 4: Model 3 + Smoking, Drinking, HDL, TG, TBIL.

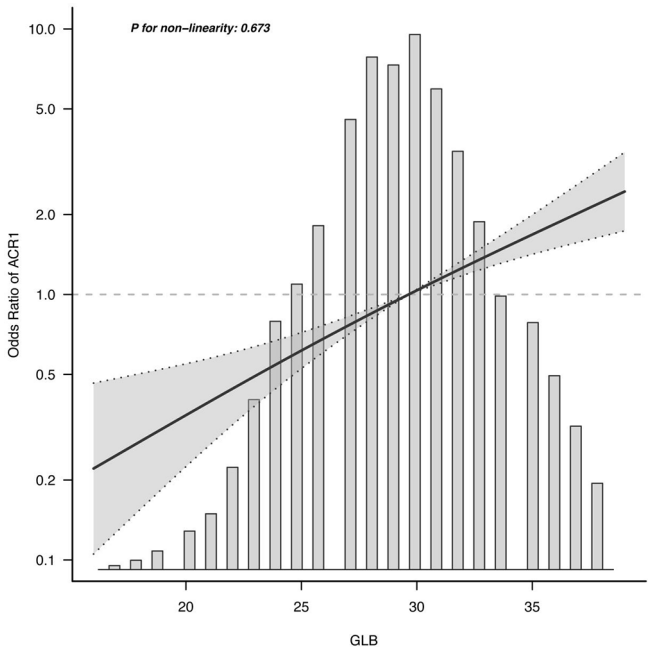

FIGURE 2 | Curve fitting of serum globulin and diabetic nephropathy.

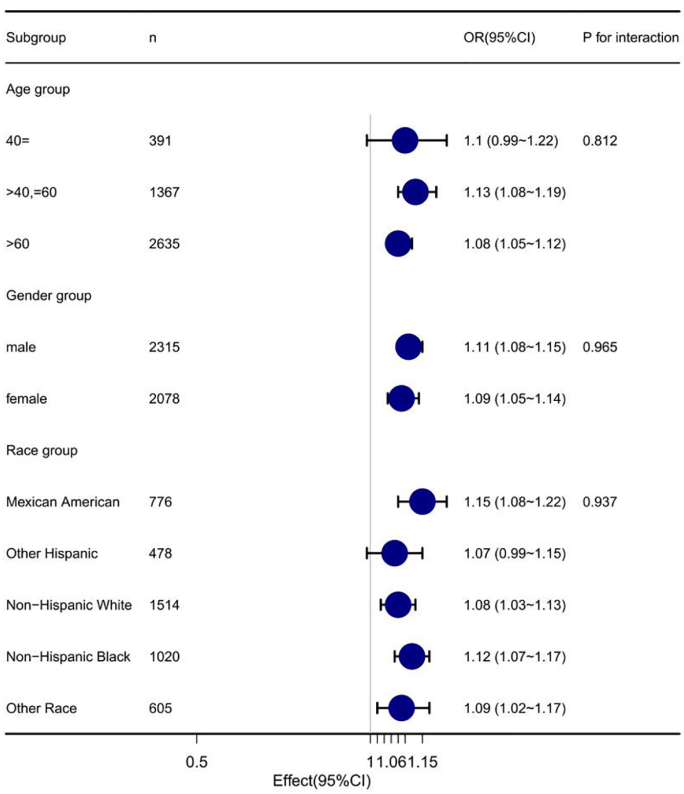

FIGURE 3 | Forest plot of serum globulin and diabetic nephropathy.

population inclusion was limited by the NHANES database only including some normal populations, excluding other countries and some special populations (e.g., pregnant women, cancer patients, etc.). Whether the relationship between GLB and diabetic nephropathy applies to this population is unclear.

CONCLUSION

In conclusion, the results of this cross-sectional study revealed that GLB was significantly positively correlated with the occurrence of diabetic nephropathy in diabetic patients. However, the specific mechanism and whether it is applicable to other populations need to be further studied. This study provides a new perspective for exploring the pathogenic factors of diabetic nephropathy.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: All data are available on the NHANES website.

AUTHOR CONTRIBUTIONS

XH conceived the idea; JW and FL wrote the manuscript; RK collected and read the literature and revised the article; XH read through and corrected the manuscript. All authors read and approved the final manuscript. XH is corresponding author of this paper.

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Risk of major adverse limb events in patients with type 2 diabetes mellitus receiving sodium glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists: A population-based retrospective cohort study

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Background: Both sodium glucose cotransporter 2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) have cardiovascular protective effects in patients with type 2 diabetes mellitus. However, the comparative risk of GLP-1RA versus SGLT-2i for major adverse limb events remains unknown.

Materials and methods: We studied a nationwide cohort involving 123,048 diabetes patients 20–100 years of age who initiated a SGLT-2i or GLP-1RA during 2012 and 2017. The patients in the two groups were matched by propensity score (PS), and incidence rates for hospitalization for major adverse limb events, critical limb ischemia (CLI) and lower extremity amputation (LEA), were assessed. Cox proportional hazards regression was applied to estimate hazard ratios (HRs) between patients receiving SGLT-2i as compared with GLP-1RA. The modification effects of age, a history of established cardiovascular disease, and chronic kidney disease were examined. In addition, use of dipeptidyl peptidase-4 inhibitor (DPP-4i) was chosen as a second active comparator.

Results: After PS-matching, a total of 13,378 SGLT-2i and 13,378 GLP-1RA initiators were identified. Use of SGLT-2i was not associated with an increased risk for hospitalization for CLI and LEA, either compared with GLP-1RA (HR, 1.13; 95% CI, 0.77–1.65 and 1.27; 95% CI, 0.63–2.55, respectively) or compared with DPP-4i use (HR, 1.06; 95% CI, 0.75–1.50 and HR, 0.80; 95% CI, 0.42–1.53, respectively). Although the study was underpowered to explore potential effect modification, a trend of higher risks for LEA was noted among SGLT-2i users with cardiovascular disease as compared with either GLP-1RA or DPP-4i.

Conclusion: Use of SGLT-2i was not associated with higher risks for hospitalization for CLI and LEA as compared with reference drugs. Further large-scale studies are needed for a precise risk estimation.

KEYWORDS

sodium-glucose cotransporter-2 inhibitor, critical limb ischemia, lower extremity amputation, glucagon-like peptide-1 receptor agonist, dipeptidyl peptidase-4 inhibitor, type 2 diabetes

Introduction

Critical limb ischemia (CLI) is one of the most devastating patterns of peripheral artery disease (PAD), but often an under-recognized complication for patients with diabetes mellitus. The onset of CLI is often dramatic, causing considerable morbidity and mortality, especially from subsequent management with major lower extremity amputation (LEA) (Faglia et al., 2009). With clinical and public health efforts, a decline in rate of LEA was observed in the past two decades but the case number has been rising since 2019, particularly in young and middle-aged adults (Geiss et al., 2019; Paul et al., 2021).

Novel anti-diabetic agents, sodium-glucose co-transporter 2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA), have shown promising effects on cardiovascular protection in patients with type 2 diabetes (Zinman et al., 2015; Marso et al., 2016; Neal et al., 2017; Wiviott et al., 2018; Gerstein et al., 2019). However, the potential risk of CLI or LEA associated with these agents remains an issue of great concern. In the CANagliflozin cardioVascular Assessment Study (CANVAS), the use of canagliflozin has doubled the risk for LEA among patients with established cardiovascular disease (CVD) or multiple risk factors (Neal et al., 2017). On the other hand, other evidence from clinical trials, including those involving other SGLT-2i (i.e., empagliflozin or dapagliflozin), did not show meaningfully harmful effects (Li et al., 2018; Scheen, 2018; Verma and Bhatt, 2019). Evidence from observational studies, including some comparing SGLT-2i with GLP-1RA (Chang et al., 2018; Ueda et al., 2018; Fralick et al., 2020; Hsiao et al., 2021; Patorno et al., 2021; Paul et al., 2021), was divergent and conflicting (Chang et al., 2018; Ryan et al., 2018; Ueda et al., 2018; Fralick et al., 2020; Caparrotta et al., 2021; Hsiao et al., 2021; Li et al., 2021; Patorno et al., 2021; Paul et al., 2021), probably due to heterogeneity in terms of study design and analysis, specific types of SGLT-2i, characteristics of the included populations, and the choice of comparator drugs. Given complex and multifactorial reasons that drive diabetes patients toward amputation instead of revascularization procedures, few studies had evaluated comprehensively the safety of SGLT-2i, as compared with GLP-1RA, on the composite major adverse limb outcome: CLI, which was at the late stage of the broad spectrum of PAD (Bonaca and Beckman, 2018). Moreover, based on the signal warning about the risk of using canagliflozin from the CANVAS trial, questions remain regarding to whether this is restricted to a specific drug or a class effect that also applies to other SGLT-2i (Khouri et al., 2018). Due to unavailability or limited availability of the data concerning patients' risk factors and lack of measurements about disease severity in previous studies, potential residual confounding by these clinical parameters remains a concern and the comparability between SGLT-2i and reference drugs is still problematic.

In light of these, we conducted a retrospective cohort study based on the nationwide population-based data. With clinical laboratory data and empirically abundant information that would serve as proxies for existence or severity of important risk factors for CLI and LEA, propensity score (PS) models were built for extensive covariate control. Under the hypothesis that use of SGLT-2i was not associated with higher risks for major adverse limb events, we compared the risks of CLI and LEA among patients who initiated empagliflozin and dapagliflozin, the most widely used medications in the SGLT-2i class in Taiwan during study period, with those initiated GLP-1RA between PS matched groups. The reasons that GLP-RA was chosen as a comparator are as followed: it is also a second-line treatment for diabetes (Dong et al., 2022a); it shares similar cardioprotective property with SGLT-2i (Dong et al., 2022b); it has not been reported with an increased risk for lower limb adverse event; and evidence from previous studies has shown great similarity

between SGLT-2i and GLP-1RA initiators in age and cardiovascular risk profiles, which are two crucial risk factors for lower limbs adverse events (Fralick et al., 2019; Fralick et al., 2020). In addition, we hypothesized that the risk estimates of lower limb adverse events should be robust when the comparison was made with different reference drugs. Thus, the other class of incretin-based antidiabetic agent, dipeptidyl peptidase-4 inhibitor (DPP-4i), was selected as an alternative active comparator to SGLT-2i in examining the risk for CLI and LEA.

Materials and methods

Data source

The data used in the current study were obtained from the Applied Health Research Data Integration Service of the National Health Insurance (NHI) Administration, Taiwan (case number: B201905310001 and B202201140002). This set of claims data included demographics, diagnoses, procedures, pharmacy, and prescription information from outpatient visits and hospital admissions of almost all population in Taiwan, and more importantly, provided anthropometric measurements and laboratory test results uploaded from medical facilities that were not previously available in NHI Research Database (NHIRD) (Lee et al., 2021). Ethical approval for this study was waived by National Taiwan University Research Ethics Committee (202003060W).

Study population and study drugs

This dataset exclusively contained all the patients, either outpatient or hospital admission, diagnosed with diabetes mellitus (International Classification of Diseases: ICD-9-CM codes of 250 or ICD-10-CM codes of E08, E09, E10, E11, or E13). Those who began to receive SGLT-2i or GLP-1RA from the NHIRD between 1 January 2012 (when the first GLP-1RA was reimbursed by NHI) and 31 December 2017 were included as study population. During the study period, two SGLT-2i (dapagliflozin, empagliflozin) and two GLP-1RA (liraglutide, dulaglutide) were widely used in Taiwan; therefore, the present analysis focused on these four drugs (see Supplementary Table S1 for codes). The cohort entry, or the index date, was defined as the first day of study drug dispensation. To ensure a new-user design, patients who initiated a SGLT-2i or a GLP-1RA must have had a period of 2 years without any study drug prescriptions. We also excluded patients who received both GLP-1RA or SGLT-2i and those who received more than one GLP-1RA or one SGLT-2i on the cohort entry date.

We then excluded patients with type 1 diabetes, cancer, cirrhosis, or other critical conditions such as dialysis and organ transplantation (Supplementary Table S2). Those who aged less than 20 or more than 100 years were also excluded. Subsequently, the patients who did not have any health encounter, either outpatient visit or hospital admission, within 1 year before the index date, were removed from further analysis to ensure the status of continuous NHI enrollment. Then, the patients with outcome occurrence on the index date were also excluded because the temporal relation of exposure and outcome could hardly be ascertained.

Outcomes and follow-up

Our primary outcome of interest was incident major adverse limb events, defined by the occurrence of CLI that required hospitalization for either medical or interventional treatment (revascularization or LEA) during follow-up. The occurrence of CLI was ascertained based on the existence of ICD-9/10 diagnosis or procedure codes and the NHI reimbursement codes in the inpatient claims (Supplementary Table S3). Also, in a secondary outcome definition, risks of SGLT-2i use were investigated specifically for non-traumatic LEA to facilitate comparison with previous studies.

During the follow-up, the study drug might be discontinued or changed to other medication. Drug discontinuation was defined as a more than 45-day grace period between the end of one prescription and the start of the other, while drug switch was defined as a dispensation of GLP-1RA for initiators of SGLT-2i or vice versa. According to these definitions, we applied two alternative follow-up schemes. First, in the "on-treatment" approach, the follow-up started from the index date, and ended on the date of outcome occurrence, study drug discontinuation or switch, death, or study termination (31 December 2018), whichever came earlier. Second, in the "intention-to-treat" approach aiming to capture the latent effect of the study drugs and to reduce informative censoring related to treatment discontinuation or change, the patients were followed from the index date to the date of outcome occurrence, death, or study termination.

Covariate assessment

We defined the characteristics of the patients during the 6 months before each subject's index. We assessed an extensive set of prespecified covariates (reflecting status on the index date) including demographic data, coexisting medical conditions, treatment with selected medications that were possibly associated with both the use of the study drugs and the risk of outcome occurrence. The use of healthcare services that potentially served as proxies for clinical disease severity and were potentially predictive of the risk of outcome including numbers of hospital admissions, numbers of outpatient visit

TABLE 1 Baseline characteristics of study population comparing sodium-glucose cotransporter type-2 inhibitor (SGLT-2i) with glucagon-like peptide 1 receptor agonist use before and after propensity score matching.

	Before matching (n = 123,048)			1:1 PS-matched cohort (n = 26,756)		
Covariates[a]	**SGLT-2i initiators (n = 108,920)**	**GLP-1RA initiators (n = 14,128)**	**Standardized difference**	**SGLT-2i initiators (n = 13,378)**	**GLP-1RA initiators (n = 13,378)**	**Standardized difference**
Demographics						
Age in years, mean (SD)	57.15 (12.56)	54.23 (13.89)	0.220	53.65 (13.36)	54.04 (13.77)	−0.029
Men	57.25	48.80	0.170	49.47	49.19	0.006
Overweight and obesity, %	3.78	10.47	−0.262	9.75	9.72	0.001
Smoking	1.74	1.84	−0.008	1.82	1.88	−0.005
Clinical parameters						
HbA1c, %						
>9.0	25.99	36.69	−0.232	36.06	35.86	0.004
7.0–9.0	44.47	39.60	0.099	40.53	40.20	0.007
<7.0	11.19	9.31	0.062	9.64	9.43	0.007
Missing	18.35	14.40	0.107	13.78	14.52	−0.021
Mean (SD)[b]	8.58 (1.72)	9.00 (1.84)	−0.235	8.97 (1.88)	8.96 (1.83)	0.002
eGFR, ml/min						
≥90	38.16	39.17	−0.021	41.81	40.78	0.021
60–89	32.66	22.77	0.222	24.25	23.82	0.010
30–59	11.59	16.05	−0.130	15.45	15.88	−0.012
<30	0.85	6.71	−0.311	3.47	3.97	−0.026
Missing	16.74	15.30	0.039	15.02	15.54	−0.014
Mean (SD)[b]	84.68 (22.12)	80.64 (30.52)	0.151	84.63 (27.10)	83.00 (28.80)	0.058
LDL−cholesterol, mg/dL						
>140	7.91	8.58	−0.024	8.66	8.53	0.005
120–140	9.32	9.17	0.005	9.47	9.31	0.006
100–119	15.22	15.25	−0.001	15.46	15.28	0.005
<100	44.00	46.91	−0.059	46.79	46.64	0.003
Missing	23.55	20.09	0.084	19.63	20.24	−0.015
Mean (SD)[b]	98.22 (32.15)	97.65 (32.68)	0.018	98.28 (32.56)	97.80 (32.55)	0.015
SBP, mmHg						
>160	3.18	5.24	−0.102	5.05	5.03	0.001
140–160	13.68	19.51	−0.157	19.23	19.35	−0.003
120–139	28.84	41.95	−0.277	42.39	41.81	0.012
<120	9.48	13.48	−0.125	13.91	13.48	0.013
Missing	44.81	19.83	0.554	19.41	20.32	−0.023
Mean (SD)[b]	133.05 (16.47)	133.29 (16.63)	−0.015	133.10 (16.76)	133.18 (16.51)	−0.005
Comorbidities						
Hypertension	66.78	67.05	−0.006	66.00	66.21	−0.004
Ischemic heart disease	24.70	19.33	0.130	18.55	18.92	−0.010
Myocardial infarction	3.33	1.73	0.102	1.55	1.70	−0.012
Coronary artery angioplasty or stenting	2.86	1.49	0.094	1.35	1.53	−0.015
CABG	0.78	0.74	0.005	0.70	0.73	−0.004
Cerebrovascular disease	9.77	8.98	0.027	8.64	8.66	−0.001
Ischemic stroke	6.10	5.27	0.036	5.03	5.12	−0.004
Hemorrhagic stroke	1.39	0.96	0.041	1.07	0.97	0.010
Cardiac dysrhythmia	7.22	5.66	0.064	5.27	5.47	−0.009
Congestive heart failure	8.42	7.59	0.030	7.15	7.12	0.001

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TABLE 1 (*Continued*) Baseline characteristics of study population comparing sodium-glucose cotransporter type-2 inhibitor (SGLT-2i) with glucagon-like peptide 1 receptor agonist use before and after propensity score matching.

Covariates[a]	Before matching (n = 123,048)			1:1 PS-matched cohort (n = 26,756)		
	SGLT-2i initiators (n = 108,920)	GLP-1RA initiators (n = 14,128)	Standardized difference	SGLT-2i initiators (n = 13,378)	GLP-1RA initiators (n = 13,378)	Standardized difference
Peripheral vascular disease	2.34	4.22	−0.106	4.12	3.92	0.010
Hyperlipidemia	75.49	77.14	−0.039	77.69	77.19	0.012
Chronic kidney disease	8.28	15.39	−0.222	12.63	13.27	−0.019
Charlson comorbidity index, mean (SD)	2.56 (1.75)	2.97 (1.89)	−0.221	2.89 (1.91)	2.89 (1.85)	<0.001
Anti-hyperglycemic medication use						
Any insulin	22.83	56.36	−0.730	54.22	54.13	0.002
Basal insulin	12.27	44.85	−0.774	42.18	42.31	−0.003
Premixed insulin	6.96	16.07	−0.288	14.95	15.15	−0.006
Metformin	89.09	84.77	0.128	87.10	86.57	0.015
Sulfonylurea	55.75	56.89	−0.023	56.76	57.06	−0.006
Glinides	0.93	1.75	−0.071	1.44	1.62	−0.015
Pioglitazone	19.51	20.99	−0.037	21.92	21.02	0.022
α-glucosidase inhibitors	17.29	19.96	−0.069	19.35	19.58	−0.006
DPP-4i	31.92	39.16	−0.152	38.12	37.99	0.003
Number of oral anti-hyperglycemic medications[c], mean (SD)	2.14 (1.04)	2.24 (1.07)	−0.085	2.25 (1.09)	2.24 (1.07)	0.008
Non- anti-hyperglycemic medication use						
ACEIs or ARBs	61.28	61.88	−0.012	60.39	60.82	−0.009
β blockers	36.39	33.92	0.052	32.36	32.87	−0.011
Calcium channel blockers	27.87	28.60	−0.016	27.48	27.62	−0.003
Diuretics	14.86	19.42	−0.121	17.37	17.85	−0.013
Other anti-hypertensive agents	5.08	6.59	−0.065	5.86	5.83	0.001
Nitrates	13.52	11.37	0.065	10.68	10.94	−0.008
Ivabradine	0.37	0.16	0.040	0.19	0.16	0.009
Valsartan + sacubitril	0.42	0.19	0.041	0.22	0.18	0.008
Aldactone	4.46	4.40	0.003	3.99	4.10	−0.006
Eplerenone	0.11	0.08	0.011	0.10	0.07	0.010
Anti-arrhythmic agents	3.36	2.88	0.027	2.75	2.87	−0.007
Digoxin	1.66	1.32	0.028	1.47	1.32	0.013
Aspirin	32.42	29.65	0.060	28.33	28.97	−0.014
Clopidogrel	8.32	6.34	0.076	5.81	6.16	−0.015
Warfarin	1.04	1.02	0.002	1.02	0.97	0.005
New oral anticoagulant	2.27	1.33	0.071	1.28	1.32	−0.003
Statins	62.62	61.59	0.021	61.09	61.29	−0.004
Fibrates	13.15	14.45	−0.037	14.64	14.33	0.009
Number of cardiovascular-related medications[d], mean (SD)	2.84 (1.91)	2.80 (1.96)	0.018	2.71 (1.93)	2.73 (1.93)	−0.014
Healthcare utilization						
Echocardiography	11.99	10.41	0.050	9.49	9.96	−0.016
Carotid ultrasonography	3.67	3.46	0.011	3.42	3.39	0.001
Transcranial ultrasonography %	2.37	2.10	0.018	2.12	2.09	0.002
Lower extremity arterial ultrasonography	0.94	1.44	−0.046	1.35	1.35	−0.001
24-h ECG examination	2.45	2.18	0.018	1.98	2.06	−0.005
BNP, proBNP, or NT-proBNP test	4.85	5.26	−0.019	4.79	4.93	−0.006

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TABLE 1 (*Continued*) Baseline characteristics of study population comparing sodium-glucose cotransporter type-2 inhibitor (SGLT-2i) with glucagon-like peptide 1 receptor agonist use before and after propensity score matching.

Covariates[a]	Before matching (n = 123,048)			1:1 PS-matched cohort (n = 26,756)		
	SGLT-2i initiators (n = 108,920)	GLP-1RA initiators (n = 14,128)	Standardized difference	SGLT-2i initiators (n = 13,378)	GLP-1RA initiators (n = 13,378)	Standardized difference
Prescriber's specialty						
Cardiologist or cardiovascular surgeon	23.82	4.75	0.566	4.40	4.95	−0.026
Endocrinologist	35.06	67.74	−0.692	67.52	66.92	0.013
Other specialty	41.12	27.51	0.290	28.08	28.14	−0.001
Number of hospitalizations, mean (SD)	0.21 (0.53)	0.29 (0.62)	−0.150	0.28 (0.64)	0.28 (0.60)	<0.001
Number of hospitalization due to CV-related episodes, mean (SD)	0.16 (0.47)	0.21 (0.53)	−0.105	0.20 (0.55)	0.20 (0.51)	−0.004
Number of hospitalization due to genito-urinary infection-related episodes, mean (SD)	0.02 (0.17)	0.04 (0.22)	−0.076	0.04 (0.22)	0.04 (0.21)	0.007
Number of hospitalization due to diabetic ketoacidosis, mean (SD)	0.00 (0.05)	0.00 (0.07)	−0.039	0.00 (0.07)	0.00 (0.07)	0.001
Number of outpatient visits, mean (SD)	17.67 (11.10)	19.54 (12.09)	−0.161	19.23 (12.16)	19.27 (11.94)	−0.003
Number of outpatient visits due to CV−related episodes, mean (SD)	7.47 (5.02)	7.98 (5.66)	−0.096	7.83 (5.49)	7.83 (5.55)	−0.001
Number of outpatient visits due to genito-urinary infection-related episodes, mean (SD)	0.37 (1.44)	0.52 (1.81)	−0.091	0.50 (1.72)	0.50 (1.77)	−0.003

C statistics for PS model: 0.814.

[a]Data presented as percentage unless otherwise specified (SD, standard deviation).

[b]Statistics among patients without missing value.

[c]Oral anti-hyperglycemic medications as listed above.

[d]Cardiovascular-related medications as listed above.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft surgery; CV, cardiovascular; ECG, electrocardiogram; NT, N-terminal (Abbreviations that have been defined in the main text are not listed here).

due to cardiovascular episodes, specialty of study drug prescribers, and whether patients received cardiovascular-related laboratory test or examinations were also assessed (Supplementary Tables S4, S5 provides detailed covariate information). Systolic blood pressure and laboratory test results, including glycated hemoglobin (HbA1c), serum creatinine, low-density lipoprotein (LDL)-cholesterol, within 90–180 days before the index date were used to balance the baseline characteristics between the two comparison groups (Supplementary Table S6). CKD-EPI equation, incorporating age, sex, and serum creatinine, was used to calculate estimated glomerular filtration rate (eGFR) (Levey et al., 2009).

Statistical analysis

We applied propensity score matching design to balance baseline characteristics between two treatment groups. We estimated baseline PS by using logistic regression models that contained all variables shown in Table 1 to predict the probability of initiating SGLT-2i. The missing-indicator method was used to handle missing information on four important clinical parameters. Instead of excluding patients with missing data, the method adds an extra category in the variable to indicate the value is missing; for example, the HbA1c values (%) were categorized as: >9.0, 7.0–9.0, <7.0, and missing. Therefore, each participant can still be included in the analysis, reducing the loss of statistical power (Choi et al., 2019).

A nearest-neighbor algorithm without replacement was used to perform 1:1 match between SGLT-2i and GLP-1RA initiators. The process allowed a maximum matching caliper of 0.025 on the PS scale. For each covariate, the standardized difference less than 0.1 was regarded as well balance between treatment groups (Austin, 2011).

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome with SGLT-2i as compared with GLP-1RA in the eligible cohort before and after PS matching. Kaplan-Meier curves were plotted to demonstrate curves of cumulative incidence of the outcome over time among PS-matched cohorts. Schoenfeld residual tests were used to assess the proportional-hazards assumption.

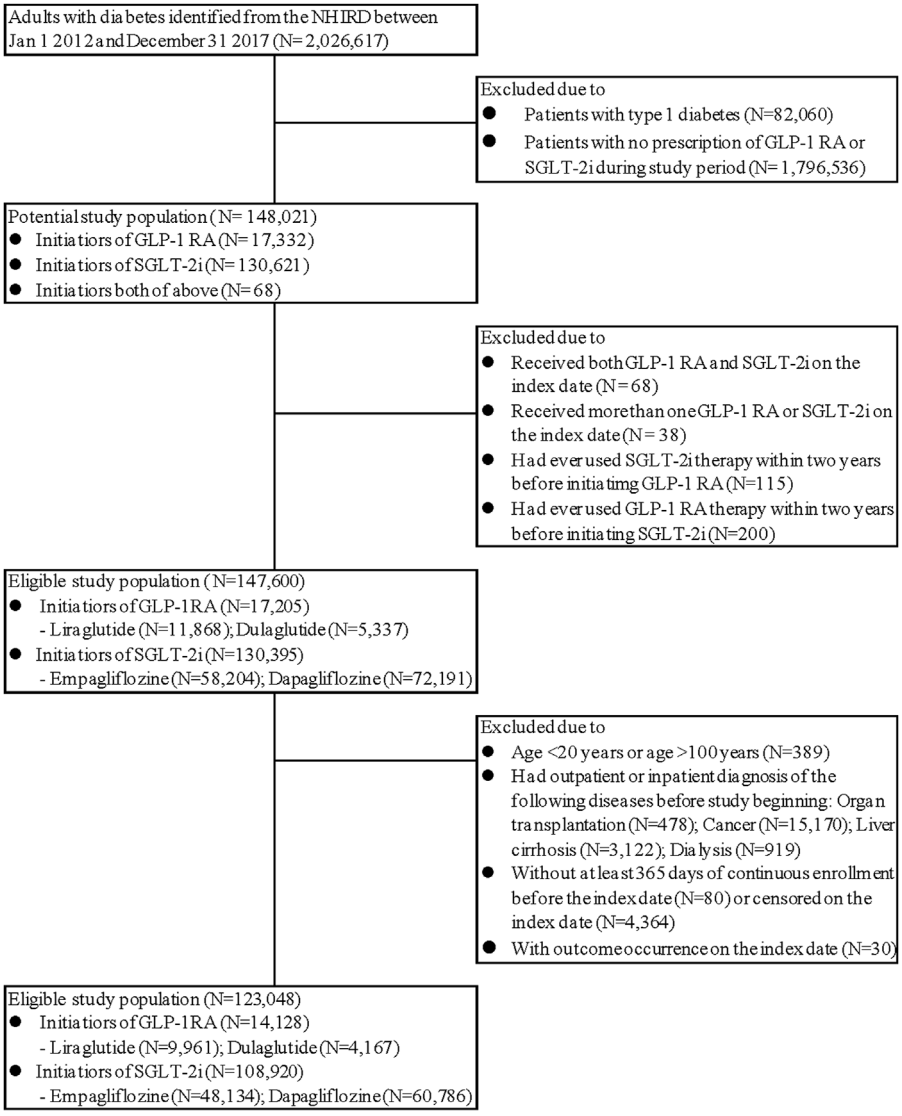

FIGURE 1
Study cohort assembly. (SGLT-2i versus GLP-1RA).

Auxiliary and subgroup analyses

New users of dipeptidyl peptidase-4 inhibitors (DPP-4i) was chosen as a second active comparator group to address the comparative risk of SGLT-2i use with other anti-diabetes agents on hospitalized CLI and LEA (See Supplementary Figure S1 for criteria and assembly of the second cohort comparing SGLT-2i with DPP-4i). Subgroup analyses were performed according to age (>60 and <60 years), the presence of established CVD, previous diagnosis of chronic kidney disease (CKD) or baseline eGFR<60 ml/min/1.73 m^2. Effect modification was assessed according to these prespecified risk factors and examined by looking at overlap of the 95% confidence intervals between subgroups.

In auxiliary analyses, HRs for acute limb events were evaluated after excluding patients with peripheral vascular disease or CLI or LEA at baseline to avoid misclassifying underlying disease as outcome.

Finally, the risks of acute limb events associated with the use of empagliflozin and dapagliflozin was estimated separately. We re-estimated the PS and re-matched patients for each pairwise comparison in each auxiliary and subgroup analysis. All analyses

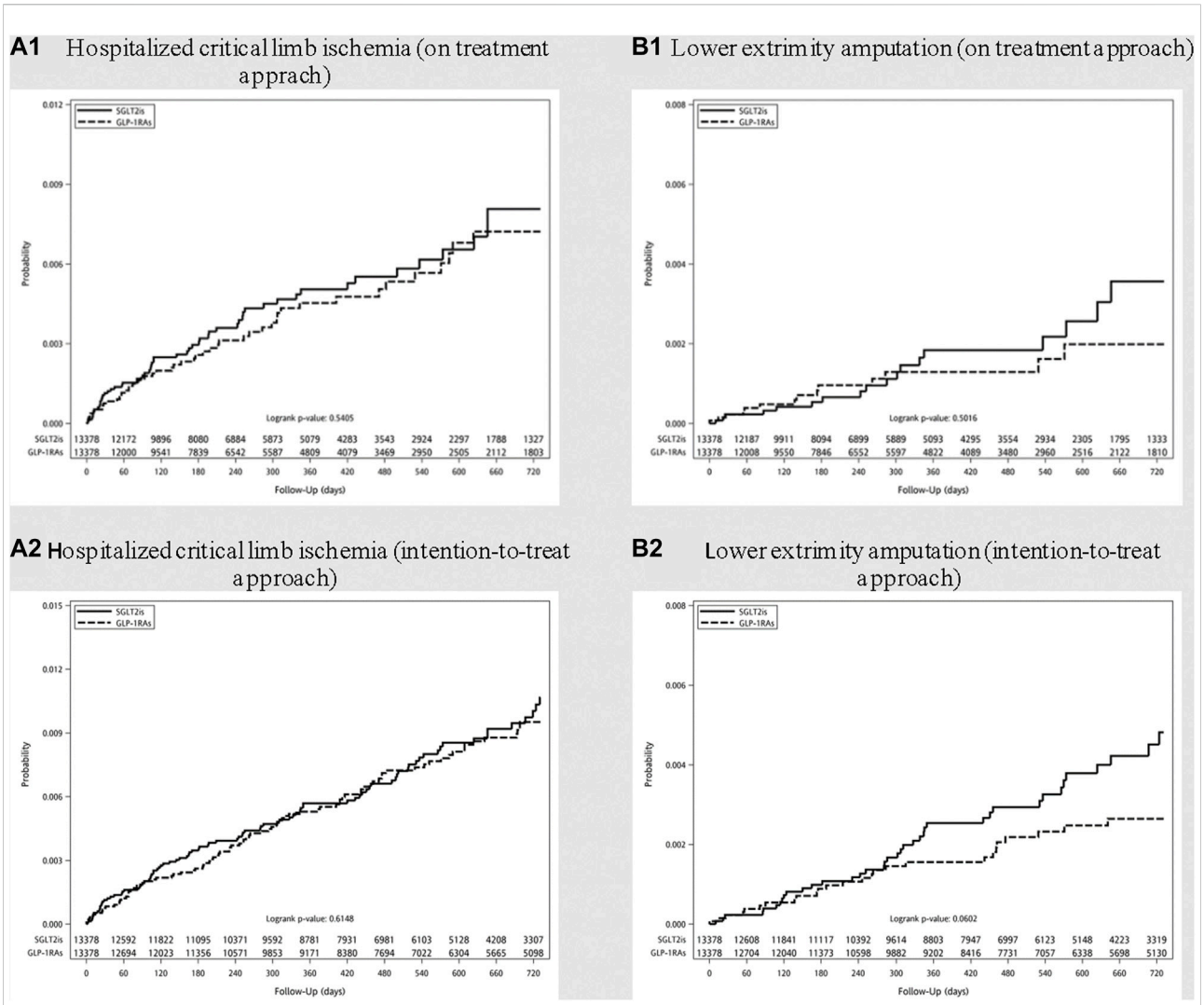

FIGURE 2
Cumulative incidence curves of **(A)** hospitalized critical limb ischemia and **(B)** lower extremity amputation among diabetes patients initiating sodium-glucose cotransporter type-2 inhibitors (SGLT-2i) and glucagon-like peptide 1 receptor agonists (GLP-1RA) after propensity score matching. (On treatment approach: A1 and B1; Intention-to-treat approach: A2 and B2).

were performed with SAS software, version 9.3 (SAS Institute). All reported *p* values are two-sided.

Results

Study population

Out of nearly two million type 2 diabetes adults, a total of 123,048 patients fulfilled the inclusion criteria, including 108,920 SGLT-2i and 14,128 GLP-1RA initiators (Figure 1).

Before PS matching, the patients who initiated SGLT-2i were older, more likely to be men, more likely to have ischemic heart disease or myocardial infarction, and more likely to have received a filled prescription for metformin; GLP-RA initiators had higher HbA1c level, had higher Charlson comorbidity index, were more likely to have diagnosis associated with obesity and CKD, and were more like to receive a filled prescription for insulin, DPP-4i and diuretics (Table 1, left). After PS matching, there were 13,378 SGLT-2i and 13,378 GLP-1RA initiators. The standard difference in each covariate was lower than 0.1, indicating that both groups were well balanced in various baseline characteristics. (Table 1, right).

Incidence and risk of critical limb ischemia and lower extremity amputation associated with SGLT-2i versus GLP-1RA.

The median follow-up time in SGLT-2i and GLP-1RA groups were 0.62 and 0.67 years, corresponding to crude

TABLE 2 Hazard ratios of hospitalization for critical limb ischemia and lower extrimity amputation comparing sodium-glucose cotransporter type-2 inhibitor (SGLT-2i) versus glucagon-like peptide 1 receptor agonist (GLP-1RA) initiators.

	GLP-1RA	SGLT-2i	
		Hazard ratio (95% CI)	
		On-treatment approach	Intention-to-treat approach
Hospitalization for critical limb ischemia			
Crude	Reference	0.88 (0.66–1.17)	0.78 (0.63–0.96)
After PS matching	Reference	1.13 (0.77–1.65)	1.08 (0.81–1.44)
Lower extremity amputation			
Crude	Reference	0.89 (0.51–1.52)	0.86 (0.58–1.28)
After PS matching	Reference	1.27 (0.63–2.55)	1.60 (0.98–2.63)

GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT-2i, sodium-glucose cotransporter type-2 inhibitor; CI, confidence interval; PS, propensity score.

TABLE 3 Subgroup analyses: hazard ratios of hospitalization for critical limb ischemia and lower extrimity amputation stratified by age, cardiovascular disease and chronic kidney disease.

	N =	GLP-1RA	SGLT-2i
			Hazard ratio (95% CI)
Hospitalization for critical limb ischemia			
Age (years)			
≤60	17,932	Reference	1.11 (0.59–2.10)
>60	8,780	Reference	1.10 (0.68–1.79)
Cardiovascular diseases			
Yes	8,636	Reference	1.56 (0.97–2.51)
No	18,118	Reference	1.19 (0.64–2.22)
Chronic kidney disease			
Yes or eGFR<60 ml/min/1.73m^2	6,654	Reference	1.42 (0.74–2.70)
No or eGFR ≥ 60	20,032	Reference	1.10 (0.67–1.82)
Lower extremity amputation			
Age (years)			
≤60	17,932	Reference	1.30 (0.49–3.50)
>60	8,780	Reference	0.83 (0.28–2.47)
Cardiovascular diseases			
Yes	8,636	Reference	2.16 (0.82–5.68)
No	18,118	Reference	1.54 (0.60–3.97)
Chronic kidney disease			
Yes or eGFR<60 ml/min/1.73m^2	6,654	Reference	1.04 (0.26–4.16)
No or eGFR ≥ 60	20,032	Reference	1.16 (0.50–2.68)

GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT-2i, sodium-glucose cotransporter type-2 inhibitor; CI, confidence interval; eGFR, estimated glomerular filtration.

incidence of 4.00 (95% CI, 3.62–4.43) and 4.52 (95% CI, 3.46–5.90) per 1,000 person-years for hospitalization for CLI; and 1.12 (95% CI, 0.92–1.35) and 1.25 (95% CI, 0.76–2.08) per 1,000 person-years for LEA respectively. The incidence rates for major adverse limb events using either on-treatment or intention-to-treat approach, before

and after PS matching, were listed in Supplementary Table S7. The cumulative incidence curves for hospitalized CLI and LEA after PS matching were shown in Figure 2.

Hazards ratios of hospitalization for CLI and LEA among new users of SGLT-2i, as compared with GLP-1RA, are shown in Table 2. After PS matching, the use of SGLT-2i was not associated with an increased risk for hospitalized CLI and LEA in comparison with GLP-1RA (HR 1.13; 95% CI, 0.77–1.65 and 1.27; 95% CI, 0.63–2.55 respectively). A lack of significantly increased risks for CLI and LEA was also noted in the analyses of intention-to-treat approach among SGLT-2i as compared with GLP-1RA initiators.

Findings in subgroups and auxiliary analyses

Table 3 presents the risks of adverse limb events in subgroups of patients stratified according to age, CVD, and CKD. None of these prespecified patients' baseline characteristics were considered effect modifiers. Consistent with the main analysis, patients taking SGLT-2i, in comparison with GLP-1RA users, did not have higher risks for hospitalized CLI and LEA between patients aged less than or higher than 60 years, and between patients with or without CKD. However, a trend of higher risks for LEA were noted among SGLT-2i users with history of CVD (HR, 2.16; 95% CI, 0.82–5.68). In auxiliary analysis, risk estimates did not change substantially when excluding patients with prior history of peripheral vascular disease (Supplementary Table S8). Risks of CLI and LEA were similar between empagliflozin and dapagliflozin when comparing with GLP-1RA (Supplementary Table S9; Supplementary Figure S2).

Risk of critical limb ischemia and lower extremity amputation associated with SGLT-2i versus DPP-4i

A separate cohort was then recruited to evaluate the risks of SGLT-2i-assciated adverse limb events using DPP-4i as a second active comparator (Supplementary Figure S1). Patients initiating DPP-4i were older and had higher Charlson co-morbidity index scores, more inpatient and outpatient health service utilization, and higher percentage of CKD or eGFR<30 ml/min as compared with SGLT-2i (Supplementary Table S10). DPP-4i users also had meaningfully higher cardiovascular burden in terms of more cardiovascular-related diseases, medications use, and higher cardiovascular-related healthcare access. During follow-up, substantially lower crude incidence rates for hospitalized CLI and LEA were noticed in SGLT-2i users in comparison with DPP-4i (Supplementary Table S11). However, after PS matching, the effect estimates of SGLT-2i versus DPP-4i for adverse limb events shifted dramatically from 0.41 to 1.06, suggesting a high probability of confounding. (Supplementary Table S12; Supplementary Figure S3). As compared with DPP-4i use, SGLT-2i use was not associated with significantly altered risks for hospitalized CLI and LEA, and consistent results were shown in subgroup analysis (Supplementary Table S13). However, potential higher risks for LEA were also noted in SGLT-2i, as compared with DPP-4i, among patients with CVD (HR, 2.06; 95%, CI 0.81–5.25).

Discussion

The results from this nationwide cohort study indicated that initiating SGLT-2i was not associated with significantly altered risks for hospitalized CLI and LEA as compared with initiating GLP-1RA. There was no association with lower limb adverse events either when the comparison was made between SGLT-2i and DPP-4i initiators. Although the study might be underpowered to explore potential effect modification, a trend of higher risks for LEA was noted among SGLT-2i users with CVD as compared with either GLP-1RA or DPP-4i.

One of the potential mechanisms of action for adverse limb events associated with SGLT-2i use is its diuretic effect that leads to hemoconcentration and increased blood viscosity, making poorly perfused peripheral tissue more prone to ischemia. However, some evidence derived from clinical trials did not suggest an increased risk when SGLT-2i was compared with placebo or other antidiabetic drugs (Inzucchi et al., 2018; Li et al., 2018; Scheen, 2018; Perkovic et al., 2019; Miyashita et al., 2020). With regard to real-world data comparing GLT-1RA and SGLT-2i, results were conflicting. Using registries from Denmark and Sweden, Ueda et al. (2018) reported a 2.32-fold increase in risk for LEA among SGLT-2i users compared with GLP-1RA ones. The work by Fralick et al. (2020) classified participants from three large U.S. health insurance databases into four groups according to whether they were older or younger than 65 years and whether they had or did not have CVD. It turned out that patients prescribed with canagliflozin had a significantly higher risk of LEA than those for whom GLP-1RA were prescribed (HR: 1.73, 95% CI: 1.30–2.29) only in the subgroup older than 65 years with coexisting CVD (Fralick et al., 2020). However, other studies from the United States showed that SGLT-2i, as compared to GLP-1RA, posed a non-statistically significant risk to major adverse limb events (Chang et al., 2018) or was associated with an increased risk only among older adults (Patorno et al., 2021). Paul et al. (2021) reported that the risk of LEA was not higher in SGLT-2i (including 46% canagliflozin users) versus GLP1-RA but lower while compared with DPP-4i. A recent multi-institutional study in Taiwan reported a 38% reduction in major adverse limb events among initiators of GLP-1RA as

compared with SGLT-2i, majorly empagliflozin and dapagliflozin, suggesting a detrimental effect of SGLT-2i (Hsiao et al., 2021). Our study found that treatment with SGLT-2i, empagliflozin or dapagliflozin, as compared with treatment with GLP-1RA, was not associated with increased risk for CLI and LEA. However, as seen in subgroup analysis, a potential increased risk for LEA could be speculated among patients with baseline CVD. Since only a small percentage of population had established PAD or CVD at baseline, further studies focusing on high-risk patients are needed. Whether the risk of lower limb adverse events associated with SLGT-2i use is a class effect or drug specific remains uncertain.

Previous studies had suggested strong similarity among SGLT-2i and GLP-1RA initiators in terms of age and cardiovascular risk profiles, which are two crucial risk factors for lower limbs adverse events (Fralick et al., 2019; Fralick et al., 2020), and a similar pattern was found in our study as well. Meanwhile, initiators of DPP-4i in our study, the second active comparator, were older, more likely to have poor renal function, and associated with more cardiovascular related burden at baseline than those of SGLT-2i, in agreement with that reported in previous studies (Fralick et al., 2019; Patorno et al., 2019). Effect measures of SGLT-2i for lower limb adverse events changed considerably from protective to close to null after PS matching, indicating great confounding effect by baseline characteristics among comparison groups. Although we found a marginal negative association between SGLT-2i use and lower limb adverse events while comparing with DPP-4i use, biases from residual confounding remain a notable issue for consideration.

Strengths of this study are as followed. The outpatient pharmacy claims database contains almost all anti-diabetics prescriptions dispensed in Taiwan with high validity for drugs exposure. The complete follow-up of the NHIRD beneficiaries avoids potential selection bias encountered in hospital-based studies. We included a comprehensive list of inpatient diagnostic and procedure codes as well as health insurance reimbursement codes for lower limb revascularization and amputation in order to have more complete outcome ascertainment. In addition, most prior related studies were only claims-based. The current study incorporated crucial clinical variables of which the percentage of missing data was very low into the process of PS matching. The baseline characteristics of the two comparison groups could be closely matched so that the distribution of risk factors and the severity of diabetes and CVD were highly comparable. Since PS matching of variables or proxies associated with disease severity could achieve balance for unmeasured characteristics and minimize unmeasured confounding factors (Patorno et al., 2018), potential confounding by indication was largely mitigated.

Our study has several limitations. First, despite having controlled for a large number of potential confounders and clinical parameters, we could not exclude the possibility of residual confounding, such as body mass index (BMI) or duration of smoking. Second, because the continuous treatment rates of the study drugs were low and it was not until May 2016 that SGLT-2i was reimbursed by NHI, the length of follow-up was limited; the median time of follow-up was 0.62–0.67 year for the on-treatment approach and extended to 1.23–1.53 year for intention-to-treat approach. However, since the diuretic effect of SGLT-2i, which is postulated as the mechanism for lower limb adverse events, is more evident in the early phase of treatment, we were able to capture the short-term risks, if any, of the drug (Vlachopoulos et al., 2021). On the other hand, whether the use of SGLT-2i in the long run would modify the course of the development or progression of PAD needs further investigation (Paul et al., 2021). Third, due to a low incidence of the study outcome and the limited number of patients, the results of subgroup analyses might not be precise. Lastly, our study findings were limited to four specific medications that were widely used in Taiwan. We did not further investigate other GLP-1RA or SGLT-2i for their risks on hospitalized CLI or LEA.

In conclusion, the use of SGLT-2i was not associated with the risks for CLI and LEA as compared to that of GLP-1RA. Further studies using larger sample size population, with broader spectrum of cardiovascular profiles and longer period of follow-up are needed to shed light on real-world evidence as well as to guide clinical practice.

Data availability statement

The datasets presented in this article are not readily available due to the data protection policy declared by National Health Insurance Administration, Taiwan. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by National Taiwan University Research Ethics Committee (reference number: 202003060W). The ethics committee waived the requirement of written informed consent for participation.

Author contributions

Y-HD and C-HC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Y-CL, Y-HD, and C-HC. Acquisition, analysis, or interpretation of data: Y-CL, Y-HD, J-WL, and C-HC. Drafting of the manuscript: Y-CL, Y-HD, W-SY, J-WL, and C-HC. Critical revision of the manuscript for important intellectual content: J-WL, W-SY, and L-CW. Obtained funding: C-HC and J-WL. Administrative, technical, or material support: L-CW. Supervision: J-WL and C-HC. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.869804/full#supplementary-material

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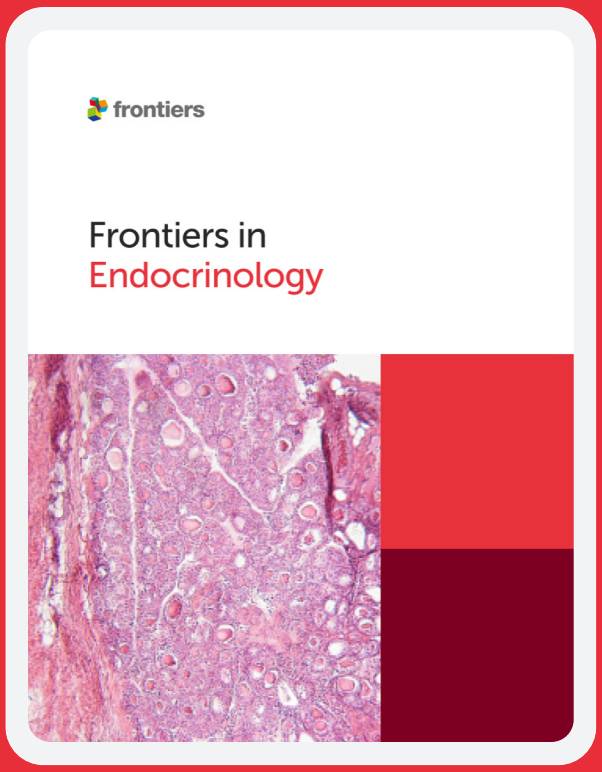

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